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THE SQUIRREL'S NEST 2015

Terrence McGarty

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THE SQUIRREL'S NEST

MONDAY, DECEMBER 28, 2015

[A GOOD IDEA DOES NOT A BUSINESS MAKE](#)

The [NY Times](#) has an article on Universities spending tuition money to "support" start up.

They state:

Ten years ago, it may have sufficed for colleges and universities like Rice to offer a few entrepreneurship courses, start-up workshops and clubs. But now hundreds of thousands of undergraduates, driven by a sullen job market and inspired by billion-dollar success narratives from Silicon Valley, expect universities to teach them how to convert their ideas into big businesses or nonprofit ventures. As a result, colleges across the United States — and elite institutions in particular — have become engaged in an innovation arms race. Universities are expanding academic programs at a breakneck pace and constructing start-up centers. Harvard opened an Innovation Lab in 2011 that has helped start more than 75 companies; last year, New York University founded a campus entrepreneurs' lab; this year, Northwestern University opened a student start-up center, The Garage.

Now I have been involved in 34 start ups in some way shape or form. I have created them, managed them, turned them around, bought them, sold them, and whatever one can do with them. Every time some new wanna be comes along I hear the same tale as to how this will be a success. After a half dozen questions that easy tasks starts to mold, to fall apart.

I have seen many of these dreamers at places like MIT where post-docs are one the one hand supported in their entrepreneurial ventures but at the same time burdened by their low paid post-doc efforts.

I did my first start up in 1969, when in Grad school, and I was just a part time consultant. I saw it go up and then collapse in just a few months. Good idea but poor execution. Also poor management.

Of the 34 that actually made it airborne, all had their challenges. Some with management, some with strategy, some with execution, some just with the market collapsing.

But perhaps Universities should do what we pay them to do. Train young people in skills that subsequently can be monetized. Academics for the most part, I have seen a few, very few exceptions, have no idea how to run anything, not even their own research efforts. So we expect that same group to "lead" students? This is literally the blind leading the blind. More tuition money down the drain. I see Universities having people teach entrepreneurial courses who have never even held a job!

To be an entrepreneur is to be the ultimate risk taker. You have no Plan B, you have burned all your boats and move forward based on your abject belief that you are right. You have no cozy University supported location.

I recall travelling the world with my Passport and credit card, country after country, building a global network. I was a dream merchant but I knew what I could do. We really do not need another App, really. We need better infrastructure, we need improved Health Care, we need a variety of real stuff, including improved environmental controls, whatever that may mean.

To get there we need educated entrepreneurs. We do not need Freshman with another App. We also do not need increased tuition driven by some Administrative vision of what entrepreneurs do. Frankly they are clueless, and worse, self serving!



Labels: [Commentary](#)

FRIDAY, DECEMBER 25, 2015

MERRY CHRISTMAS

- 1 And it came to pass in those days *that* a decree went out from Caesar Augustus that all the world should be registered.
- 2 This census first took place while Quirinius was governing Syria.
- 3 So all went to be registered, everyone to his own city.
- 4 Joseph also went up from Galilee, out of the city of Nazareth, into Judea, to the city of David, which is called Bethlehem, because he was of the house and lineage of David,
- 5 to be registered with Mary, his betrothed wife, who was with child.
- 6 So it was, that while they were there, the days were completed for her to be delivered.
- 7 And she brought forth her firstborn Son, and wrapped Him in swaddling cloths, and laid Him in a manger, because there was no room for them in the inn.
- 8 Now there were in the same country shepherds living out in the fields, keeping watch over their flock by night.
- 9 And behold, an angel of the Lord stood before them, and the glory of the Lord shone around them, and they were greatly afraid.
- 10 Then the angel said to them, “Do not be afraid, for behold, I bring you good tidings of great joy which will be to all people.
- 11 For there is born to you this day in the city of David a Savior, who is Christ the Lord.
- 12 And this *will be* the sign to you: You will find a Babe wrapped in swaddling cloths, lying in a manger.”
- 13 And suddenly there was with the angel a multitude of the heavenly host praising God and saying:
- 14 “Glory to God in the highest, And on earth peace, goodwill toward men!
- 15 So it was, when the angels had gone away from them into heaven, that the shepherds said to one another, “Let us now go to Bethlehem and see this thing that has come to pass, which the Lord has made known to us.”
- 16 And they came with haste and found Mary and Joseph, and the Babe lying in a manger.
- 17 Now when they had seen *Him*, they made widely^[d] known the saying which was told them concerning this Child.

18 And all those who heard *it* marveled at those things which were told them by the shepherds.
19 But Mary kept all these things and pondered *them* in her heart.
20 Then the shepherds returned, glorifying and praising God for all the things that they had heard and seen, as it was told them.



Labels: [Commentary](#)

TUESDAY, DECEMBER 22, 2015

[AMAZON REVIEWERS](#)

I started writing reviews on Amazon some eight years ago. I have done 235 at this point, not a massive number, but reasonable. I generally write reviews of books, professional ones, not novels, and always do so in my own name. I generally discount anonymous reviews, especially ones with less than rational name tags. I also use the reviews to see what may be wrong with a product. What breaks, what is poorly designed. Many negative reviews are just folks with a chip on their shoulder but who cares.

Now reviews have value and when Amazon decided to change their format I decided to follow the [comments](#) of those feeling I thought in a right minded manner. I am not a trained Psychiatrist but I can at times feel the chill of reading some of these comments. They appear to be folks who have no other life, who take minutia quite seriously and can be overly aggressive about small issues. Perhaps DHS and NSA should be watching these discussion groups.

Are Reviews useful? I believe so. If they are honest and present positive and negative factors then they can help the consumer. Frankly if I know who the Reviewer is then I have much more reliance on the Review. But it appears that Amazon may have an out of control process here. There are people writing thousands of reviews by getting tons of free stuff. The IRS aside, how can anyone do a credible review of so many items? It may take me a couple of weeks at least to prepare a book review. And then only if I have the time!

Thus this Review process has many flaws. Especially the anonymous elements and in addition the element of what appears to be "gift" reviews. Add to that what seems to be less than well balanced folks, well, you can see where that leads.

I have seen over the years that if you give a book a credible but bad review, the Collective which may form around the writer, such as those in the Net Neutrality space, go mad and drive your review away. A key to detecting that is a bimodal set of Reviews, five and one star, with many positive on the five and many negative on the one. That is an example of the Collective at work.



Labels: [Amazon](#)

MONDAY, DECEMBER 21, 2015

[IN CASE YOU MISSED THIS](#)

Every once in a while I recall something that is of note. Back in January [Modern Healthcare](#) reported:

The Obama administration wants 30% of payments for traditional Medicare benefits to be tied to alternative payment models such as accountable care organizations by the end of 2016. The administration also has set a goal of hitting 50% by the end of 2018. The administration wants even larger portions of hospital payments to be tied to quality- or value-based payment models. HHS indicated that it wants 85% of Medicare's hospital payments made through programs such as the Hospital Value-Based Purchasing Program or the Hospital Readmissions Reduction Program by the end of 2016. That threshold kicks up to 90% two years later. It is the first time that the federal agency has set specific goals for overhauling the payment system for standard Medicare beneficiaries, which has traditionally relied on a fee-for-service model. That system has long been criticized for providing economic incentives for providers to offer a greater volume of care regardless of outcomes. Currently, 20% of Medicare payments for traditional beneficiaries are made through alternative payments models, which also include bundled payment arrangements, according to HHS.

This is the first time we have seen specific targets. The current Administration wants to push all on Medicare to the equivalent of HMOs. Take them off what they have and slam them into an HMO or rationing type system. If you are too old, albeit healthy, if you get ill, perhaps you die. Too bad! You no longer have any choice.

Hopefully this madness will be gone in another year. Then all we have to worry about is the Terrorists that don't exist. "Keep moving, nothing to see here!"



Labels: [Health Care](#)

SUNDAY, DECEMBER 20, 2015

[SEVEN YEARS OLD](#)

After seven years, some 157,000 visitors, from 150 countries and over 3 million words, I thought I would try to summarize where we are. Now more than 10% of my life has gone into this idiosyncratic presentation of thoughts. The original intent was to follow the actions by many to the financial collapse of 2008 as well as the new leadership of the country. I was especially motivated by the prognostications of left wing macro-economists who believed all that they espoused. Namely all that was required was a trillion plus in Government money and in months things would be right again. So how did that work out Mrs. Romer?

Overall we have addressed the following issues:

1. Macro Economics: It is clear that these folks oftentimes do not even agree with themselves! What became clear to me is that macroeconomics is really just political theory. I examined

Keynes, and then followed these characters for eight years. They all seem to have keen insight into nothing. One of my favorite piques is the Pigou vs Coase controversy. Here we have allegedly Republican macro economists, rare as unicorns, espousing taxes to reduce carbon. They seem totally ignorant of solving the problem technically.

2. Health Care. My timing was good here as well. Yes, the ACA, the most massive attempt by Progressives to “tell” the rest of us how to deal with our health. So what happened? Personally I am paying 5 times more now than in 2008 and still taking no advantage of the system. God has been good so far. But who gets the money. The Millennials without jobs! You can’t make this up! Some morbidly obese 20 year old having no job but collecting for their early stage Type 2 Diabetes! Say what’s with that?

3. Russia and China. After seven years we still see nothing from Russia in Walmart. It is still China. Oil has collapsed so that Russia as an extraction economy may be hurting. China is trying to expand, but it should take a careful dance forward. It still depends on customers.

4. Cancer. We have examined cancer and its progress in understanding and care. In seven years we have seen massive changes. We have ways to deal with advanced melanoma, and even many hematological diseases. However we still have the prostate cancer problems; over 100 target genes. Moreover we have a collection of people without any basis saying to abandon any tests on men. All too frequently these cries are from women, and women who do not even practice or do clinical research in the field.

5. MOOCs. I initially thought MOOCs may have some value. Except for Prof Lander’s course the rest have been marginal at best and some outright useless. What I did examine was the tendency of anonymous participants making the most incendiary remarks on the MOOC’S discussion groups. This seems to be a pandemic characteristic of Millennials. Every opinion is valid yet they do not want to tell anyone who they are.

6. CRISPRs. Eric Lander mentioned these offhandedly in a talk a few months after they came out and I dove into them. I told my grandkids 6th Grade class to follow CRISPRs. These could be the most powerful tool yet. Also they have deadly consequences.

7. The Academy. Here I examined the Academy over seven years. It is becoming a mess. Costs are uncontrolled, student sensitivities rule, political correctness is pandemic, and our Government thinks a degree has value. What a person can “do” has value, not what “everyone gets a prize” degree.

It will be interesting to see what the coming year brings. Thanks for those who visited here. Hope I have not annoyed too many, and feel free to drop a note from time to time.



Labels: [Commentary](#)

SATURDAY, DECEMBER 19, 2015

INDENTURED SERVITUDE

I just noted the following in the [NY Times by Mankiw](#):

Another approach is to find better private mechanisms to finance higher education. Senator Marco Rubio, who is seeking the Republican nomination, wants to establish a legal framework in which private investors help pay for a student's education in exchange for a share of the student's earnings after college. In essence, the student would finance college less with debt and more with equity. The Rubio plan does not let the student get away without paying, but it does help spread the risk from the educational investment.

This is not Mankiw but is Rubio. This is a classic example of being totally blind to the problem. Higher Ed costs more for a variety of correctable reasons. They are:

1. Government mandated overhead has exploded. Namely Deans for this and Deans for that and policies here and there just add to costs.
2. Buildings costs lots to build and even more to maintain. College Presidents like to build stuff, it meets their self perceived mandate. Yet I have never met a College President who fully understood life cycle costs.
3. Services to students and staff have exploded. From new gyms, swimming pools and yes the sacred cows of football. MIT once had sports for sports sake. Now, alas, they are going Varsity.
4. Student Support has also exploded. The well coddled student has one type of support for this and one for that. Guess what? That costs, lots!

So creating Indentured Servitude is wrong, and frankly it demonstrates some terribly shallow understanding of the problem and perhaps we should ask what the leading candidate wants? Oops, you're fired! Yep, that cuts costs.



Labels: [Academy](#)

FRIDAY, DECEMBER 18, 2015

DUTCH WOMEN AND THE DEATH OF AMERICAN MEN

For almost a decade now we have been examining the details of prostate cancer, PCa. [PSA has its ups and downs](#) but for testing for aggressive PCa it is a tool, albeit one which we have shown has some issues. More tools are coming on line almost monthly, as we have also examined.

Now this week in [Nature](#) we have some Dutch woman, it appears, opining on having American men adhere to the USPTF guidelines. Now if an American man said that about breast cancer we would have an uproar! But men, well they have outlived their usefulness after a certain age perhaps.

The author states:

These findings raised two questions. First, is it possible to reduce prostate-cancer mortality if the PSA test is introduced as a screening tool? And second, is it possible to reduce the side-effects of PSA screening, including overdiagnosis? To address these questions, two randomized trials — one in the United States and one in Europe — were initiated. Both trials have reported on the effect of PSA testing on prostate-cancer mortality several times over the years, and have always contradicted each other (although it is generally accepted that within the US trial contamination substantially limited researchers' ability to identify a clinically significant screening benefit). This lack of consensus and the considerable risk of overdiagnosis associated with PSA-based screening are the main reasons that screening for prostate cancer is still highly controversial, and why there are so few population-based government-initiated screening programmes.

We had argued that both tests were flawed. The reasons; simple, they used a 1990s test metric which we now know needs to be modified and the European tests were spaced too far apart. Thus in some ways the test is akin to monitoring melanoma in such a fashion that you excise the lesion only when it bleeds and if you do that mortality is no different than watchful waiting. I do not think so.

The author concludes:

The time has come to actually implement the evidence-based guidelines into clinical practice. Medical associations should better communicate the best practice around PSA testing and strengthen the education of doctors — particularly general practitioners (GPs) who are usually the first point of contact, but are rarely up to date with the latest publications. GP requests for testing should be actively monitored to ensure the message is understood, rather than waiting for registry data to see if there has been an effect.

The evidence is quite complex. We examined a case a couple of month back and demonstrated that one test after another gave conflicting results. I would agree that most Primary Care physicians are not attuned to dealing with the results but in the US we then send them to a Urologist to see what to do next. They should be the definitive gatekeepers.

Let's try to keep men alive on an equal footing, please.

And by the way, another woman in [Nature](#) seems to bemoan the PSA test. This writer states:

Part of the shift is a result of advances in screening, which are helping doctors to zero in on aggressive cancers that need the most attention. Among the new strategies is a tool called the prostate health index (PHI), which measures three types of PSA. According to some research, the PHI is three times more specific than the standard PSA test, an improvement that reduces the number of unnecessary biopsies. Doctors around the world also now factor in a tumour's Gleason score, which assesses aggressiveness based on the way that cancer cells look under a microscope. And researchers are continually re-examining the level at which the quantity of PSA in the blood should be considered abnormal. Some evidence, for example, supports the idea that

the threshold for concern should be raised from its present value of 3–4 nanograms per millilitre to 10 nanograms per millilitre. Beyond PSA, scientists are also using magnetic resonance imaging to guide biopsies making false negatives less likely, as well as genetic tissue tests to screen for biomarkers that signal a cancer's degree of aggressiveness. These tests can be expensive, and health-insurance companies in the United States do not necessarily cover them. Many are so new, Barry adds, that there are insufficient data on outcomes. Rushing to accept newer tests before sound trial evidence arrives, in other words, might bring a repeat of the troubled PSA era all over again.

In my opinion perhaps these should be written by professionals and not what appears as "a freelance journalist". After all this is Nature not Men's Health. Just an opinion.



Labels: [Cancer](#)

THURSDAY, DECEMBER 17, 2015

[SOMETIMES SMART PEOPLE DO STUPID THINGS, NOW AMAZON](#)

I generally like Amazon. Good quality, good prices and good service. I also like to look at the Reviews, five star and one star. All too often the five star are plants but they are obvious. Sometimes the one star are just annoyed. Also ready to catch.

But now Amazon has done one of the stupidest things ever. They went and totally destroyed the reader feedback function. Some character decided to remove all data from Profile reviews and then see the reviews, remove responses, remove useful and not useful, in essence remove all feedback. One suspects they did so for mobile users.

But you see, I would never use a mobile device. Moreover they made these changes without ever asking. Reviewers really add value. Disregard the Reviewers and you Destroy Value. Dumb? You bet!

So there must be some Media Manager at Amazon with some Ego driven need to do it their way. Guys, get rid of that person. Remember your customers are your value, not the character who most likely had their Ego in a twit over their way or the highway!

Remember; if all else fails listen to the customer. (Could someone tell Bezos! He gets most other things. Get rid of this person now. Otherwise this person will cost Amazon Millions if no Billions!)

As I had noted:

Profiles, as I see them, have two functions.

- 1. They provide the reader with some understanding of who the person is reviewing the item.*
- 2. They provide the reviewer with an easy means to track the response to their reviews, to see what is useful and what is not.*

I think that the new version provides neither of the two. Change is the result of either correcting or improving. However in this case, change just seems to make things worse and of little use to either the reader or reviewer. Frankly one wonders why this was done and what it was to achieve. If it ain't broke please don't fix it!

Also for those folks in Marketing: **Remember, if all else fails, listen to the customer!**



Labels: [Amazon](#)

[WHOSE MONEY IS IT?](#)

Providing funding for "charitable" work is laudable and is frankly an obligation that comes to those who have done well. What to give to however is the individual's choice. Cancer Research, Academic Research, Social Programs, Public Benefit efforts, soup kitchens, and even individuals who with a little help can leverage their own assets subsequently for the benefit of others.

Americans are somewhat unique in that area. Americans also are unique in that they get to choose and those there is a "free market" for "charitable" work.

I saw piece today in the [NY Times](#), of course, that "tells" us what we should do. It says:

In other words, "giving back" is necessary, but not sufficient. We should seek to bring about lasting, systemic change, even if that change might adversely affect us. We must bend each act of generosity toward justice. We, as foundations and individuals, should fund people, their ideas and organizations that are capable of addressing deep-rooted injustice. We should ensure that the voices of those most affected by injustice — women, racial minorities, the poor, religious and ethnic minorities and L.G.B.T. individuals — help decide where and what philanthropy puts money behind, not in simply receiving whatever philanthropy decides to give them.

Now where is the Cancer Research, the funding of up and coming high performance students, public spaces, etc? Not there.

Charitable Giving by individuals should be individual choices not dicta from on high.



Labels: [Commentary](#)

[NOW WHO WROTE THAT?](#)

It is easy to see what Einstein wrote. His name was on the paper and the only name. Back some 50 years or so when tenure came up one looked at a pile of publications of the faculty member and that had 40-50 papers with their name on them, and only their name.

Now we have the "everyone is a winner" game where there are dozens if not thousands of names. Now really, at most maybe 2 or 3 people wrote the paper. Thousands is nonsense.

In [PLOS](#) they state:

...we still don't have solid norms for the process of deciding authorship, and it's pretty much team-dependent. Decision structure problems arise "because one or more of the authors, usually the most senior one, assumes tacit agreement and consensus when there is none and then decides on co-authoring with little or no discussion" – as well as suppression of dissent, groupthink, squeaky wheels, and what they call "the jackass factor". Power dynamics are central, and until we understand and tackle that, some people will continue to "exploit their friends and also those who are in less powerful positions than themselves". Authorship practice remains astonishingly murky. All science's incentive problems converge in it and feed from it. It deserves more care.

Well is the process murky because of what? One could argue that it is the process of Government funding that drives this chaos.

Now in [BioMedCentral](#) they articulate a "new" way to attribute contribution. Specifically:

Today in GigaScience we launch a project to spearhead this through our Author Contributorship Badges. The badges are based on a taxonomy around contributorship developed by the Wellcome Trust, MIT, Digital Science, and others in partnership with CASRAI (Consortia Advancing Standards in Research Administration), National Information Standards Organization (NISO), and the research community...These contributorship badges, in conjunction with other badges around open practices, put credit back into the hands of researchers and offer funders and universities alternative data to obscure author lists and Impact Factors.

I really have difficulty with this process. There is a "badge" movement afoot, I think kind of like Boy Scout Merit Badges but not as good. This "badge" movement will add more contention and confusion. Again, back to Albert, how would that work again?



Labels: [Academy](#)

SATURDAY, DECEMBER 12, 2015

[THE DOWNSIDE OF AWARD GALAS](#)

Hollywood for decades has celebrated itself over and over. There now are close to a dozen major award events for movies, television and the like and many times that for popular music. The folks get all dressed up, sit in some California type room, laud themselves, and get significant media coverage, the ultimate selfies.

Now we see this in Science. The moneyed folk in California, it appears part to "celebrate" themselves, are now hosting an event to award prizes in a similar social environment. This is no Nobel Prize, no King, no tux type attire. It is Hollywood on El Camino.

[Nature](#) has an interesting piece on this. They state about the photo:

From left, former Twitter CEO Dick Costolo, Emmanuelle Charpentier, Jennifer Doudna and Cameron Diaz.

Yep, a full fledged Hollywood star, right there in the Valley! You can bet this will continue. Now I can see awards, professional societies give them out all the time. They are "peer" awards. The White House has been getting in the act as well, and of course there is a lot of Hollywood there as well.

Perhaps "Science" should think twice about what could be pure commercialism. The existing structures work quite well, or at least they seem to. Science is unlike Hollywood, usually no agents. But watch out folks, that too may change. Beware the hubris!

But wait! [MIT](#) has a Hollywood movie person for Commencement Speaker! Now this you really can't make up. In 1971 at my PhD Commencement I had no idea who spoke. Who cared! But now a Hollywood social advocate!

As MIT says:

This is an exciting choice of speaker," says Chancellor for Academic Advancement ..., the longstanding chair of MIT's Commencement Committee. "..... couples a passion for his art with a passion for making the world a better place, much as our students couple a passion for science and technology with a passion to improve the world. I am sure his message will inspire our students to follow that passion and tackle some of the world's great challenges, such as in water, health, or education."

How about getting a job, curing cancer, developing new technologies....it seems this Hollywood thing is getting a bit out of control.....



Labels: [Science](#)

[THE POLITICS OF CANCER](#)

The book by DeVita, [The Death of Cancer](#), is a well told tale of one in the fight against the disease. DeVita is well known and well accomplished in the field. His book tells the tale of dealing with many of the characters, especially in Washington, whose actions all too often is just not only counterproductive but can cause true harm. He tells the tale with keen insight and a wonderful turn of the phrase.

I recall seeing my first cancer patient while working in a medical center in the late 1950s. I was learning the basics when the Lab head asked me to come in and look at a blood slide of an eight year old. I think I knew something but this slide was filled with lymphocytes, a Leukemia. At the time this was a death sentence. In fact unbeknownst to all one could not then identify the type of leukemia, just that this eight year old would not make nine.

DeVita comes to the stage at the same period. Not only could it not be diagnosed but the cure was beyond reach. He becomes one to lead the fight.

However in a [New Yorker](#) Review the author, not a physician as best as I can tell, nor even related to the field, takes some strong shots at the author^[1]. The author states:

For the past half century, he has been at the forefront of the fight against one of the world's most feared diseases, and in "The Death of Cancer" he has written an extraordinary chronicle. DeVita's book is nothing like Siddhartha Mukherjee's magisterial "The Emperor of All Maladies." Mukherjee wrote a social and scientific biography of the disease. DeVita, as befits someone who spent a career at the helm of various medical bureaucracies, has written an institutional history of the war on cancer. His interest is in how the various factions and constituencies involved in that effort work together—and his conclusions are deeply unsettling.

DeVita has his career well established with a half century record of achievement and success. The book recounts the hurdles he had to jump and the intense difficulty of working in Washington. I am reminded of a friend's spouse who went to DC as an Assistant Secretary. A mighty position. I warned her to beware of the professional "back stabbers". Washington, unlike any other location seems to have a professional corps of "back stabbers", nothing personal, it is just their job.

Two years later the individual informed me after they had moved on that at first I was the only one with such bad news, all others said good luck and take the hill. But alas the professional "back stabber" came out and did their job. DeVita brilliantly recounts them, including the antics of Senator Kennedy. The problem is that it is these very institutional barriers which are more critical than a sociological understanding of cancer.

The author in the *New Yorker* further recounts:

Later, when DeVita and his fellow N.C.I. researcher George Canellos wanted to test a promising combination-chemotherapy treatment for advanced breast cancer, they had to do their trial overseas, because they couldn't win the cooperation of surgeons at either of the major American cancer centers, Memorial Sloan Kettering or M. D. Anderson. When the cancer researcher Bernard Fisher did a study showing that there was no difference in outcome between radical mastectomies and the far less invasive lumpectomies, he called DeVita in distress. He couldn't get the study published. "Breast surgeons made their living doing radical or total mastectomies, and they did not want to hear that that was no longer necessary," DeVita writes. "Fisher had found it difficult to get patients referred to his study, in fact, because of this resistance." The surgeons at Memorial Sloan Kettering Cancer Center were so stubborn that they went on disfiguring their patients with radical mastectomies for years after Fisher's data had shown the procedure to be unnecessary.

The fact is that surgeons for decades brought hospital the big money and thus they ruled. Threatening their purse could be problematic at best. DeVita was right, and he pushed forward. Then the author notes:

^[1] <http://www.newyorker.com/magazine/2015/12/14/tough-medicine>

But here “The Death of Cancer” takes an unexpected turn. DeVita doesn’t think his experience with the stubborn physicians at Memorial Sloan Kettering or at Yale justifies greater standardization. He is wary of too many scripts and guidelines. What made the extraordinary progress against cancer at the N.C.I. during the nineteen-sixties and seventies possible, in his view, was the absence of rules. A good illustration was Freireich’s decision to treat Pseudomonas meningitis by injecting an antibiotic directly into the spinal fluid.

This is where the argument takes a brisk turn indeed. This is the beginning of the battle with the FDA and complexity of Clinical Trials. Anyone who has any proximity to Clinical Trials knows their cost and complexity. Each new therapeutic goes through some variation and a 3 Phase human trial with enormous costs and time. Safety first and then efficacy. Typically the trial patients are the sickest.

Take for example the new therapeutics in melanoma. Using combined therapies on Level 2 patients may be even more productive but the cost and time is extraordinary. Can this be changed, should it be changed? DeVita gives an experiential and emotional argument for why it can and should.

The author ends with:

When DeVita returned to Memorial Sloan Kettering years later, as the physician-in-chief, the hospital got better. But DeVita didn’t last, which will scarcely come as a surprise to anyone who has read his book. “The problem with Vince,” the hospital’s president reportedly said, in announcing his departure, “is that he wants to cure cancer.”

I do not know how best to read this remark. You want a physician to seek to cure your disease. Often patients are willing to commit to that step. I have even recently seen patients, close friends, take that “petri dish” approach, and yes, get cured. So perhaps we need more DeVitas.



Labels: [Cancer](#)

MONDAY, DECEMBER 7, 2015

[RETURN OF THE SCRIBE](#)

Augustine of Hippo allegedly "wrote" all of his massive works by means of scribes. That was in the 4th and 5th century. Scribes were employed extensively throughout the Roman world and managed to survive at least halfway through what we know as the Middle Ages.

It appears as if they are returning with a vengeance thanks to the ACA! All hail the Scribe!

As noted by [Kaiser](#):

A national campaign for electronic health records is driving business for at least 20 companies

with thousands of workers ready to help stressed doctors log the details of their patients' care — for a price. Nearly 1 in 5 physicians now employ medical scribes, many provided by a vendor, who join doctors and patients in examination rooms. They enter relevant information about patients' ailments and doctors' advice into a computer, the preferred successor to jotting notes on a clipboard as doctors universally once did. The U.S. has 15,000 scribes today and their numbers will reach 100,000 by 2020, estimates ScribeAmerica, the largest competitor in the business. After buying three rivals this year, it employs 10,000 scribes working in 1,200 locations.

Another source for an increase in health care costs! They accompany a physician into the office with a patient and as the physician examines the patient the Scribe records all that happens.

Now we do see some major issues:

1. Scribes are unregulated and are privy to highly sensitive information. What I may tell my physician I may not want some minimum wage typist to be privy to.
2. Scribes may copy the wrong thing, or too much. Watch out for the lawyers. Once it is written it cannot be unwritten, easily!
3. Scribes cost money. Not only do they get paid for their rime but the physician should review and remark on what they wrote. That just adds costs if you will.

The list of Scribe issues continues. But as that Congressperson said; "...you have to pass it in order to see what is in it..."

Welcome to America! Oh yes, perhaps we can get those buggy whips back again when we go all green.



Labels: [Health Care](#)

SECURITY, PRIVACY AND DATA GATHERING

Back in 1977 I went to an IEEE meeting at Cornell where there was a big flap by NSA and others over the release of the Rivest et al crypto schemes. At the time I had the opportunity to watch over some Eastern Europeans who were in DC but in Ithaca, there they were. Surprise, no.

Out of those meetings came a way to combine the then crypto scheme approved by NIST and the new RSA scheme. Namely one could use DES as a shared key system but use RSA to send the keys in a secure manner and then cycle through various DES keys using RSA. Works fairly well and even then was doable whereas today it is dirt cheap.

The second issue was authentication. Namely the problem of assuring from whom the message came from. Today we use certificates but then and I assume still now we use complex systems as we had developed then. Our application in the late 70 was the deployment of sensors using seismometers to check for Soviet nuclear testing. We wanted to have authenticated data and not

Soviet spoofs.

Today we look for patterns as to who is talking to whom. Assuming people do not try to confuse others then this may be possible over big data systems. However for a couple of decades now we have seen the development of anonymizers. Now [MIT researchers](#) announced their latest scheme.

They state:

If an adversary has infiltrated the server, however, he or she can see which users are accessing which memory addresses. If Charlie's message is routed to one address, but both Alice's and Bob's messages are routed to another, the adversary, again, knows who's been talking. So instead of using a single server, Vuvuzela uses three. Corresponding to the three servers, every message sent through the system is wrapped in three layers of encryption. The first server peels off the first layer of encryption before passing messages on to the second server. But it also randomly permutes their order. So if, for example, Alice's message arrived at the first server before Bob's, and Bob's arrived before Charlie's, the first server will pass them to the second in the order Bob, Alice, Charlie, or Charlie, Bob, Alice, or the like. The second server peels off the second layer of encryption and permutes the message order yet again. Only the third server sees which messages are bound for which memory addresses. But even if it's been infiltrated, and even if the adversary observed the order in which the messages arrived at the first server, he or she can't tell whose message ended up where. The adversary does, however, know that two users whose messages reached the first server within some window of time have been talking. And even that is more information than Vuvuzela's designers want to give away.

Namely they flush everything they have across the net and confuse any adversary. Cute, but I suspect this is but one of many such schemes. Hiding in plain sight, hiding in noise, etc all follow a similar path.

Thus the questions which this poses are:

1. In encryption, any junior engineer could implement an AES/RSA system which would be quite difficult to break. In fact a "whack a mole" feature one could argue would make it unbreakable. In fact such a system would be outside the transmission path, and thus one could care less about iPhone encryption, you do not rely upon it.
2. Authentication is critical. If two adversaries desire to speak then they must be certain as to whom each is. This is an authentication problem and one cannot expect to use Certificates here. Yet there also a large collections of options.
3. Patterning is the means of looking at data flows and trying to see what they infer as to the actions of parties. Systems like the one above demonstrate that the complexity of this can be increased exponentially. In fact it can be made almost fool proof.

Thus the screams and moans as to making all systems open is just that; scream and moans. Any adversary already has a wealth of tools, many most likely funded by Government contracts and

in the public literature.

Remember 1977! When RSA came out you could guess who was in the audience. Today, different faces but same result.



Labels: [Security](#)

MONDAY, DECEMBER 7, 2015

[PEARL HARBOR: THEN AND NOW](#)



Above is my father's ship, USS Albert W Grant, in Manus for repairs, after the Battle of Leyte Gulf in October 1944. This was the beginning of the end for Japan. Its fleet destroyed but Okinawa was still ahead, thousands of Japanese aircraft dive bombing in suicide manner the ships in the landing force. Some felt that Japan was on the brink of surrender, I am assured that none at Okinawa thought the slightest as such.

But on December 7th in 1941 the US was attacked and we went to War, total and devastating war. Millions died as a result of the actions of Japan. But Japan attacked military sites. Our recent "war" was precipitated by an even more deadlier attack on civilians while the only defense were unarmed National Guard Fighters from several hundreds of miles distant.

Now we have been attacked again, and again, and again, most recently in California. The response is tepid at best. Perhaps we need better history lessons.



Labels: [History](#)

SATURDAY, DECEMBER 5, 2015

[SOME THOUGHTS ON PLANT EVOLUTION IN THE URBAN JUNGLE](#)

Plants evolve, often more rapidly than animals. We may not notice it since we don't look closely at them. But they do. In a recent paper on plant evolution in [The American Journal of Botany](#) the

authors remark:

Why might urbanization influence plant evolution? Clearly, urban development changes both the biotic and abiotic environment in ways that could alter natural selection and adaptive evolution within plant populations. Urbanization may also influence nonadaptive evolution due to altered gene flow, genetic drift, or nonrandom mating. For example, urban development causes habitat fragmentation given that buildings and roads are a common feature to every city, where extensive pavement, concrete, and alteration of natural habitats is the rule rather than the exception. This fragmentation can limit dispersal and gene flow, leading to greater genetic differentiation between populations. It can also influence the size of populations and thus the importance of neutral evolution because genetic drift will be greater in smaller populations. Finally, urban areas can alter mating patterns (e.g., increased selfing) through changes in pollinator communities...

The authors then make several predictions:

1. *Urban and non-urban populations will differ in the amount of genetic diversity*
2. *Urbanization will alter natural selection on populations*
3. *Neutral evolution will be greater in urban areas*
4. *Genetic divergence between urban and non-urban populations will be proportional to the size of urban areas*
5. *Insect-pollinated plants will evolve greater self-pollination or clonal growth in urban areas*

Now I would argue a bit differently. The primary influence on urban diversity will be driven by humans. Humans select plants that they like, like the triploid Hemerocallis. They become invasive via human attraction. They are sterile but aggressive growers pushing out other plants. They are a typical invasive species. Also the introduction of foreign species may very well lead to cross breeding that would have been impossible otherwise. Yet successful growth may be inhibited. Also the use of pesticides and similar plant control biotics will cause a shift in classic evolutionary manners.

Thus the five predictions above I believe are at most a small part of the complexity of urban development. For example I have more than twice the tree species on my small acreage than indigenous plants would provide. Some of the trees are quite hardy and aggressive such as Ginkgo and Metasequoia.

I believe that a more details analysis and monitoring would be quite useful, and that what the authors propose may be quite limited.

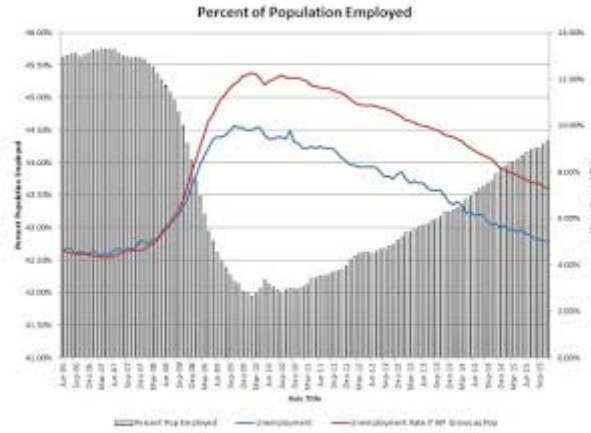


Labels: [Botany](#), [Commentary](#)

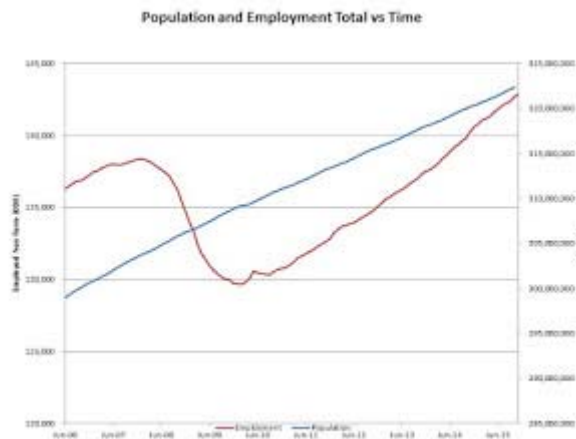
[EMPLOYMENT DECEMBER 2015](#)

We have been following employment for seven years now and the pattern is clear; there is a large systemic gap in permanently unemployed and the ratio of those employed outside

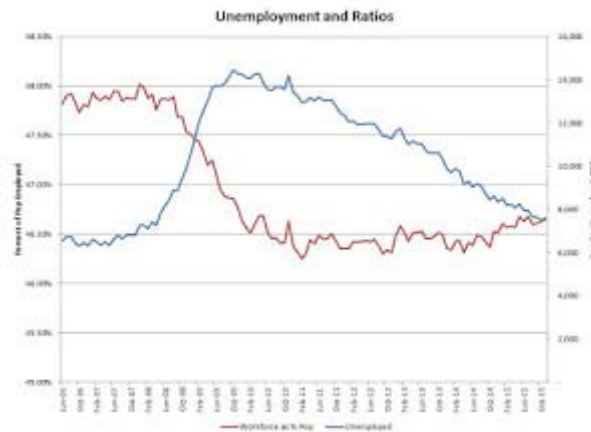
Government to inside Government is decreasing to almost 1:1. Perhaps at some time some folks will take notice.



First our standard curve. Unemployment per the Government is down but the unemployment using 2006 participation rates is still in excess of 7%.



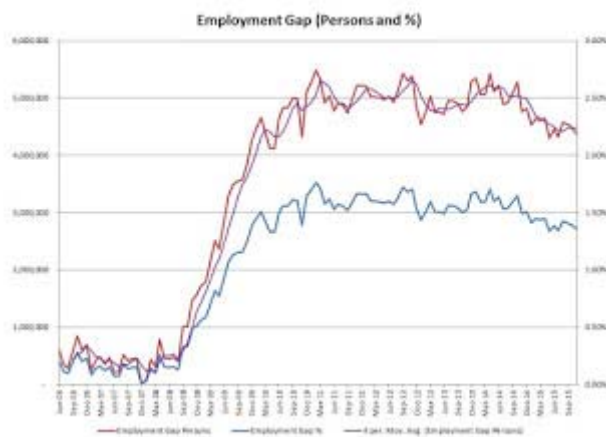
Population continues to increase and the employment continues to grow keeping the gap at the point with a lower participation rate. There is no way we can recover to 2006.



This shows the participation rate bottoming out with no movement forward.



The above details the gap between actual increase and target increases.



Finally the above details the systemic unemployed, now about 3.5 million. Had we recovered these numbers we would have a much healthier economy with less money going to these people and more tax revenue generated.

It should also be noted that starting in 2016 we will see the ACA taxes increase significantly and this should be a throttle on any consumer growth.



Labels: [Economy](#)

FRIDAY, DECEMBER 4, 2015

[THE PHD: VALUE AND USE](#)

[Nature](#) has a small piece on the growth of PhDs and their alleged mis-direction. My observations are based upon 50 years of doctoral/post-doctoral involvement with time spent in and out of academia.

What is a PhD good for? Perhaps a good question. It takes time, money, dedication, delayed gratification. It produces a highly trained and filtered individual. It is an individual who has intellectually achieved as well as having demonstrated an ability to dedicate great resources with limited returns for a longer term benefit. What is the benefit? The ability to see and produce what the less well trained individual does, perhaps. It should not be a training ground for Lab Tech replacements, low cost, well trained worker bees who when they are burned out are replaced by new worker bees, an endless supply.

In Germany many PhDs go into industry. There must be more Doctors of some specialty in Germany per sq km than any other species. I think I even seen some Dr so and so at the Munich ticket counter service passengers. So the education per se is not the issue. The issue is; how is it used.

The Nature article states:

The numbers show newly minted PhD students flooding out of the academic pipeline. In 2003, 21,343 science graduate students in the United States received a doctorate. By 2013, this had increased by almost 41% — and the life sciences showed the greatest growth. That trend is mirrored elsewhere. According to a 2014 report looking at the 34 countries that make up the Organisation for Economic Co-operation and Development, the proportion of people who leave tertiary education with a doctorate has doubled from 0.8% to 1.6% over the past 17 years.

So in the US we are producing them at a great rate. But they can and should find places in industry. The Academy does not need them, cannot use them, other than as cheap labor, and their use is maximized monetizing those skills, not trying to hang on. They should be aware of that from the get go. Back in the 60s at MIT I knew of few of my classmates finishing PhDs trying to find teaching spots. They wanted jobs, and for a while there were a few, then Nixon collapsed the country in 1971, and none were around. At least we could become electricians!

Now here Nature states the crux:

One reason is that there is little institutional incentive to turn them away. Faculty members rely on cheap PhD students and postdocs because they are trying to get the most science out of stretched grants. Universities, in turn, know that PhD students help faculty members to produce the world-class research on which their reputations rest. “The biomedical research system is structured around a large workforce of graduate students and postdocs,” says Michael Teitelbaum, a labour economist at Harvard Law School in Cambridge, Massachusetts. “Many find it awkward to talk about change.”

Yes, cheap labor, in hope of some dream. In fact they would be better off in industry, and industry would be better for using them and the assets they bring. All too often industry, especially MBA type managers, view PhDs as "head in the cloud types" or "single focus" types. In reality the PhD can do more than any MBA, they can create value not just transfer or worse destroy value. The PhD should be viewed as a peer, one who can add as much value to an establishment as any other and at times more. The PhD should also understand that value statement as well. The PhD should not be held captive as cheap labor.

Nature concludes:

But there are signs that the issue is becoming less taboo. In September, a group of high-profile US scientists (Harold Varmus, Marc Kirschner, Shirley Tilghman and Bruce Alberts, colloquially known as 'the Quartet') launched Rescuing Biomedical Research, a website where scientists can make recommendations on how to 'fix' different aspects of the broken biomedical research system in the United States — the PhD among them. “How can we improve graduate education so as to produce a more effective scientific workforce, while also reducing the ever-expanding PhD workforce in search of biomedical research careers?” the site asks.

The change is simple. Let the PhDs know from the get go that they should, can, and must seek to "market" their talents, and not just their PhD research, and they they should seek jobs not short term low paid and low return task work. This is not just a problem in the bio area, it is quickly becoming a pandemic across many fields, engineering included. Why should any PhD in engineering do a post-doc? Get a job, use your skills, make something, and get out of the dream world of academia.



Labels: [Academy](#)

[DEVITA, CANCER, AND A MUST READ](#)

DeVita's book, [The Death of Cancer](#), is a personal recollection of one of the most well-known cancer specialists in the world. In a sense it is an Odyssey tale of a highly competent and prolific person who flows with his times and manages the Scylla and Charybdis of Government work. The book is well written and reflective of the man and his times. DeVita started out during the Vietnam era when any male graduating from Med School found themselves, unless otherwise excused, ready for immediate assignment to some military unit. Many of the top students were fortunate to get to go to NIH which was DeVita's fate, and it was this flow of talent in the late 60s which made NIH and NCI one of the best institutions in the world. Thus the tale of DeVita and cancer starts here with NCI and a flow of excellent talent.

DeVita describes his work on the use of multiple chemotherapy regimens and the resistance from the likes of Farber in Boston, hardly an uncommon occurrence especially in Medicine. This was the MOPP therapy that most now know as a major breakthrough in Hodgkin's. The discussion on how he and the team managed to persist and managed to go through the then significant administrative a bureaucratic complexities is amazing.

The discussion on his involvement in the “War on Cancer” and the political games is quite interesting especially for anyone who has not spent a tour of duty in Washington. There were games within games and DeVita was at times a willing participant but as see in the book and excellent observer. His description of the political gamesmanship is worth the read if nothing else. It is also worth the while for anyone seeking to grasp how Washington functions, and why it may work at times and often falls into total disarray.

On p. 159 I was interested to see the interlocutory between Benno Schmidt and Jim Watson while Watson was I gather performing one of his classic poses. This also is worth the read. I have had my students return from a talk by Watson and ask me: “Does he really think Physicians and Engineers are useless?” But I gather that is Watson, a scientist at heart.

On p 219 there is a great discussion of his time at MSKCC, a world renowned institution but at times falling behind in certain areas. DeVita states: “MSKCC had the potential to be the best cancer center in the world, it wasn’t” is a powerful statement and at times quite true. MSKCC has powerful backers and Board members and although it may try from time to time to be at the lead there is always the chance that it becomes insular. The lesson DeVita brings out here should be a warning for many such institutions.

On p 247 DeVita discusses the recent Hanahan and Weinberg paper on Cancer, a follow on to what the two authors had written in 2000. This is a paper on the hallmarks of cancer and is looked upon as a sine qua non in the literature. DeVita lauds it at length and rightly so. Yet what this paper also shows is that we have learned a great deal but the “War on Cancer” is just getting harder the more we learn. One could argue that the recent Hanahan and Weinberg paper albeit prescient and insightful lacks the depth on epigenetic factors which we are seeing more and more in cancers. The more that is learned the more complex the disease.

On p 253 DeVita discusses the inflammation relationship. We often ask what causes cancer and the more we understand inflammation the more we can see the nexus. This is a useful and important discussion as well.

On p 258 DeVita makes an interesting statement:

“In my opinion, when there is less than a 10% chance of the cancer recurring after a patient passes his or her cancer’s critical period, then the patient should be told, in all likelihood, he or she is cured.”

This is a powerful statement and one a physician with extensive clinical experience is wont to utter. However one should parse the statement. First, how does one determine a 10% chance? In prostate cancer we can perform a prostatectomy and monitor PPSA for several years and then see a met occur. When did the 10% level occur? Second, what is a critical period? How do we define it for each cancer? Then the catch phrase of “in all likelihood” is something the patient may or most likely not hear. Cancer patients often has selective hearing.

Overall the book is highly enlightening and a must read for anyone interested in the progression of cancer therapy. Also DeVita’s discussion of his battles with the FDA and Sen. Kennedy’s blatant interference with NCI if it in his opinion interfered with the FDA was quite interesting. DeVita bares the political quagmires of Washington and demonstrates that progress can often be made despite the Government overhead by dedicated and highly competent individuals.



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

THURSDAY, DECEMBER 3, 2015

AN EXCELLENT CONTRIBUTION TO THE LITERATURE

The book by [Mydlo and Godec](#), [Prostate Cancer](#), is an exceptionally good text for practicing urologists and residents to get an understanding of the current understanding of this disease, prostate cancer (PCa). PCa is a complex disorder, and is unlike many other cancers. On the one hand almost all PCAs are indolent, namely the patient will most likely die of something else, but the small percent that have an aggressive form die very rapidly. The primary tool for detection has been the PSA tests which were virulently attacked by the USPTF. It can be argued that the data they based their opinion on was flawed but we leave that for time to tell, unfortunately at the cost to the patient. The genetics of PCa is also highly complex.

Unlike so many other cancers where we can identify a specific target such as BRAF in melanoma, BRACA in breast cancer and ABL fusion in CML, PCa is a mass of speculative genetic changes. Also the treatment of PCa is becoming more problematic. The options are several; surgery, radiation, implants, and even “watchful waiting” which in a sense is let hope and see what happens. The problem is that PCa metastasis is insidious and unlike breast or melanoma the path is circuitous and uncertain.

This book is introduced at a time when all of these issues are facing the physician. The question is; what does the physician recommend as a course of action to a patient? All too often the patient presents with a diagnosed PCa and based upon the patient’s own investigations finds his path to a recommended therapy. Whether that is the best for this patient is usually uncertain.

On p3 the authors open with a direct assessment of the USPTF, one which I would strongly recommend reading for any practitioner. It is short, well written and on point. This in a sense sets this rest of the work in clear perspective; unlike the USPTF, this is a “what is the best for the patient” work.

The book is structured along standard lines.

The first several chapters deal with a wide variety of current issues such as the genetics, the androgen receptor issues, and fusion. All are done at a reasonably high level for the practitioner. This is clearly not a book on the detailed genetic issues associated with PCa. Chapter 5 is an interesting chapter since it discusses the issues of Gleason 6 and is it even a cancer. This is a compelling question since as we are discovering the genetic makeup is often more telling and that may mean the genetic makeup of the most aggressive cell. Chapter 6 is another significant chapter since it deals with HGPIN. HGPIN has for a decade or more been synonymous with a progression to PCa. However that is not inevitable. The interesting cases are those where there is a HGPIN at initial biopsy and then it disappears and never returns. The question then is; how significant a prognostic issue is HGPIN?

Chapter 11 discusses MRI imaging in localized PCa. MRI imaging is becoming more common and is becoming an element in integrated biopsies with real time ultrasound. This is a useful chapter for the urologist to become familiar with an imaging technique which will become a

more integral part of diagnosis and prognosis. However as with all modalities it may add significantly to the costs and also may cause increased biopsy covers for what may not be significant observations.

Chapter 13 is an excellent discussion on PSA screening. PSA is a useful but sometimes problematic measure. PSA increases with prostate volume and age as well as with pathological changes. Differentiating them is complex. The physician must balance reasonableness with the risk of being too insensitive to the changes. Chapter 17 discusses hereditary PCa. This is mostly a discussion of genetic inheritances that result in PCa. However we also know that there is a strong correlation between first degree relative PCa and PCa in the patient. This is correlative and not causative, whereas what in in this chapter seems to be much more causative.

Chapters 26 thru 41 discuss the complexities of surgical treatment and the presentation is clear and up to date. Chapters 42 thru 48 discuss radiation therapies with equal presentation. Chapters 52 thru 57 discuss some advanced issue of PCa therapy. This includes several biologics as well as androgen therapies.

Chapter 66 is an interesting chapter in that it discusses new markers for diagnosis and prognosis. On the diagnosis side there are many ways to enhance PSA and related measures including PCA3. One of the recent tests such as 4K have seemed to be of some use in assessing the chance of there being PCa prior to biopsy. Although I have had experience with this test and positively specifically it is still as I write this not FDA approved. There are also almost a dozen genetic tests used on PCa cells after biopsy to ascertain a prognosis for subsequent aggressive potential. Many of these are still being tested but generally they also provide guidance. However the conundrum is using them for prognosis when the result is poor and there is no significant treatment available.

Overall this is an excellent up to date summary of PCa, its diagnosis, prognosis, treatment and the state of the science that surrounds it. It clearly meets the needs of the practitioner. Its weakness in my view, and that of one involved more deeply on the genetics side, is that it would have been helpful to have delved a bit more deeply in the genetics of PCa. Unlike many other cancers PCa is highly heterogeneous and it seems that each week one sees another several genes putatively involved. Thus one can appreciate perhaps avoiding this area since it may be out of date by publication.

This is an excellent and up to date text and a worthy addition to what is currently available.



Labels: [Cancer](#)

THURSDAY, DECEMBER 3, 2015

[THE NEW TSAR](#)

The book, [The New Tsar by Myers](#), is a well done bio of Vladimir Putin. To set my observation space regarding this work, I was in Russia from 1995 thru 2004, in Saint Petersburg and

Moscow, starting my telecommunications company, and with partners who were from the same world as Putin. These folks knew me since in the 70s I had been part of the US Comprehensive Test Ban Treaty talks and had one on one contact with various Russians. I managed a bit of Russian language, adequate to get about, and even joke after a few vodkas. Thus I had been closely aware of Russia, the Russians, and the KGB world. Unlike most Americans I had no larger company backing and I needed in country partners, many of whom are covered in Myers tale. I saw Moscow via the Metro, the streets, the stores, the homes. I saw vodka used to brush teeth because the water is so infested it is barely adequate to flush toilets. Yet the streets looked like Tokyo at night, a change which occurred in less than ten years.

Myers takes on a journey which has as its focus Putin, but for all purposes it is a journey on the change of Russia from Communism to what it is today. In a sense, the Orthodox Church has replaced the Communist Party for the masses, a milder means of establishing the mandated role of the rulers. This comes out in Myers work by the telling tale of Putin being baptized as a child. Myers did not really explore the depths of this ongoing cooperation but he does provide certain pieces. Myers follows Putin and attempts to give some depth to the man by his movement from young KGB “employee”, to the accidental head of the FSB (formerly the KGB) and then to President. In a sense Putin’s life is almost Forest Gump like, just being there when the bus went by and getting on to see where it took him next.

Unlike a Tsar, one who was born to “greatness” and knew it by birth, Putin just happened to be at the right place at the right time with the right attitude. The appointment of Putin as President by Yeltsin was a turning moment, for up until that moment he was an effective administrative functionary, but then he was thrown headlong into the top leadership slot. His KGB past was his backstop. His trusted friends, if any, were from that time and space. Key among them was Sergei Ivanov, a KGB general and longtime associate. Ivanov flows in and out of Myers book but it would have been worthwhile to have explored him in more depth.

The discussion by Myers concerning Putin and Bush is also telling. At first, after 9/11, there was a bond, but as the US managed to take its aggressive single handed approach to Iraq that bond fell apart. Putting understood Iraq, albeit from afar via Afghanistan and Russia’s disaster. Bush did not, and his team also did not. Thus, the quagmire. There is also the discussion on boundaries and NATO and Russia’s near abject terror of a NATO encroachment. Why the US never truly understood the need for Russia to have a buffer is amazing. Russia just needs neutral borders, ones not militarily aligned with the West.

Myers does a reasonable job on Putting I and Putin II. Namely Putin I is the accidental president. This is a period of his ascending to the highest rank. Much of this time he is learning and expanding. Then after his hiatus, he is now Putin II, no longer accidental, but deliberate and with a depth of team players to make him untouchable in Russia. The problem is when we see Putin II we see in many ways the old KGB tactics. Myers discusses many of the allegations of assassinations and corruption.

The book is exceptionally well written and is a major contribution to the understanding of Putin. But the book also demonstrates that Putin II is a moving target and evolving and expanding

player on the world stage, a man who is much more comfortable in his new role rather than the accidental presidency that pushed him to the forefront.

If Myers' book does anything, it should enlighten some in Washington as to whom they are dealing with. He is a Russian, has a Russian mind, and in a sense a Russian soul. One must understand Russia at least a little to understand Putin. Kennan had such an understanding. Very few have had such in the US since then.



Labels: [Russia](#)

[CRISPR AND THE SEARS CATALOG](#)

In a recent paper by Graham and Root^{2[1]} at MIT/Broad the authors provide an interesting list of CRISPR facilitators. It is akin in many ways to the old Sear catalog. For folks who may be much too young to remember the Sear catalog, if one lived quite a distance from a large store, or if you just wanted to spend time looking at what you could get, Sear sent out 3" thick tissue paper catalogs. They had page after page of "stuff", and Amazon before Amazon.

In the paper by Graham and Root one finds a much thinner version of this for CRISPRs, but with activating the URLs attached one can get the equivalent feeling. A complete set of Sears Craftsman tools, but for assembling genes via a piece by piece method.

Recall that CRISPR is that targeting sequence of an RNA to attach to a specific part of a gene so that the Cas9 protein can cut the gene at the end of the PAM sequence. Also recall that we can use different proteins from Cas9 to make offset cuts. Cas9 makes cuts opposite one another which often leads to possible reconnection problems.

The CRISPR-Cas9 combination is but one of many that can apparently be used. Changing Cas9 for other proteins lead to altered cutting mechanisms which we have discussed previously. There are in the Graham and Root paper four fundamental applications. They are:

1. Cutting or Knock Out (KO) where a gene sequence is cut from a chromosome.
2. Pasting or Knock In (KI) where a gene sequence is added.
3. Inhibition where a gene expression is inhibited by creating a block to a transcription factor.
4. Activation where an activator is effected by the CRISPR Cas9 action.

In some sense types 3 and 4 are also done by methylation or indirectly via miRNAs.

^{2[1]} <http://www.genomebiology.com/2015/16/1/260> Graham and Root, Resources for the design of CRISPR gene editing experiments, Genome Biology (2015) 16:260

Graham and Root first discuss design factors and they state:

The following considerations and guidance apply to many types of CRISPR-based experiments:

The delivery method for Cas9 and sgRNAs can be transfection or transduction. Viral transduction is required for pooled screens. More consistent activity can be provided by selection of Cas9-expressing, CRISPR-active cells. CRISPR activity can be variable across cell types and should be experimentally confirmed case by case.

The delivery mechanism is a critical factor. How does one get the combos into a cell? Some recent work indicated that a cell can make its own Cas9 and then inject the CRISPR. The challenge is also targeting specific cells. In some areas one has looked at this approach almost as a weaponized system and the delivery mechanism is as critical as the actions themselves.

One should select sgRNAs to maximize the likelihood of high activity and specificity. The current state of knowledge provides useful guidance for selecting target sites and sgRNAs, but predictions of efficacy and especially of specificity are currently far from perfect. Table 1 describes tools now available to assist in this process. New tools and strategies are arising frequently as the understanding of CRISPR technology improves.

The sgRNAs used to select the gene sequences are not always that selective and have less than perfect specificity. This can be complicated in a wild type environment where the genes may be present in a certain large percentage but intra-species variations are possible.

Multiple sgRNAs per target gene (typically ranging from three to eight) should be employed wherever possible, first, to provide more opportunities to achieve the desired on-target modification and, second, to evaluate concordance of the phenotypic effects of multiple independent reagents to prioritize results most likely to be on-target — that is, causally linked to the intended genetic perturbation.

Toolkits for better targeting and specificity are essential.

Validation of genetic models and phenotypes is essential. Confirmation of on-target efficacy is important for selecting good cell clones to use for subsequent experiments and to establish the specific gene edits produced. Experimental assessment of off-target effects of sgRNAs can also inform clone selection.

The targeting is still not perfect. It is also not clear what effects such epigenetic factors such as methylation will have.

They do discuss the usefulness of this technique in examining the functions of genes by KO analyses. However as we learn more about genes we see that are a mass of interconnected strings and the one gene one function model of Mendel has outlived its usefulness.

They conclude by stating:

One major goal is to achieve more efficient, predictable editing. If it were possible to convert every cell in a population to the desired genotype, the painstaking work of selecting and characterizing individual clones would be reduced or eliminated. This would make it feasible to engineer large numbers of clonal cell lines, or even to engineer specific alleles at a screening scale. It would also make it far more efficient to produce cells with multiple edits. One approach is to re-engineer Cas9 for desirable characteristics, including altered PAM sequences, better packaging into virus, better binding and cutting efficacy and higher specificity. The hunt is also under way for better type II Cas9 proteins or other type II CRISPR proteins that might possess performance advantages, or to provide altogether new activities. The adoption of new CRISPR systems might necessitate new studies to determine their on- and off-target behavior and ideal design parameters.

This paper is well worth using since it is a balance of what is achievable and provides an exceptionally useful tool box for those working in the area. The only issue is that the area is changing so rapidly that the tool box may have to be updated frequently.



Labels: [CRISPR](#)

WEDNESDAY, DECEMBER 2, 2015

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

In an article about an Estonian company the [CSM](#) states:

Velmenni, an Estonian tech company that has installed Li-Fi in its offices, says that the technology has achieved speeds of up to 224 gigabits per second in the lab and 1 gigabit per second in real life, where transmissions must contend with other factors such as movement and interference from other light sources. An office or industrial park could be outfitted with smart LED bulbs that could send data and provide illumination simultaneously

Well 50 years ago we called this optical communications. I even did a PhD in the area back then and a colleague connected two mountains in New Hampshire, Wildcat and Mt Washington, optically back in the 60s.

One of the problems with optical is that it does not bend. Now the CSM states:

There's a catch, though: Because light can't pass through walls or other obstacles, a Li-Fi access point can cover only a single room. That means multiple smart LEDs will be needed to cover an apartment or a house with speedy wireless coverage. But on the other hand, wireless interference will be greatly reduced.

WiFi does not go "through" walls as well. It does refract and it does reflect, thus having multipath to work with, something I did some 40+ years ago.

So what is new here? In my opinion not much. So why the outbursts from the media? I guess they just do not understand. It does fill up pages.



Labels: [Commentary](#)

MONDAY, NOVEMBER 30, 2015

[PIGOU, THE GOVERNMENT AND ECONOMISTS](#)

I am not a fan of Pigou taxes. Also many alleged right wing leaning economists support this tax. Yes it is a tax. A tax is anything the Government takes from a provider of goods or services, or an individual or company, and then decides on its own how to use those funds. Taxes do not solve problems they provide a currency for politicians to garner favor.

In a recent piece by Masur and Posner (Toward a Pigouvian State, U Penn Law Rev, V 164, p 93) the authors extol the virtues of such a tax. They state:

A Pigouvian tax is a tax equal to the harm that the firm imposes on third parties. For example, if a manufacturer pollutes, and the pollution causes a harm of \$100 per unit of pollution to people who live in the area, then the firm should pay a tax of \$100 per unit of pollution. This ensures that the manufacturer pollutes only if the value of the pollution-generating activities exceeds the harm, such that the social value of those activities is positive.

Now simply the Pigou tax is a way to control the costs of externalities. The classic case is a railroad whose trains emit sparks and the sparks ignite corn fields. The Pigou tax would have the Government assign a tax on the railroad as an incentive to improve the rails and eliminate the tax. What happens? The Government collects the money, the railroad increases its prices, the corn still burns down but the politicians have more money to spread around for votes! Not very efficient unless you are a politician.

The Coase approach is to allow each person harmed to sue the railroad at some minimal cost and to have laws allowing that. Then the railroads will get tired of the law suits, the farmers will get reimbursed and we employ more lawyers outside of the Government. Somewhat of a win-win type result.

The authors of this piece state:

Finally, a more fundamental objection to Pigouvian taxes comes from Ronald Coase's classic article, The Problem of Social Cost. Coase attacked Pigouvian taxes because they do not take into account the possibility of bargaining. Consider the example of the factory that pollutes and causes harm to neighboring residents. According to Coase, the neighbors could pay the factory to reduce pollution; if they do so, the socially optimal level of taxation is achieved without the necessity of government intervention in the form of a tax. And if (as seems likely) the government

may err in setting the tax, then the outcome will be inferior to one that is reached through bargaining.

What Pigou taxes do for pollution and emissions is to tax those who could least afford it, and make them pay for the benefit of the politician. Coase is correct. Pigou is just another tax and spend liberal supported by Republicans, especially economists!



Labels: [Economics](#)

WEDNESDAY, NOVEMBER 25, 2015

[NEWSPAPERS SHOULD NOT GIVE MEDICAL ADVICE](#)

In an editorial, yes an editorial, in the [NY Times](#) they state:

An editorial in the journal ([JAMA](#)) suggested that the pendulum has swung too far against prostate cancer screening and that it is time to focus on ways to use the screening test more effectively, perhaps by reserving it for men at high risk based on such factors as race, ethnicity, age, family history and the results of rectal exams. Men facing only an average risk of dying from prostate cancer might simply have blood tests and possibly biopsies every other year and undergo surgery or radiation only if there is evidence that they have a tumor that is growing and becoming more aggressive.

The problem is identifying risk. We try Bayesian risk analyses. Namely if a patient has a family member with an aggressive form of PCa and that is a first degree relative then we assign that patient as high risk. Sometimes that works, but not always. The real risk is the genetic profile of the cancer cells distant from the prostate. But how do we find them, and in fact what specific profiles are we looking for? Frankly there are no answers.

[Recently we examined a patient profile](#) that was confusing to any Bayesian, and I am one. Let me reiterate it simply:

1. The Pt had a father with a highly aggressive form leading to death. From a Bayesian perspective this gave the Pt a 20-30% chance.
2. The Pt had a biopsy with HGPIN. This raised the risk to 50%.
3. The HGPIN was no longer apparent on a second 24 core US biopsy. This lowered the risk to 20-30% again.
4. The Pt saw a PSA velocity well above the maximum, now raising PCa risk to 50%+.
5. The Pt was assayed with a 4K test which resulted in a less than 1 percent range.
6. However a concomitant MRI in anticipation of a biopsy revealed 3 small lesions. This raised the Bayesian risk to 75 percent.

7. An integrated MRI/US 24 core biopsy was all normal and this reduced the Bayesian risk back to a less than 1 percent range.

This Bayesian approach shows the problems, not only with PSA, but what we understand about a priori data and its influence. The suggestion above from the Times:

Men facing only an average risk of dying from prostate cancer might simply have blood tests and possibly biopsies every other year and undergo surgery or radiation only if there is evidence that they have a tumor that is growing and becoming more aggressive.

is in my opinion [based upon years of extensive review and analysis](#) a nonsense proposal. Why? Simply, the [literature is full of the complexity of PCa genomics](#). PCa can metastasize in less than three months in certain cases. It can enter the blood stream and seek a nice home in the bone. Then the game is lost. Why is an editorial board even suggesting this without any detailed evidence. In fact the evidence is still conflicted. So it is best to keep quiet or follow a conservative path, even for a liberal paper.



Labels: [Cancer](#)

[WILSON AND HISTORY](#)



My grandmother, Hattie Kruger, is shown above just prior to her arrest and incarceration without trial by Woodrow Wilson and his minions. They became the Lorton 7, jailed for demanding the vote, force fed with rubber hoses, and watered down with fire hoses. Left to rot until Wilson in his regal manner decided to send them on their way.

So I am amazed to find the [Times](#) finally coming to the realization that this dyed in the wool Virginian from 19th Century roots may have had a checkered past as far as it goes. One wonders where the women have been for the past fifty years and why now it come to light that perhaps he is not the type of person one may want to honor.

History has a way of slowly getting to the point. And one of the points is that Wilson was not a really nice person. Hopefully Princeton gets the point.

Unlike some, I never thought there could be a for and against Princeton or any other institution

keeping a Wilson accolade. His actions with women and African Americans are the antithesis of what American stands for, or at least should. Removal is the only alternative and it is an imperative.

Oh and yes, Happy Thanksgiving!



Labels: [Politics](#)

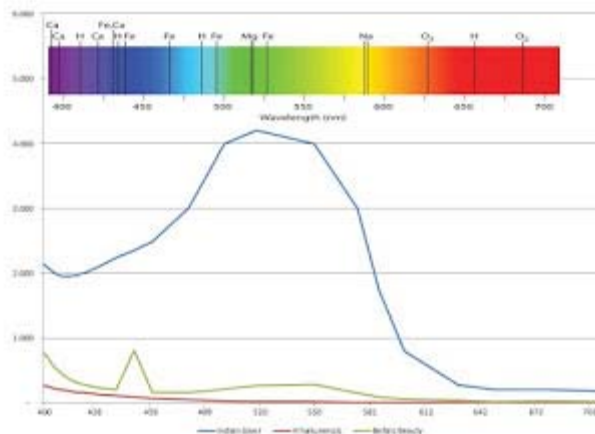
SATURDAY, NOVEMBER 21, 2015

[GUEST BLOGGER 2](#)



Hello I'm Bella I've blogged on here before. Today I spent a day with my wonderful grandfather, we made molecules and did spectro photography. Spectro photography is measuring the color. We measured the color of some of the day lilies he owns. We wanted to see what the day lilies absorbed. We put the methanol and the daylily pigment in to a machine which measured the pigment which is in the graph below.

The higher the bar the more absorption. The Indian Giver below absorbs a lot of purples, blues, yellow, and green. It then goes down hill and does not absorb much red, this is why it was a dark red. Thanks for reading my guest blog.



Labels: [Commentary](#)

TUESDAY, NOVEMBER 10, 2015

GETTING OUT OF HAND

The [Inquirer](#) remarks about the EU now investigating Google about Google Maps. They remark:

*Brussels asks Google's mapping rivals whether they feel bullied. **EUROPEAN REGULATORS** are investigating whether Google has been supplanting native mapping applications and devices with its own Google Maps, thus causing a competition vacuum. A questionnaire obtained by Bloomberg has been sent to rival companies asking for any evidence that the prevalence of Google Maps has damaged sales of rival devices such as TomTom, Garmin and HERE. Officials will also be looking for data on user numbers, preinstallation of mapping apps and the costs faced by cartographers to make mobile-ready versions of their work.*

You really can't make this up. This is what happens when people have too much time on their hands. They should be out shearing sheep or something. One wonders how an entity providing a free service that works well can threaten others. Now I use Garmin as a GPS device, refuse to get an android phone and pay Verizon an exorbitant amount. But if one wants to then go use Google and not Garmin. But then why not feel bullied by Verizon, sorry it would be BT, or DT, or whatever other state entity controls the phone systems.

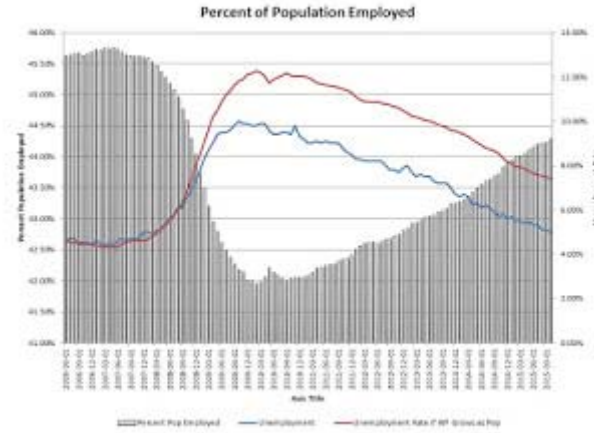
But no, get those nasty Americans, after all they are free! Perhaps not for long, depends on the elections.



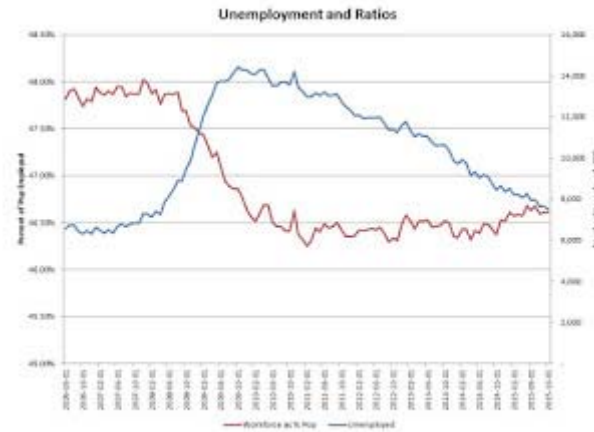
Labels: [Google](#)

FRIDAY, NOVEMBER 6, 2015

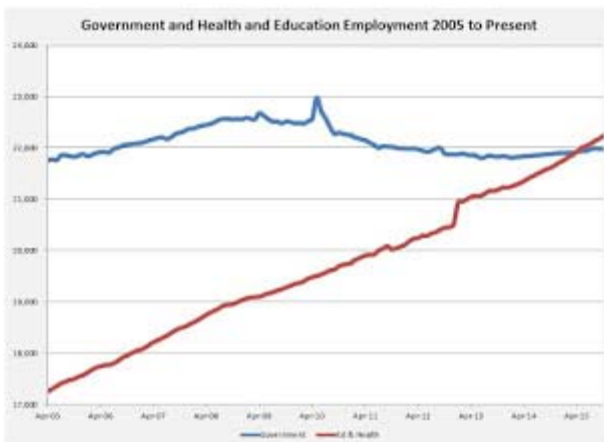
EMPLOYMENT NOVEMBER 2015: NOT REALLY THAT GOOD



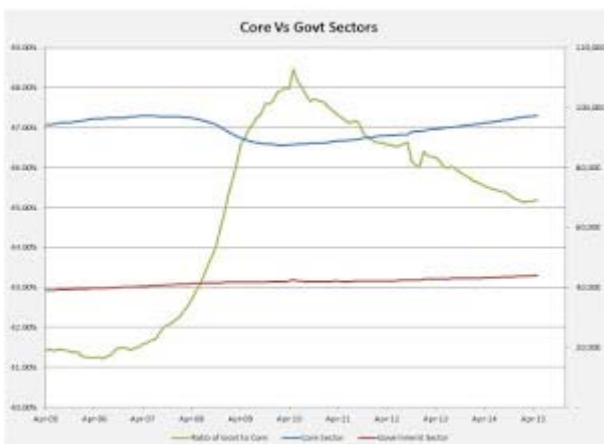
If we look at the most recent numbers we see a 5% unemployment but a still weak participation rate. Seven years later we are seeing the Romer predictions of January 2009. So much for economists.



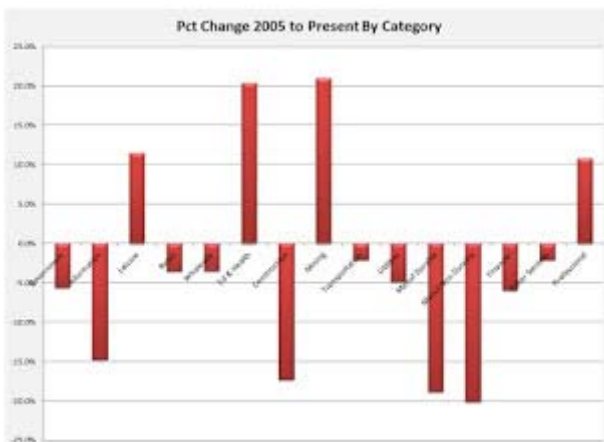
The participation rate is still bottomed out and we really see little movement. This is a structural problem.



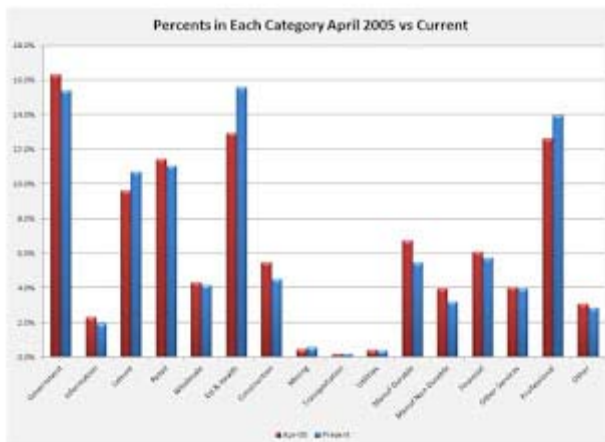
Although Government employment remains flat as a percent we see Education and Health keep climbing. This is a real problem since they are now paid more and more by the taxpayer.



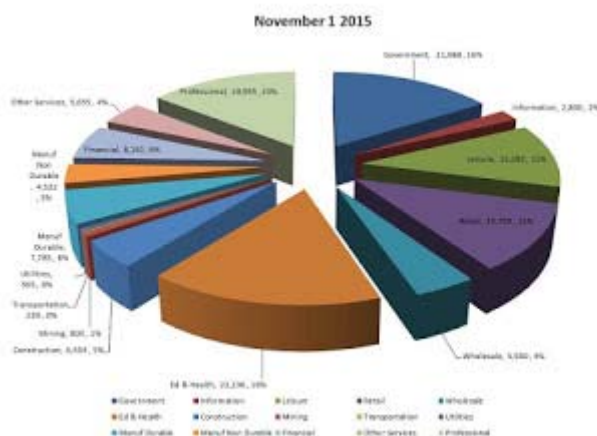
The plot above is core vs Government by people and the ratio of core to Govt is flattening.



The above shows the percent change over the last ten years and E&H has the largest percent and Manufacturing the greatest decline. This is the concern that few mention. It was manufacturing that paid for H&E and this switch is also a systemic problem.



The above is the comparison between now and ten years ago. Again Ed and Health shows a great pop up.



Finally the above shows the current details.

Overall the 5% is nice but participation is too low and the growth is in the wrong places. Why we get no discussion of this is amazing! There is still a very rocky road.



Labels: [Economy](#)

TUESDAY, NOVEMBER 3, 2015

[GET A JOB!](#)

Institutions like Harvard and Princeton were originally founded to train people for the Ministry and Law. It was not until almost 200 years later that Hopkins started in Medicine. MIT, yes a Technical Institute in 1865 started as a Land Grant school to train in the sciences and technology.

Liberal Arts education was not something for the masses. After WW II most of the men going to college did so to get a job, to improve themselves and their families in an economic sense.

In a recent speech at [Stanford](#) the individual states:

The original rationale behind an American liberal arts education – to play a vital role in democratizing privilege – "is under attack, or is being forgotten," Robinson said. Now, universities by and large do not attempt to "prepare people for citizenship and democracy." Instead, they educate them to be members of a "docile, most skilled, working class."

Frankly that illusion is one reason why we may have so many unemployed. Many who have the chance to go to College think they must be broadly educated. Then they become aware after graduation that they are unemployable. Studying Medieval History is enlightening and entertaining but as we have seen it may not prepare you well to manage a multi-billion dollar high tech company.

Stanford, MIT, and other technically focused institutions hardly put out docile anything. Look around and what do you see? Creative and questioning but technically competent and productive creators of value.

What is under attack is the idea that going to college is an interlude in life, that it should be some mind exploring period between adolescence and adulthood. In reality it is a training ground for life, highly competitive and a means to an end, namely a job. Sorry about that but the illusion is why we have some many disappointed and unemployed kids at home.



Labels: [Academy](#)

SUNDAY, NOVEMBER 1, 2015

"THE SMARTPHONE"; AN APPLIANCE?

Appliances are very useful human tools. However a good appliance does one thing very well. Take a toaster. A toaster makes toast. Just that. But if it is a good toaster it makes good toast. A refrigerator keep things cold. A stove heats things up. My digital camera takes wonderful pictures at very high resolution of plants. My microscope camera takes great high resolution pictures of slides. My toothbrush does a great job on my teeth.

Get the point.

Now a smartphone is really an appliance integrator. It is a phone, a camera, a video recorder, a message device, a web browser, and email device, a player of tunes, a display device for images, and it wants to take over all my bodily functions.

Now [PCWorld](#) reports:

*The percentage of US adults who own a smartphone or tablet has skyrocketed in recent years, while PC ownership has held more or less steady. That's the takeaway of a new Pew Research Center survey **Why this matters:** that clearly illustrates the rapid rise of "post-PC" devices. According to the survey, 68 percent of adults in the United States currently own a*

smartphone, up from 35 percent four years ago. Meanwhile, 45 percent own some form of tablet, up from three percent in 2010. Pew's data shows that desktop and laptop ownership has remained more or less flat over the last decade. According to Pew, 73 percent of survey respondents currently own a desktop or laptop, compared to 71 percent in 2004. Traditional PC ownership trended slightly upward until the early part of this decade before tailing off somewhat the last two or three years. Pew's data reinforces what we already know—that fewer people are buying new PCs, and that more people are turning to mobile devices like smartphones. IDC, the research arm of PCWorld's parent company, predicted in August that PC sales would slip by 8.7 percent this year and decline an additional 1.1 percent in 2016 before bouncing back some in 2017.

I do not own a smartphone, in fact I despise them. For example on any subway in New York just look down and there you have every passenger playing on the device. Five years ago it was some other Apple device playing music, not it's Candy Crush. There are millions clicking on the screen and strange noises beeping out. No one reads the newspaper anymore on the train, no a single person. A person could walk through bare naked and not a single person would notice! Yes that happens a few times each day but it is New York.

So what about this appliance thing? Well I have a desktop machine for heavy duty stuff. I have a large laptop for on the road heavy duty stuff. I have an all solid state high end lap top/tablet for go to meeting stuff, like emails and web browsing, like a large smartphone but with brains. Then I have an appliance that is used for phone calls, a cell phone. I can partition my appliances and this allows me to look around on the subway at the humans focused on Candy Crush.

So what is the point? PC sales excluding laptops are appliances for doing complex things. I do complex word processing, spreadsheets, Python programming, complex data editing, image processing, and the like. My high end laptop/tablet (Dell XPS 13) is light and functional to do some complex tasks. As for the phone, call me if you have a problem, but you better have a proposed solution. Unlike some of the folks I see in the AM on my bike exercise who walk on their smartphones endlessly gabbing, my calls last less than 90 sec! Have a nice day. Oh yes, and unlike some of the Presidential candidates, I do not use twitter! And I have not figured out how my smartphone can make toast.



Labels: [Commentary](#)

SATURDAY, OCTOBER 31, 2015

[GENETIC NETWORK MODELLING](#)

The bench biologist is in a continual search mode for some new gene interaction. What new gene can be a, not the, cause of say prostate cancer. At the other extreme is the systems biologists who use their mathematical models to propose reactions. The intersection of these two is not that fruitful as of yet.

In [Science](#) the authors conclude:

Models are simplified (but not simplistic) representations of real systems, and this is precisely

the property that makes them attractive to explore the consequences of our assumptions, and to identify where we lack understanding of the principles governing a biological system. Models are tools to uncover mechanisms that cannot be directly observed, akin to microscopes or nuclear magnetic resonance machines. Used and interpreted appropriately, with due attention paid to inherent uncertainties, the mathematical and computational modeling of biological systems allows the exploration of hypotheses. But the relevance of these models depends on the ability to assess, communicate, and, ultimately, understand their uncertainties.

The process is iterative. Models are built, tested, found lacking, and then reiterated. The challenge is that these are quite complex and of massive dimensions. Perhaps methods akin to 19th Century thermodynamics may play a role, gross constructs like enthalpy and Gibbs free energy, but perhaps not.

It will take time to get these models to work properly, but they are needed as a cornerstone of true science.



Labels: [Genetics](#)

FRIDAY, OCTOBER 30, 2015

[THE GOVERNMENT AGAIN](#)



I like Amazon, I mean I really like Amazon. If you have a problem they solve it near instantaneously and you are happy. Maybe we should have them take over the Government. They get things right, get them inexpensively, get them on time, and give customers satisfaction.

Now their only Achilles heel is that in the New York area they rely upon the USPS. Yes, the Post Office, yes the Government. During the winter the good old mailman just drops packages off on the snow pile, and I had better get there before the snow plows, yes again Town Government, gets to try and knock them off and crush them to bits. All too often the USPS loses packages but reports them delivered, and then when asked never responds. They are "tracking" the package but most likely it went to package heaven some where. The result is Amazon immediately sends a replacement. Good for Amazon and bad for the USPS.

You can tell the Government they messed up but you might just as well try and reach another

galaxy. No one there and frankly they just don't care. Well why should they? They can't get fired, remember the Army balloon, they have great pensions, and in New Jersey they have multiple ones, and they get life long health care etc. And of course our taxes go up to keep them all happy.

So as we start off this campaign season, perhaps we could put a cardboard Amazon box up on the stage to remind us that someone does get it right and does think of us.



Labels: [Commentary](#)

[THE ARMY AND THE BALLOON](#)

Government keeps giving and giving. If things seem down, just look to our Government for a good chuckle. Back to the Balloon. As [ArsTechnica](#) notes:

*The wayward JLENS aerostat, which left a trail of power outages caused by the 6,000 feet of cable it dragged for over 160 miles on Wednesday, was hit by a barrage of shotgun fire to remove its remaining helium. Approximately 100 shotgun blasts were fired at the balloon by Pennsylvania State Police, according to US Army Captain Matthew Villa, an Army spokesperson, who said that firing on the balloon was the easiest way to remove the remaining helium gas in the grounded radar aerostat. The Army still has not determined how the JLENS aerostat broke loose. But the military has labeled the incident as a **Class A mishap**, an aviation accident classification for events that took no human life but caused over \$2 million in property damage or caused injury. Anyone who suffered property damage from the JLENS' tether will have to file claims with the Army.*

Class A indeed. And try to ever collect from the Army. But it did show how to attack the Grid, just get a big balloon.

The key question is who will be held to account? This should be a career breaker for some gree suit.



Labels: [Government](#)

WEDNESDAY, OCTOBER 28, 2015

[VIRAL ATTACK ON MELANOMA](#)

Several years ago [we started following TVEC a viral attack](#) approach on melanoma. According to [Nature](#):

An engineered herpesvirus that provokes an immune response against cancer has become the first treatment of its kind to be approved for use in the United States, paving the way for a long-awaited class of therapies. On 27 October, the US Food and Drug Administration (FDA) approved a genetically engineered virus called talimogene laherparepvec (T-VEC) to treat advanced melanoma. Four days earlier, advisers to the European Medicines Agency had endorsed the drug. With dozens of ongoing clinical trials of similar 'oncolytic' viruses, researchers hope that the approval will generate the enthusiasm and cash needed to spur further

development of the approach. "The era of the oncolytic virus is probably here," says Stephen Russell, a cancer researcher and haematologist at the Mayo Clinic in Rochester, Minnesota. "I expect to see a great deal happening over the next few years."

We expected this back in 2012 and have been following closely. We now have a three prong attack on melanoma:

1. Pathway
2. Immunological
3. Viral

One suspects that we shall see all three being used in some form of cocktail. Nature continues:

Administering T-VEC in combination with cancer immunotherapy could prove particularly effective, notes Stephen Hodi, an oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts. In June 2014, a small clinical trial by Amgen suggested that this combination may boost effectiveness over that of the immunotherapies alone. And researchers continue to look for ways to improve T-VEC. In particular, they would like to be able to deliver the therapy systemically, so that the virus could target tumours in organs that are difficult to reach with an injection. This would require a technique to prevent the body from mounting an immune response to the virus prematurely, which would disable it before it could reach and kill tumour cells, says Howard Kaufman, a cancer researcher at Rutgers Cancer Institute of New Jersey.

The progress continues now that we understand some of the cause.



Labels: [Cancer](#)

REMEMBER THE HINDENBURG

When we go to Seaside Park, at least what little is left of it, we pass by Lakehurst the site of the Hindenburg explosion. I guess the Navy got the idea that big balloons can be a bit difficult to deal with. Now perhaps the Army did not get the message. On the loose is a power grid killing monster. We don't need a George Will to tell us of the threat, we have developed and now deployed our own such weapon, and it is slowly drifting across central Pennsylvania wiping out the grid.

Perhaps we need some hunters out there, perhaps that was the reason for the Second Amendment, to get those white whales down and stop the power outages!

As [ArsTechnica](#) reports:

One of the two tethered aerostats that make up the Joint Land Attack Cruise Missile Defense Elevated Netted Sensor System (JLENS), has broken loose from its moorings and is now drifting over Pennsylvania. Two Air National Guard F-16 fighters are monitoring its movements, but the trailing tether has already taken out power lines in Pennsylvania, causing blackouts in Bloomberg as it got closer to the ground. JLENS' twin aerostats are (or were) supposed to

provide airborne early warning and targeting of low-flying airborne threats coming in from the Atlantic, covering a radius of 300 miles with their look down search and targeting radar. They have been the subject of much controversy because of the cost of the program; a recent Los Angeles Times report called the \$2.7 billion dollar project delivered by Raytheon a "zombie" program: "costly, ineffectual and seemingly impossible to kill."

Yes indeed, just in time for Halloween, a Zombie Project! Let's see who get reassigned, any guesses.

Oh and yes, I think there is another debate tonight. Any guess who will focus on this?

Oh yes and one more thing! CNN keeps bemoaning that it may explode. It is Helium stupid, a Noble Gas, inert, not Hydrogen! The worst that will happen is a few folks will talk like Donald Duck for a short while! What has happened to our educational system. And also, not radio like with the balloon, even amateur aircraft fliers have such a link to get control. Even the drones on Amazon! They put \$200 M of electronics and no "phone home". Is this just a Halloween joke or for real?



Labels: [Commentary](#)

SUNDAY, OCTOBER 25, 2015

[HURRICANES AND STATEN ISLAND](#)



Three years ago, before Sandy hit, I remarked in this Blog that Staten Island was a prime location for its wrath. Why? It has been before and things have just gotten worse. In the early 1950s there were several massive Hurricanes and flooding went from the shore to Hylan Blvd. From Hylan in it was 2-3' underwater. Of course then there homes were at best summer shacks and the City had not improved anything.

Then in the late 50s and early 60s I was the NY City Lieutenant Lifeguard in charge of Ocean Breeze section. Every day, for almost 5 years, I watched as the Verazzano was built on one side and as people moved into the swamps that had been the buffer in the last Hurricanes on the other side. Sooner or later they too would be under water again.

Then in the 80s they moved Staten Island Hospital and a Mental Health clinic to the middle of the very same swamps. Worse yet, the road along the beach was raised so that if water even came across it, the water would then stay in this swamp land, now several yards below what was sea level. It became a natural pond, and when the next hurricane came it would become a veritable salt water swimming pool, unfortunately filled with homes. And the homes were filled with people who would not leave.

So along comes Sandy. We sadly know what happened; death and destruction.

Now the [New Republic](#) bemoans the situation. They state:

Of the nine buyout committees that sprung up on Staten Island after Sandy, three—Oakwood Beach, Ocean Breeze, and Graham Beach—would successfully organize a state-managed, federal buyout. In April of last year, Barbara Brancaccio, the press representative for the Governor's Office of Storm Recovery, said that the State had no intention of purchasing the entirety of Staten Island's eastern shore, limiting the eligible communities to those already selected. For those left out of the buyout the only sure thing is that their homes are worth less than they were before the storm made residents and policymakers aware of the true cost of living beside a rising sea. Here on the damp fringes of what was once the most powerful city in the world, Staten Islanders are retreating from the coast because they have recognized the limits of the built environment's ability to buffer them from a changing natural environment, and the limits of the government's ability to buffer them from unfair and inequitable development.

The problem is that no one should ever have been allowed to build there, especially the hospital. I had seen the destruction to sea grass in the 50s, water knee deep on Hylan Blvd, and God knows how deep in the salt marshes.

So who is at fault? Most likely the City, whoever that may mean, who frankly should have known better. It had happened before, it happened in Sandy, and yes it will most likely occur again. The outer harbor is a dangerous body of water as tides come and go and as the winds can raise the water even higher. Midland Beach is a wonderful recreation area.

The ocean is a risky place to put anything at sea level. Sea level just is not reliable. People should question why building permits were even give for such locations, at least that is my opinion. This is not a first, it not the beginning of the end, it is an ongoing well-known process.



Labels: [Commentary](#)

[UNDERSEA CABLES](#)

Some seventeen years ago [I presented a paper to Members of the Russian Duma](#) regarding a Russian Transit Cable system. I had said:

This Business Proposal articulates the strategy on how to implement the concept of taking transit traffic from the Atlantic to the Pacific across Russia. Apparently, others, like RosTeleCom, GTS

and at least one other team seeking to use National Rail and National Electric Utility fiber optic infrastructure are also working on a similar approach. A special opportunity to break ahead of them all has been distilled. The Consortium of companies represented herein, has the ability, facilities, contacts, and skills necessary to accomplish this task.

Then some three years ago we considered a trans Arctic system paralleling the systems to the south in the Indian Ocean and allowing for improved East-West transport. Unfortunately Ukraine and other steps intervened. The Arctic is a powerful opportunity to combine communications with environmental monitoring. It also provides for a back-up of the Indian and Pacific routes. Canada and the US could do likewise.

However as reported today in the [NY Times](#) the Russians, according to US sources, may be creating a threat to these systems. They report:

Russian submarines and spy ships are aggressively operating near the vital undersea cables that carry almost all global Internet communications, raising concerns among some American military and intelligence officials that the Russians might be planning to attack those lines in times of conflict.

Well frankly we do have a multiplicity of satellites as well as wireless systems, many real time deployable. Any such "cuts", which happen all the time, would at worst disrupt iPhones in Mumbai. Not an earth shattering event. Perhaps they could do the same in New York and it would make pedestrian traffic safer from collisions.

The key question is that of survivable strategic links. Collapse of Commerce might disrupt Russia a bit but it would be devastating to China. We have to my knowledge no items in Walmart from Russia but thousands from China. Thus in a strange way China may be more concerned that the US.

Then again setting cables across China may make for secure land based commercial assets. Just a thought.



Labels: [Russia](#)

SUNDAY, OCTOBER 25, 2015

[AGINCOURT, LEYTE AND CHARGE OF THE LIGHT BRIGADE](#)

*We few, we happy few, we band of brothers;
For he today that sheds his blood with me
Shall be my brother; be he ne'er so vile,
This day shall gentle his condition.
And gentlemen in England, now abed,
Shall think themselves accursed they were not here;
And hold their manhoods cheap whiles any speaks
That fought with us upon Saint Crispin's day.*



Today, October 25th marks the anniversary of these three battles. Agincourt, where Henry V defeated the French and its Nobles and thus changing France forever, in 1415, The Charge of the Light Brigade led by Lord Cardigan against Russian forces during the Battle of Balaclava on 25 October 1854 in the Crimean War leading to a massive loss of life for no gain, and October 25th 1944 the Battle of Leyte Gulf in which my father and his shipmates defeated the last remnants of the Japanese Navy, leading to the final defeat of Japan.



Labels: [Commentary](#)

SATURDAY, OCTOBER 24, 2015

[THE VALUE OF RESEARCH](#)

Universities perform a great deal of research and much of it is funded by Government money. What value do we apply to these results? The [WSJ](#) has an interesting article which alleges it has little value. Generally I would agree. Much of University research is "training", namely training students to do research if ever they get the chance.

The author, Matt Ridley, first states:

linear model of how science drives innovation and prosperity goes right back to Francis Bacon, the early 17th-century philosopher and statesman who urged England to catch up with the Portuguese in their use of science to drive discovery and commercial gain. Supposedly Prince Henry the Navigator in the 15th century had invested heavily in mapmaking, nautical skills and navigation, which resulted in the exploration of Africa and great gains from trade. That is what Bacon wanted to copy. Yet recent scholarship has exposed this tale as a myth, or rather a piece of Prince Henry's propaganda. Like most innovation, Portugal's navigational advances came about by trial and error among sailors, not by speculation among astronomers and cartographers. If anything, the scientists were driven by the needs of the explorers rather than the other way around.

Most everything comes about by trial and error. Just look at Watson and Crick, at least as

Watson states it.

They continue:

When you examine the history of innovation, you find, again and again, that scientific breakthroughs are the effect, not the cause, of technological change. It is no accident that astronomy blossomed in the wake of the age of exploration. The steam engine owed almost nothing to the science of thermodynamics, but the science of thermodynamics owed almost everything to the steam engine. The discovery of the structure of DNA depended heavily on X-ray crystallography of biological molecules, a technique developed in the wool industry to try to improve textiles.

Indeed, being able to measure something leads to change. Suddenly having an X ray crystallography of DNA tells one that it is a helix, and a double not triple helix. Then go play with the stick model.



Finally they state:

In 2003, the Organization for Economic Cooperation and Development published a paper on the “sources of economic growth in OECD countries” between 1971 and 1998 and found, to its surprise, that whereas privately funded research and development stimulated economic growth, publicly funded research had no economic impact whatsoever. None. This earthshaking result has never been challenged or debunked. It is so inconvenient to the argument that science needs public funding that it is ignored. In 2007, the economist Leo Sveikauskas of the U.S. Bureau of Labor Statistics concluded that returns from many forms of publicly financed R&D are near zero and that “many elements of university and government research have very low returns, overwhelmingly contribute to economic growth only indirectly, if at all.”

My observations are somewhat upsetting but most likely correct:

1. That "organized r&d" is a total waste of time, I have been there. One needs a clear competitive product focus. I would argue that CRISPRs advances because of competition, not pure research.

2. Government funded research just sustains the Government funders not the results. All too often the funders have been assigned funds and they need boxes checked and paper written. No one ever rewards a Government employee for a breakthrough, also they never get fired for no results.

3. Publicly funded research such as NASA is almost all worthless to the economy, Tang and what else? I have been there. NASA results are at best good for NASA.

4. How do we judge or value research, by the economic advantage or by changing the way we think? I have been asked that question in prior lives. I never found anyone who had an answer. Take the Pharma world. Good research generates a profitable drug.

5. CRISPRs are now a hot topic, a tool for the genome tool kits which will have massive impact....lots of claims to parentage! Also lots of patent and start up actions. It is clear what the results could be.

6. Universities perform "research" which in reality is just "make busy work" to "train" students on how they should behave going forward, how many PhD theses really led to anything? They just allowed the faculty to see if the student would go through hoops

So for the Higgs particle, string theory, and the like, they are training grounds to train future academics. Yet is there still a chance for some Patent Examiner in some obscure place to write three world shattering papers? Doubtful they would get published but there is now the Internet, so who cares about those Peer Reviewers anyhow!

The real question of good research is its ultimate value and that then begs the question of what do we mean by value. Consider the Human Genome Project. It was essentially a competitive venture between a Government and private entity. That worked and the result will have significant merit. I believe it speaks for itself. Then we have for example neuro research on how the brain works. That is really hard, and really hard stuff goes no where for decades and then as is often the case something pops. But it is impossible to predict just what that is.

Now consider Cancer research, namely looking for ways to stop its progression if not cure it. Pharmas do some here but they often build on what comes from others work, namely the risk takers who left Academia and started something. They may have been supported pre start up by Government post-doc work but they MUST leave that haven of sorts and start a real company. High risk and potential high return.

The problem is that Government funding is all too often rans with political calculations. The funder wants to look good so they get someone who is already good. A cycle, But every so often we get sparks, again the genome or CRISPRs. These are real innovations, they are not Silicon Valley Apps, software that does nothing productive.

Thus somewhere between Government funding and Silicon Valley trend following is the world of real research, a game changing way to do something.



Labels: [Academy](#)

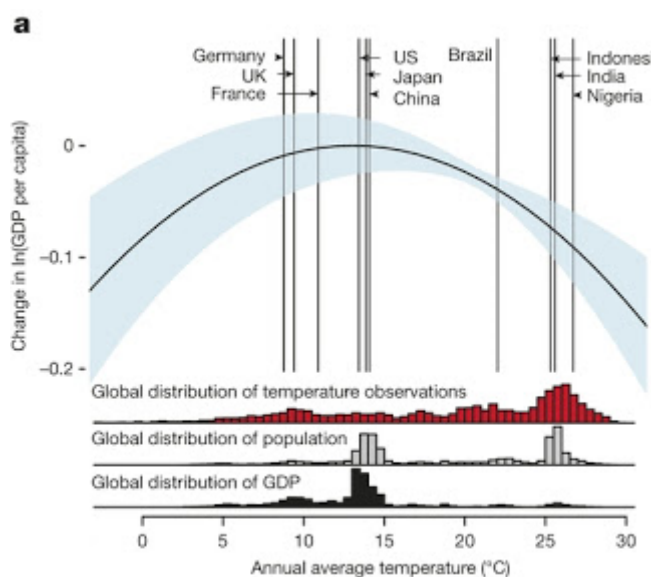
BEWARE OF CORRELATIONS! THEY ARE NOT CAUSATION!

In a recent [Nature](#) article the authors contend that "Global Warming" will result in drastic drops in certain national GDPs.

They state:

If societies continue to function as they have in the recent past, climate change is expected to reshape the global economy by substantially reducing global economic output and possibly amplifying existing global economic inequalities, relative to a world without climate change. Adaptations such as unprecedented innovation or defensive investments²⁵ might reduce these effects, but social conflict or disrupted trade—either from political restrictions or correlated losses around the world—could exacerbate them.

As best as I can tell their analysis is predicated on the following chart:



Namely they plotted GDP versus average temperature for countries. They then contend that if say the US were to rise in temperature then we will look like Nigeria. Huh?

The also state:

Growing evidence demonstrates that climatic conditions can have a profound impact on the functioning of modern human societies, but effects on economic activity appear inconsistent. Fundamental productive elements of modern economies, such as workers and crops, exhibit highly non-linear responses to local temperature even in wealthy countries. In contrast, aggregate macroeconomic productivity of entire wealthy countries is reported not to respond to temperature, while poor countries respond only linearly. Resolving this conflict between micro and macro observations is critical to understanding the role of wealth in coupled human–natural

systems and to anticipating the global impact of climate change . Here we unify these seemingly contradictory results by accounting for non-linearity at the macro scale. We show that overall economic productivity is non-linear in temperature for all countries, with productivity peaking at an annual average temperature of 13 °C and declining strongly at higher temperatures.

But wait. They do not as far as I can tell demonstrate direct causation. Alabama is hotter than Maine but we have lots of factories in Alabama and few in Maine. Texas is hotter than North Dakota but there is a much higher GDP there than in North Dakota. There does not appear to be any causal relationship established.

This is pure abject conjecture in my opinion. I guess we shall see this paper referenced in the weeks and months to come. In my opinion it is at the very best abject conjecture and at the very worst poorly crafted propaganda.



Labels: [Global Warming](#)

[LIBRARIES AND THE SOURCE OF KNOWLEDGE](#)



There still seems to be a lingering group who think the “Library” is still the old brick and mortar facility, controlled by a group of stodgy old lady librarians, and who keep tabs on all the “books” in “their” collection. The NY Times notes today^{3[1]}:

But today, the principal danger facing libraries comes not from threats like these but from ill-considered changes that may cause libraries to lose their defining triple role: as preservers of the memory of our society, as providers of the accounts of our experience and the tools to navigate them — and as symbols of our identity. Since the time of Alexandria, libraries have held a symbolic function. For the Ptolemaic kings, the library was an emblem of their power; eventually it became the encompassing symbol of an entire society, a numinous place where

^{3[1]} <http://www.nytimes.com/2015/10/24/opinion/reinventing-the-library.html?action=click&pgtype=Homepage&module=opinion-c-col-right-region®ion=opinion-c-col-right-region&WT.nav=opinion-c-col-right-region>

readers could learn the art of attention which, Hannah Arendt argued, is a definition of culture. But since the mid-20th century, libraries no longer seem to carry this symbolic meaning and, as mere storage rooms of a technology deemed defunct, are not considered worthy of proper preservation and funding.

With all due respect one should note that Libraries have managed to get an ever increasing piece of our tax dollars through mandated funding and no accountability. Take New Jersey as an example. The State mandates a percent of the gross Real Estate taxes go immediately to the Library. They state^{4[2]}:

The minimum funding statute for joint and municipal libraries (N.J.S.A. 40:54-8) sets the minimum funding rate at 33 cents on each \$1,000 of equalized value of all assessable property in the town. This minimum funding amount is the total of what your local municipality must, at minimum, allocate in its budget, according to the law.

Thus consider a simple example:

Assume the home is assessed for \$900,000. In our town that is the average assessment, they are done at market level.

Now for each such home the $\$0.33 \times 900$ or \$300 of their property tax goes to the Library.

Now assume there are 5,000 HH in the town then the total to the Library is \$1.5M. That is just the mandated “contribution”. Now add businesses etc and we get a hefty amount mandated and growing every year! This is for a library of some half dozen people loaded with old novels that are generally un-read.

The “Library” today is on the Internet, it is accessing primary sources, original documents, books themselves. It is “free” and knowledge is shared. Knowledge is consumed. One can tell a book has been “consumed” by its appearance. It looks devoured. Libraries do not have such books; one would be fined for such behavior.

The old brick and mortar library is an archaic establishment of the past. Free WiFi? You can get that anywhere; try the train station or any coffee shop. Need information on CRISPRs, try Google and definitely not some stodgy old librarian.

So what purposes do these old buggy whip Libraries serve? Meeting rooms, hang outs? It is not at all clear. I have been in our town for over 35 years and have never taken a book from the library. I use Amazon, ABE Books, or the used book shop in town! And yes, I use the Internet! Frankly the last place I would ever go would be the Library....It is Government controlled information....and they get paid by our taxes with no oversight.

^{4[2]} From the NJ Library Association on FAQ for the Municipal Library Tax Levy Law (P.L. 2011, c. 38) See http://www.njleg.state.nj.us/2010/Bills/PL11/38_.HTM and also the <http://njla.org/content/pl-2011-c38-s2068a2679a3240>

Thus perhaps the writer from the Times should reconsider the facts of the 21st Century. As Alexandria was burned down by the advancing hordes from the sands of Arabia perhaps we should exult that it will be much more difficult for the hordes to burn down the Internet.



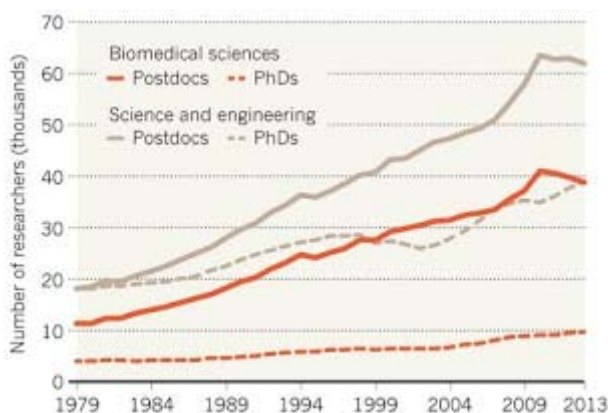
Labels: [Libraries](#)

FRIDAY, OCTOBER 23, 2015

POSTDOCS AND PRODUCTIVITY

I am continually surprised as to the size of the post doc world especially in engineering. In a recent [Nature](#) article they report a drop in the total post docs. They state:

From 1979 to 2010 the number of US postdocs in the biomedical sciences has risen steadily, from just over 10,000 to more than 40,000. But in the past three years, the tide has turned, according to official statistics. The population of US biomedical postdocs fell 5.5% between 2010 and 2013, to just under 38,000, with losses getting bigger each year, notes a study published on 6 October — although the number of new graduates with science PhDs continues to rise



The above is from Nature as referenced. What is interesting is the ratio of new PhDs to Post Docs, it appears to be dramatically different in Bio from Sci and Engr. That is a measure of the length of time as a post doc.

The true measure is that post docs are all too often used to replace technicians. The techs are employees and get paid more and have benefits. The post doc is at best a journeyman level position with no security.

Also there is a problem of lumping Science and Engineering. I would suspect that most PhDs in Engineering get jobs, for that is where one learns one's craft especially in engineering. Most Engineering Post docs seem to be foreign students being used as super techs. Then they return to wherever.



Labels: [Academy](#)

THURSDAY, OCTOBER 22, 2015

[RUSSIANS AND RUSSIAN](#)

The Guardian has a wonderful piece on [Russian and the Russians](#). Perhaps Kennan and his kind would have appreciated the nuance but it is clear the US today is clueless. I recall my days in Russia, and when I heard "Nyet problemi" I knew we had a real problem. Russians unlike the Poles, who tell you what they think you want to hear, often speak in opposites. Namely they have a tendency to say just the opposite of what it is. Now if you are a Russian you can readily interpret it and respond accordingly.

The closest to this barrier of language is an Irishman telling a joke to a German. First German's have as best as I have experienced no sense of humor. The Irish, from firsthand personal existential experience, have a bit of a perverse sense. Thus a German doctor telling his patient that the biopsy was benign may hear an Irish patient remark, "And I was so much looking forward to a prostatectomy!". Humor dissonance at its best!

The Guardian recounts:

For example, in 1995 after a summit with President Bill Clinton, Boris Yeltsin poked gentle fun at reporters who had poured cold water on hopes for a successful meeting. He said: "You predicted our meeting today would fail", which the interpreter translated (not knowing how Yeltsin was going to continue) as "You were writing that today's meeting was going to be a disaster." Yeltsin then went on: "I would say that it was you who failed." The interpreter foolishly decided to stick with the ill-chosen word "disaster" and translated Yeltsin's gentle rebuke as: "Well, now I can tell you that you're a disaster," – much stronger and more comical than Yeltsin had intended. Clinton was convulsed with laughter for a full minute, wiping tears from his eyes and hugging Yeltsin in appreciation of this witty joke – which in fact Yeltsin had not made. Yeltsin himself looked completely baffled, wondering why his wry comment had provoked such a wild reaction.

Now if one is speaking in Russian, albeit with my limited skills, one would even hear something else. I am reminded of my "I don't give a rat's ass!" comment and how my Russian friends tried to transliterate that one. It ended up with a few hours at the bar over vodka reminiscing over various similar senseless remarks in both languages.

But words mean something, but as Alice remarked, all too often they mean what we meant them to not what they are thought to have meant.

It would help that politicians who have really not spent time in other countries try to get better translators and not try to do it on the fly. This even applies to American English and that language spoken in Britain! Or parts of New Jersey.



Labels: [Russia](#)

THURSDAY, OCTOBER 22, 2015

MIT AND CLIMATE CHANGE

[MIT](#) announced its "Plan" to deal with Climate Change. To that end they announced:

...MIT has developed a five-year plan to enhance its efforts in five areas of climate action, whose elements have consensus support within the MIT community:

- *research to further understand climate change and advance solutions to mitigate and adapt to it;*
- *the acceleration of low-carbon energy technology via eight new research centers;*
- *the development of enhanced educational programs on climate change;*
- *new tools to share climate information globally; and*
- *measures to reduce carbon use on the MIT campus.*

The process is laudable but as one commentator noted:

You missed Step One...convince the skeptics of the validity of your conclusions. The non-believers are not bad people, they just do not understand the basis for your conclusions. To some the names of scientists and MIT itself are not convincing enough to get them to commit. They see MIT getting years of funding as self serving and therefore mistrust the conclusions.

Indeed the steps seems a bit self serving. MIT is already and has been at it for years examining alternative, ie non carbon based, energy, understanding the mechanisms behind various pollutants and carbon off shoots, as well as large scale networks and the like. Thus one wonders what is new here other than more overhead and possibly less research.

The comment indicating that the non-believers are not "bad people" is quite valid and unlike those who attack anyone who thinks differently tends to use logic and facts and not vitriolic methods to communicate.

Unlike some who look at their political opposition as the "enemy" one must look at them as groups with whom they would engage in discussion.



Labels: [Climate Issues](#), [MIT](#)

MORE CRISPRS

The [NIH](#) has announced several new additions to the CRISPR world of slicing proteins. As they state:

An international team of CRISPR-Cas researchers has identified three new naturally-occurring systems that show potential for genome editing. The discovery and characterization of these systems is expected to further expand the genome editing toolbox, opening new avenues for biomedical research. The research, published today in the journal Molecular Cell, was supported in part by the National Institutes of Health. "This work shows a path to discovery of

novel CRISPR-Cas systems with diverse properties, which are demonstrated here in direct experiments,” said Eugene Koonin, Ph.D., senior investigator at the National Center for Biotechnology Information (NCBI), National Library of Medicine (NLM), part of the NIH. “The most remarkable aspect of the story is how evolution has achieved a broad repertoire of biological activities, a feat we can take advantage of for new genome manipulation tools.” Enzymes from the CRISPR system are revolutionizing the field of genomics, allowing researchers to target specific regions of the genome and edit DNA at precise locations.

“CRISPR” stands for Clustered Regularly Interspaced Short Palindromic Repeats, which are key components of a system used by bacteria to defend against invading viruses. Cas9 — one of the enzymes produced by the CRISPR system — binds to the DNA in a highly sequence-specific manner and cuts it, allowing precise manipulation of a region of DNA. Enzymes such as Cas9 provide researchers with a gene editing tool that is faster, less expensive and more precise than previously developed methods. The three newly-characterized systems share some features with Cas9 and Cpf1, a recently characterized CRISPR enzyme, but have unique properties that could potentially be exploited for novel genome editing applications. This study highlights the diversity of CRISPR systems, which can be leveraged to develop more efficient, effective, and precise ways to edit DNA.

The "toolbox" for gene editing is expanding at an ever increasing rate. The original Cas9 enzyme which was the baseline for CRISPR work cut the gene at specific but opposite sites. That was good but the newer versions allow for "sticky" ends which dramatically reduce the chance of recombination errors.

We believe that this is but the beginning of an ever expanding set of such tools and well worth following.



Labels: [CRISPR](#)

TUESDAY, OCTOBER 20, 2015

[HUMAN INTELLIGENCE](#)

In the spy game there are various means and methods to gather information. The US has been for several decades building a massive set of technical means, including the NSA and its collection of every bit of useless information. The other side of the spy game is human intel, namely stuff gathered by sitting in a bar or coffee shop, pretending to be someone else, or just looking around to see what is happening. The US under previous Spy Masters and Presidents has eschewed this human form, too messy, and requires certain types of people.

Now along comes the CIA DCI hack. In [Wired](#) is the tale, and you really can't make this up. It is from the script of Three Days of the Condor. A group of sharp "kids" managed to elicit "secure" information from Verizon, surprise surprise, and then with that hacked the DCI's email account on AOL. Verizon should never have bought that but that is a tale for another day.

They state:

The hacker, who says he's under 20 years old, told WIRED that he wasn't working alone but that he and two other people worked on the breach. He says they first did a reverse lookup of Brennan's mobile phone number to discover that he was a Verizon customer. Then one of them posed as a Verizon technician and called the company asking for details about Brennan's account. "[W]e told them we work for Verizon and we have a customer on scheduled callback," he told WIRED. The caller told Verizon that he was unable to access Verizon's customer database on his own because "our tools were down." After providing the Verizon employee with a fabricated employee Vcode—a unique code the he says Verizon assigns employees—they got the information they were seeking. This included Brennan's account number, his four-digit PIN, the backup mobile number on the account, Brennan's AOL email address and the last four digits on his bank card.

For those who do not remember, that is Human Intel, they did not need to have satellites or massive data centers. I wonder if this will change anything? Doubtful.....after all they are Government employees, perhaps Verizon should shake the tree a bit.



Labels: [Government](#)

BROADBAND ON COPPER?

There is a lot of copper wire around which has provided the old telephone service we know and understand. I still have a classic old copper based phone, use it in the office all the time, good quality voice and secure, unless there is some Government tap. But that is another story.

Now people have been eschewing copper as being too slow but Shannon's Theorem really does not say that and I recall meetings at the old Bellcore some 30 years ago where they discussed Mbps speeds. Now BT in the UK has Gbps speeds.

[Total Telecom](#) reports:

BT on Tuesday came out fighting in favour of copper, revealing it has reached connection speeds topping 5 Gbps using XG.fast technology. The tests were carried out in partnership with Alcatel-Lucent at the U.K. incumbent's Adastral Park R&D centre in Suffolk. It achieved aggregate speeds of 5.6 Gbps over 35 metres of BT cable, a new record for full-duplex data transmission over a standard single line, according to the telco. At more than 100 metres, the speed dropped substantially, albeit to a still impressive 1.8 Gbps. BT said this is significant because most U.K. homes are within 100 metres of their nearest distribution point.

Theoretically one can use this existing infrastructure with a wireless backbone to get those Gbps speeds to homes out in the "no where" lands. You do not need the millions that New York is proposing, you can do it now with what is there. Just get the consumer to buy the modem!



Labels: [Broadband](#)

MONDAY, OCTOBER 19, 2015

HOW LONG WILL MICROSOFT SURVIVE

One thing I learned in business was "*If all else fails, listen to the customer.*" That apparently never occurs to Microsoft. Take a recent complaint about updates on W10.

As [PCWorld](#) notes:

If there's one Microsoft policy that has drawn the ire of IT managers over the course of its Windows 10 rollout, it's the company's decision to require that all users install cumulative updates without control over which packages a system receives. It's such a point of contention that a group of thousands of grumpy customers have petitioned company CEO Satya Nadella to change Windows 10 update practices. Customers want more control over what's added to their systems, but they're also concerned about what happens when they can't avoid installing an update that breaks key functionality. Cumulative updates include all the updates Microsoft has released for the branch of Windows 10 a customer is using.

This is just another one of hundreds of "it's our way or the highway" attitude of Microsoft. I think I have finally disabled the never ending attempts to download and install W10 on perfectly fine systems. But on W10 apparently no chance!



Labels: [Microsoft](#)

ELIMINATING CANCER

Economists are often thought of as the broad thinkers who can provide out world with the best ideas on how to solve problems and improve our lives. Take Global Warming and carbon emissions. Their solution is a "free market" approach of taxing carbon. As noted in a recent [Nature](#) piece on an upcoming meeting:

A global carbon price — so far excluded from consideration in international negotiations — would be the ideal basis for a common commitment in our view. A price is easy to agree and handle, relatively fair, less vulnerable to gaming than global cap-and-trade systems, and consistent with climate policies already in place, such as fossil-fuel taxes and emissions cap-and-trade.

Now since this is considered the approach, not research and development, not engineering, but taxing, I thought we could do the same for Cancer. We know that cancer kills people, rather harshly at that, so why not have a Cancer Tax, stop all that R&D, close down the hospitals, eliminate the drugs; just tax it. It is a Jonathan Swift like solution. Swift suggested cooking Irish babies to eliminate the problem, a bit harsh but many English took his suggestion to heart, so we would just tax Cancer, not the victims, just the disease.

Then according to economists it should "clear the market", and with the tax money we could allow the Government to spend more, say on increasing Government salaries. With no hospitals,

no doctors, no drugs, we drop health care burden to near zero, with people dying off real quickly, we reduce the demand for Social Security and Medicare, and with the added taxes, well we get a balanced budget!

Just think how smart these economists are! We don't need R&D, that just allows people to survive longer, with a cure, we need more people turnover. Thus the Cancer Tax, also a Carbon Tax, and yes we can most likely tax anything the Government folks think is bad for us.

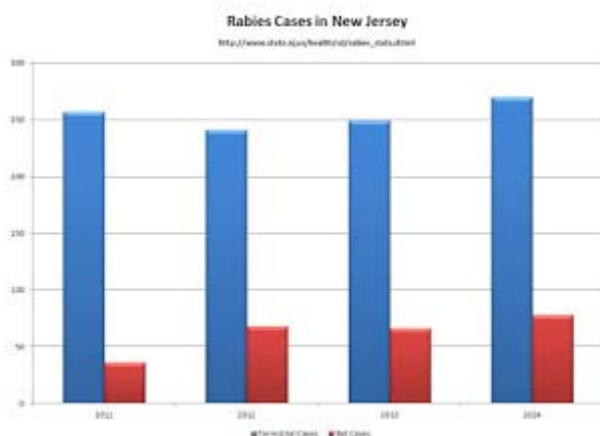
I think there is the view that if all one has is a hammer then everything one sees looks like a nail. It may very well apply here.



Labels: [Economics](#)

SUNDAY, OCTOBER 18, 2015

BATS



Most of us have never seen bats. Bats are those rodents with wings that fly around at night allegedly eating insects. We are told the insects are bad for us and ipso facto the bats are good for us. Now bats carry rabies and one in ten bats in New Jersey are rabid. Rabies is a horrible disease, a viral infection, single stranded RNA virus, that slowly eats up the nervous system turning the victim into a drooling and neurologically deficient slime mold.

Now one must remember that the Government has declared the "little brown bat" a protected species. It may kill humans but we must not touch this carrier of deadly disease. It is akin to the Administration declaring ISIS a protected class and anything we do to them a "hate crime". Only Government can make such a logical nexus.

As the [NJ Health Department](#) states:

The 5 year average of bat rabies cases from 2010 - 2014 was 57 per year. In 2014, 78 bats (out of 1,385 submitted for testing) were diagnosed with rabies, representing the highest number of rabid bats documented in a calendar year. However, the percentage of confirmed rabid bats has stayed relatively constant at about 4 - 6% of the bats submitted for testing.

In 2013 there were 66 rabies cases from bats in New Jersey. Much more than ISIS attacks. Now [NH PR](#), that left wing radio station in NH, in fact almost the only radio in Northern NH, which is why it is so conservative, states:

Obviously, bats are really important in our eco-system because they are the greatest predator of nighttime insects. As von Oettengen explained, NH hosts eight species of bats (among them: Little brown bat, Long-eared bat, Tri-colored bat, Small-footed bat, Big-brown bat), so that adds up to a lot of insects consumed.

Now what is so wrong with these insects? I like bees, I like wasps, I even like Lady Bugs. So these vultures go out at night and consume all the insects pollinating my plants! These folks must be plant haters. No nocturnal plants get pollinated!

The NHPR continues:

There are small things we can do to help. If you're comfortable living with bats in your attic, eaves or barn, leave them be. Or you could put up a bat house. Preston put one up in her yard in a hot, sunny place and had nineteen bats living there by the end of the summer.

Yeah, try and sell a house with bat fecal matter all in the attic infested with rabies! Are you out of your mind! Well now let me tell you what I really think of bats.....



Labels: [Commentary](#)

FRIDAY, OCTOBER 16, 2015

[MICROSOFT AND WINDOWS 10](#)

Microsoft has tried over 40 times to download W10 to one of my computers, about the same for the other 8. That means 320 possible attempts. I think I finally shut it out by finding solutions of Google. But hour after hour of wasted time and my bandwidth. I have one new laptop with W10, it is OK, but I guess I will soon be seeing pop up ads from Microsoft. I would never buy anything from them nor would I consider buying from anyone who uses them to advertise. But alas the company in my opinion is going to the dogs.

I want an OS, so sell me one, don't make my life horrible with its attempts to monetize a relationship that does not exist. I really dislike Microsoft, but I also dislike colonoscopies and understand that they may be beneficial, in a limited amount.

I wonder if some smart lawyer will find a way to file a massive class action suit. The time wasted avoiding W10 and the time and productivity lost if perchance you download it and your drivers all die off. I assume the Microsoft lawyers have thought of this, perhaps not. This could make for a very wealthy law firm. Perhaps...not being a lawyer...I seen many in action...but this smells like it could have legs. Watch for the shorts on Microsoft...time will tell.



Labels: [Microsoft](#)

[MEDICARE AND WHO PAYS?](#)

Over the past few years I have analyzed the falacy that Medicare is a "gift" to those getting it. In the [NY Times](#) today there is a piece on the increased costs of Medicare. They state:

Even some affluent beneficiaries could struggle with the higher costs. For those with incomes of more than \$214,000 a year, Medicare actuaries say, premiums next year could exceed \$500 a month, up from about \$335, if Congress does not change the law. Financially struggling state governments are expressing concern because they are responsible for many low-income beneficiaries.

Now this means that a family making \$214,000 in New York or New Jersey is paying the highest income tax for Federal and State and in addition is paying 3% (actually 2.9%) on the \$214,000, or about \$6,000 per person, plus a MediGap plan of about \$4,000 per person, so we have \$20,000 per family on a \$214,000 salary or almost 10% of the salary going for Medicare in addition to 50 years of contributions!

Whereas some 30 year old with no job and a family gets to ride for \$50 per month!

What is wrong with this picture? Oh and yes, there is a deductible as well, and drugs are barely covered. And also these costs are NOT tax deductible! So this is what the ACA has brought, taxing the older folks to pay for the younger ones without jobs. Generational warfare?



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

THURSDAY, OCTOBER 15, 2015

[EXCELLENT TPP SUMMARY](#)

The TPP trade agreement may have far reaching implications. The [CFR](#) has an excellent summary that is well worth reading. Of course the muddle is in the details which we have little access to. But reading the CFR overview shows how broad this is.



Labels: [Government](#)

WEDNESDAY, OCTOBER 14, 2015

["SEEK, AND YE SHALL FIND": MATTHEW 7:7](#)

One of the interesting effects of modern medicine is that we can find things that we never thought were there. A hundred years ago one went to the physician when one had a complaint. The physician then examined the patient and considered the complaints and then made a diagnosis, if possible. The a treatment is available was prescribed.

Today we do lots of tests and find things we would never have susp[ected] were there, many just the vageais of the human. The more we look the more things we are likely to find. Kidney stones, gall stones, osteoarthritis, etc.

Now along comes a new set of tests for those who can chell out \$50,000 each time, the full body MRI and full genome scan. As [Xconomy](#) reports:

Top executives and others who come to Health Nucleus for their annual physical will receive a battery of medical tests, including many that are not FDA-approved because they are so new (and unproven), said Brar, who is the current president of the American Academy of Private Physicians. Health Nucleus was able to sidestep FDA restrictions on the clinical use of experimental tests by operating—at least initially—as a clinical research project under Institutional Research Board (IRB) protocols,

A comprehensive workup at Health Nucleus would include:

—Whole genome sequencing of all 6 billion DNA base pairs (According to Health Nucleus, most DNA tests today examine less than 2 percent of the entire human genome.)

—Genome sequencing of the microbiome—the microorganisms that live in the human gut and on the skin.

—Metabolome sequencing of the small-molecule metabolites found in the human body.

—Whole-body medical imaging with advanced MRI (medical resonance imaging) from GE that enables Health Nucleus to quantify the exact volumes of unhealthy visceral fat, the various components of the brain and other tissues that may reveal the progress of disease.

And of course the price:

Executives and others who arrive for a Health Nucleus checkup would pay \$25,000 or \$50,000 each, depending on the number of people in the group

That is just for all this data. The problem with this approach is in my opinion several fold:

1. Clearly those with the \$50K get the tests, the rest of humanity do not.
2. Tests will always find something, the incidentaloma. Then what?
3. Research does not research just those people who can pay to be Lab rats, it should cover a broader base of the population.
4. When do we treat something? That is always the question. Take Prostate Cancer. If your family history is such that aggressive types was present at a close proximity, say First degree, then a good bayesian would treat. If however no one ever died in your family of the disease then perhaps one could wait.
5. The data is overwhelming, and one should have a plan and process to deal with it. Not clear here.
6. Cancer is real sneaky. Yes germ line genetic problems may be a warning, say BRCA. Yet having your genome may not be the answer for somatic cells which have become methylated. Or

we have mRNAs popping up where they should not.

One suspects this type of thing will appeal to many who can afford the tests, but larger samples would be useful.



Labels: [Health Care](#)

FRIDAY, OCTOBER 9, 2015

[SAINT VLADIMIR](#)



When I returned to Russia the first time after the collapse, I believe it was 1993, it was to Saint Petersburg, not Leningrad. What I noticed even then was that the Churches were filled, weddings, funerals, old women, young people. In less than 3 years religion returned.

Then for my ten years in and out of Moscow I saw the churches rebuilt to a state that exceeded even the best under the Czars. The Metropolitan of Moscow, the alleged, and historically the actual, successor to the Bishops of the Church, regained their positions and aligned themselves with the Government, Putin especially.

In the Montefiore piece in today's [NY Times](#) I believe he gets some but not all of the depth. His piece should be read, especially by those in Washington. They seem clueless. I suspect they have no idea of the 30 Years War, but I put that aside.

You see the Metropolitan in Moscow is the successor to the Bishop of Constantinople, a clear un-broken line back to Peter. The Bishop of Rome was abandoned during the Avignon Papacy, when the French Kings controlled what was the "Papacy", the Bishop of Rome, who moved to Avignon. That broke the unbroken line. Moscow sees itself unbroken, Rome was demolished for over 100 years. No wonder Moscow is not interested in a conversation.

But the Metropolitan speaks for the people and he speaks for Putin. The Orthodox Church has replaced Communism in a way Lenin and Stalin would never have believed. The Montefiore piece is only part of the tale. Cyril and Methodius sent Christianity to the Slavs and ironically it had become part of the Russian soul. They have a strong and well founded belief in their destiny, and Putin is not acting foolishly, he is acting to accomplish that destiny.

Remember the window in Prague when the Papal delegate was thrown out onto the dung heap. Thirty years of religious war. Who will be landing on the dung heap this time. Doubt it will be Saint Vladimir.



Labels: [Russia](#)

WEDNESDAY, OCTOBER 7, 2015

[KENDALL SQUARE](#)

I have seen Kendall Square for well over 55 years and have seen it from the days of a well worn 19th Century factory location to what it is today, a hub for biotech.



In a recent article at [A Slice of MIT](#) they discuss the evolution of the area. They state:

As part of the new initiative, the MIT Museum will move to a new building next to the T station, opening out onto a park with Ping-Pong tables, fire pits in winter, public art, and other amenities...all ventures will set aside 5 percent of their square footage for 'innovation space.' ”
... “You could imagine years from now going and tracing something back to Kendall Square that really changed the world,’ says MIT Treasurer Israel Ruiz “If through our efforts we will have made it possible to solve something that we otherwise wouldn’t have been able to solve, that will be the best prize.”

The problem that they seem to have missed, and missed in a really big way is that of traffic flow. It appears that Google has absconded with all the parking places in the Marriott garage, and the parking rates if one existed have gone from \$11.50 a day to over \$50! Beats mid-town New York. Public transportation on the T is useless if you are trying to get to one of the buildings inside the area, halfway between the Green and Red Lines. Traffic flow still has to deal with the narrow streets great for 18th century horse traffic.

It would have been nice if MIT and the City of Cambridge would have done some Urban Planning. Just putting in more buildings does not work. It comes to a stand still.



Labels: [Commentary](#)

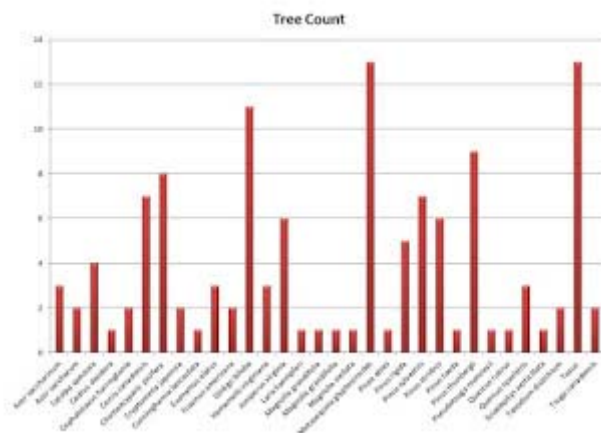
THURSDAY, OCTOBER 1, 2015

TREES AND DIVERSITY

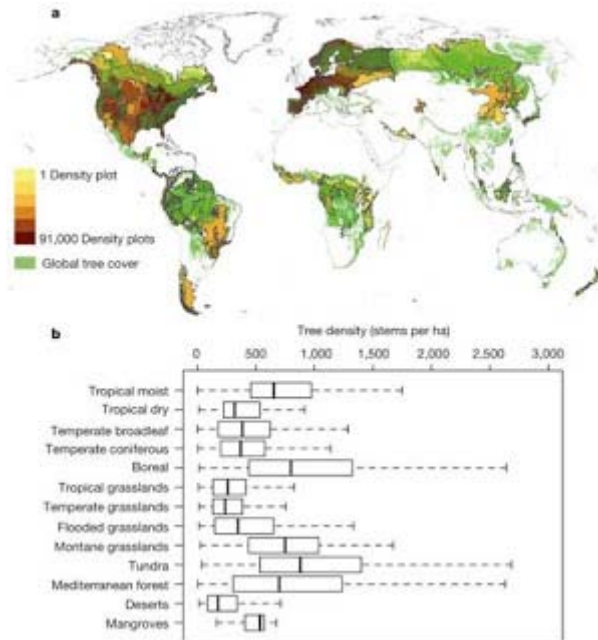
In a recent [Nature](#) article the authors estimate the number of trees on the globe. Their conclusion is:

The global extent and distribution of forest trees is central to our understanding of the terrestrial biosphere. We provide the first spatially continuous map of forest tree density at a global scale. This map reveals that the global number of trees is approximately 3.04 trillion, an order of magnitude higher than the previous estimate. Of these trees, approximately 1.39 trillion exist in tropical and subtropical forests, with 0.74 trillion in boreal regions and 0.61 trillion in temperate regions. Biome-level trends in tree density demonstrate the importance of climate and topography in controlling local tree densities at finer scales, as well as the overwhelming effect of humans across most of the world. Based on our projected tree densities, we estimate that over 15 billion trees are cut down each year, and the global number of trees has fallen by approximately 46% since the start of human civilization.

Now I decided to map my small patch of land in New Jersey, about 13,000 sq feet. Some 2,000 sq feet is my Hemerocallis "Lab" where we do genetic research. There is a house, a driveway and some 124 trees. Yes, some 124 trees, of some 32 different species. I have the densest collection of Ginkgos and Metasequoia in North America. Did not know that until I did the count. Both from China and both extinct in nature. And both bearing seed and quite healthy.



The above is the details. Now if we compare this to the Nature article we see:



Note that from the above Nature date our density of 928 trees/Hectare is well near the highest level on the chart.

So what does this say? Well we humans are lovers of plants, in my case specimen trees and Hemerocallis. We have managed to repopulate near extinct species.

There may be hope after all.



Labels: [Commentary](#), [Global Warming](#)

WEDNESDAY, SEPTEMBER 30, 2015

IS MEANINGFUL USE MEANINGFUL?

The EHR/EHR is moving forward in its Government mandated manner but signs of revolt may still be simmering. In [MedPageToday](#) they report:

...Amherst, Mass, said that three of the physicians who left her practice in the last year did so because of frustration with the Meaningful Use requirements. She said the practice underwent an expensive audit associated with the program that lasted more than a year, which had the ironic effect of delaying other programs aimed at improving patients' health. If Stage 3 goes into effect, ... said, she will be obliged to stop accepting Medicare patients, leaving 1,500 elderly and disabled patients without a primary care doctor. "I couldn't take care of my patients and take care of myself," she said. Another physician mocked the requirement for a certain percentage of patients to use online patient portals to communicate with doctors. He said he has his secretary log in his patients, most of whom are geriatric, so that they can send "a note of clinical relevance... which says 'hi'."

There are levels of problems here. First is the ability of the physician to enter "meaningful" data.

For the most part it is cut and paste. Second is the ability to look at trends. Medicine often is seeing if anything has changed; HbA1c, PSA, BP, weight, etc. Change and rates of change are critical. I see this in monitoring HbA1c and PSA levels, yes PSA levels. Sample blood glucose are useless, HbA1c is a 90 day average. It has value. Single PSA is meaningless, velocity is prognostic. Most EHR make one fumble for those metrics. Third, try and get them to interconnect! Even in an integrated hospital system. Take New York Presbyterian. Cornell does not communicate with Columbia, and patient portals are separate and patient appointments are catch as catch can.

They continue

...a pediatrician from Leominster, Mass., agreed that certain metrics were inappropriate for certain specialties. "I think of this every time I check the blood pressure on a screaming 3-year-old who has an ear infection." And a number of physicians, ..., commented on the futility of punishing providers for the failures of technology vendors. Stack said he has the knowledge and expertise to take a patient whose liver has ruptured through numerous protocols and into the operating room in just enough time to keep the patient from bleeding to death internally. "I shouldn't have to write the software code for the electronic health record at the same time."

It continues:

a professor at Harvard University and a researcher for the Children's Hospital Informatics Program at Boston Children's Hospital, said EHRs should be as adaptable as the apps on an iPhone. "If the makers of Angry Birds want to add a new bird they don't have to fly to Cupertino... to figure out how to do that."

I could not have said it better myself!



Labels: [Electronic Medical Records](#)

TUESDAY, SEPTEMBER 29, 2015

GOT YOUR GOAT



I like the Canadians. They seem to give us our best comedians and good stories.

In the [National Post](#) we have the one about the goat:

A goat that bunkered down at the Tim Hortons in Martensville, Saskatchewan, has been reunited with its owners. Warman RCMP were called to the coffee shop Sunday around 4 a.m. The goat had walked into the entranceway of the building through the automatic doors and settled down for a nap. Police arrived and loaded the animal into their cruiser.

Yep, police called for a goat. Now for those not familiar with goats, this is not uncommon.



Labels: [Commentary](#)

[HOW TO SPEND MONEY, OURS!](#)



It was not enough for the FEDs under the Stimulus to dump billions into broadband, with questionable results at best, but now NY State appears to be jumping in as well with State Taxpayer money.

The [New York Broadband](#) plan will, it appears, give away some \$500 million to build out broadband. They state:

Governor Cuomo has launched the largest and most ambitious investment in statewide broadband deployment in the country. Through the creation of the \$500 million New NY Broadband Program, the State of New York will incentivize broadband providers to expand and upgrade networks to ensure that they reach all underserved and unserved communities in the State. The Program is designed to ensure that every New Yorker has access to high-speed Internet. The Program will be implemented by the end of 2018.

They also do address wireless which we believe is the only solution to such areas as rural New York State. BUT, who has the license? You just can't do wireless, you need a license, and most have been given out already. Any why 25 Mbps and 100 Mbps. I am always amazed at why

someone who decides to live in the wilderness need our taxpayer money for 100 Mbps access when they most likely do not have indoor toilets!

Perhaps a state voter referendum would help here.



Labels: [Broadband](#)

[DETECTING PROSTATE CANCER](#)

Prostate Cancer is a high incidence cancer in men with a small percentage being very aggressive and potentially lethal. PSA has been used for over two decades and despite the USPTF negative stand it still finds use, especially in men with a family history of aggressive PCa.

However the next step in diagnosis is a biopsy, and the classic multi core approach has its own problems. Namely it samples at best 2-3% of the prostate and for early stage PCa this may not be adequate.

Fused MRI and TRUS is now coming of age and is used more frequently. In a recent paper by [Bodman et al](#) the authors have examined the performance of such tests.

They report:

MRI/TRUS fusion–assisted targeted biopsy improves the detection rate of prostate cancer after a previous negative biopsy. Targeted biopsy is more likely to reveal clinically significant cancer than systematic biopsy; nevertheless, systematic biopsy should still be performed, even if the MRI findings are negative...The MRI/TRUS fusion biopsy approach is a promising method for detecting prostate cancer after a prior negative histological result. Combining MRI-guided targeted biopsies of suspicious lesions with a systematic 12-core biopsy protocol increases the overall cancer detection rate and leads to more clinically relevant cancers being found. Our data suggests that taking additional fusion-guided biopsies from lesions with a low risk score, based on MRI analysis, is not necessary.

Systematic biopsy remains necessary even when MRI results in inconspicuous images. The strategy of a single targeted biopsy without a systematic biopsy is not to be recommended. MRI-guided fusion biopsy holds great promise for the future but must still undergo careful verification. As no unified technical standardization or systematic training exist for this method to date, a high amount of examiner experience is necessary. Finally, because the MRI/TRUS fusion strategy has not yet been considered in the current S3 guidelines for primary diagnosis of prostate cancer, the value of this method should be analyzed in large multicenter studies.

Overall the results indicated:

Grayscale TRUS: Sensitivity % 18.3, Specificity % 90.4

MRI/TRUS: Sensitivity % 58, Specificity % 93

This can be a substantial improvement. It would be useful to have a similar model as we had developed for Grayscale TRUS using a Bayesian model.

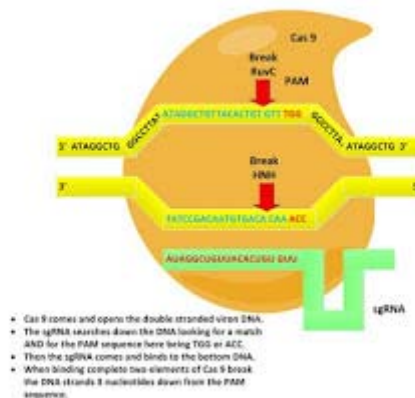


Labels: [Cancer](#)

TUESDAY, SEPTEMBER 29, 2015

[MORE ON CRISPRs](#)

We have examined CRISPRs for the past few years since their introduction. Initially we had a CRISPR with a Cas9 molecule which managed to cut DNA at specific spots. The CRISPR was designed to match a specific sequence and the Cas9 was able to recognize the PAM sequences and using certain portions of the Cas9 it could then “break” both strands at opposite positions of the DNA, a specific set of base pairs from the end of the PAM.



This then becomes a useful tool in an ever growing tool-box for DNA modification. In bacteria this cut is applied to viral DNA or RNA and it is a “natural” immune system in the bacteria. In other cells, plants and animals, it enables precise and specific gene editing.

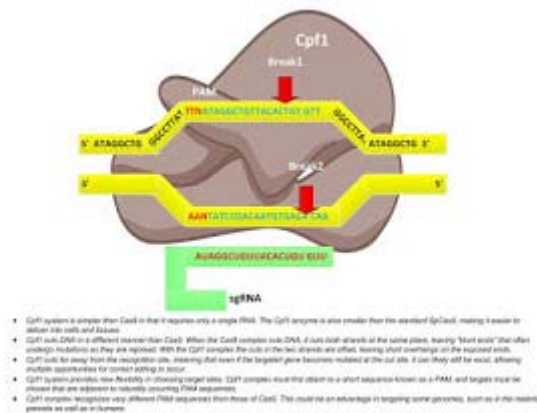
In a recent paper from Zhang’s Lab at Broad they have identified another protein which acts like Cas9. This new system is called CRISPR-Cpf1 and is identified as a class 2 CRISPR system^{5[1]}. Specifically Cpf1 is a CRISPR-associated two-component RNA-programmable DNA nuclease. It functions in a manner similar to Cas9 and targeted DNA is cleaved as a 5-nt staggered cut distal to a 5’ T-rich PAM. They have also identified two Cpf1 orthologs exhibit robust nuclease activity in human cells. In the paper in Cell they state:

The microbial adaptive immune system CRISPR mediates defense against foreign genetic elements through two classes of RNA-guided nuclease effectors. Class 1 effectors utilize multi-protein complexes, whereas class 2 effectors rely on single-component effector proteins such as

^{5[1]} <http://www.cell.com/cell/abstract/S0092-8674%2815%2901200-3>

the well-characterized Cas9. Here, we report characterization of Cpf1, a putative class 2 CRISPR effector. We demonstrate that Cpf1 mediates robust DNA interference with features distinct from Cas9. Cpf1 is a single RNA-guided endonuclease lacking tracrRNA, and it utilizes a T-rich protospacer-adjacent motif. Moreover, Cpf1 cleaves DNA via a staggered DNA double-stranded break. Out of 16 Cpf1-family proteins, we identified two candidate enzymes from *Acidominococcus* and *Lachnospiraceae*, with efficient genome-editing activity in human cells. Identifying this mechanism of interference broadens our understanding of CRISPR-Cas systems and advances their genome editing applications.

The figure below depicts their interpretation of its functioning.



It is worth comparing these two mechanisms. The Cas9 is a bit more rigid than Cpf1. As noted above and as discussed in the paper and elsewhere, this new protein complex does what Cas9 did but with many more attractive features.

In an MIT press release they state^{6[2]}:

The newly described Cpf1 system differs in several important ways from the previously described Cas9, with significant implications for research and therapeutics, as well as for business and intellectual property:

First: In its natural form, the DNA-cutting enzyme Cas9 forms a complex with two small RNAs, both of which are required for the cutting activity. The Cpf1 system is simpler in that it requires only a single RNA. The Cpf1 enzyme is also smaller than the standard SpCas9, making it easier to deliver into cells and tissues.

Second, and perhaps most significantly: Cpf1 cuts DNA in a different manner than Cas9. When the Cas9 complex cuts DNA, it cuts both strands at the same place, leaving "blunt ends"

^{6[2]} <http://mcgovern.mit.edu/news/news/system-for-genome-editing-could-increase-power-of-genome-engineering/>

that often undergo mutations as they are rejoined. With the Cpf1 complex the cuts in the two strands are offset, leaving short overhangs on the exposed ends. This is expected to help with precise insertion, allowing researchers to integrate a piece of DNA more efficiently and accurately.

Third: Cpf1 cuts far away from the recognition site, meaning that even if the targeted gene becomes mutated at the cut site, it can likely still be recut, allowing multiple opportunities for correct editing to occur.

Fourth: The Cpf1 system provides new flexibility in choosing target sites. Like Cas9, the Cpf1 complex must first attach to a short sequence known as a PAM, and targets must be chosen that are adjacent to naturally occurring PAM sequences. The Cpf1 complex recognizes very different PAM sequences from those of Cas9. This could be an advantage in targeting some genomes, such as in the malaria parasite as well as in humans.

The above four properties are quite compelling and worthy of note. Cas9 did have the problem of cutting at opposite sites and trusting that a competent and non-aberrant re-fusion was made. This discovery, assumedly after hundreds of attempts, opens the door on another dimension of the CRISPR world.

As is noted in Xconomy they state^{7[3]}:

... the Cpf1 work is still in its infancy. It's well behind CRISPR/Cas9—which researchers have used to make changes in the cells of all types of organisms, including humans. Several companies are working with CRISPR/Cas9 to create therapeutics for genetic disease. None have reached clinical trials yet.

The issue here is just how extensive is Cpf1 development and how readily available is the technology. The above presentation seems to imply an early stage. They continue:

But work with CRISPR/Cas9 to modify the human germline—eggs, sperm, and embryos—is also coming faster than expected, sparking ethical concerns. An international summit on the topic is scheduled for December in Washington, DC.

Meanwhile, researchers around the world are working to find new versions of Cas9, or new enzymes entirely, like Cpf1, to make the whole enterprise easier. “There is little doubt that... there are additional systems with distinctive characteristics that await exploration and could further enhance genome editing and other areas of biotechnology as well as shed light on the evolution of these defense systems,” Zhang (pictured above speaking at a 2014 Xconomy event) and his coauthors write in the Cell paper.

^{7[3]} <http://www.xconomy.com/boston/2015/09/25/crispr-update-could-make-gene-edits-easier-discoverers-say/>

In other words, Cpf1 is the tip of the iceberg. I'll outline three differences between Cpf1 and Cas9 that the paper's authors have highlighted as potentially important for the field. First, for those unfamiliar with CRISPR and gene editing, it helps to think of these enzymes as molecular scissors. Bacteria use them in the wild to defend themselves against invading viruses, cutting up the viral RNA and storing the pieces in a kind of immune system memory bank.

It was only in recent years that the natural system has been modified and harnessed as a gene editing tool. The enzyme—a protein—and its guide—made from RNA—need to be sent into a cell (that's one difficult trick) and hit the right spot (that's another difficult trick).

The following is the Xconomy author's description. It is a restatement of what was in the MIT release but rephrases the key differences:

Here's why Zhang and his co-authors think Cpf1 could have advantages over Cas9:

—Cpf1 only uses one strand of RNA as a guide to reach its target gene. Cas9 uses two strands. A single-strand system might lead to simpler, cheaper designs and easier delivery of the enzyme-guide complex into cells.

—Once delivered into the cell's nucleus, Cpf1 makes staggered double-stranded cuts in the target DNA, whereas Cas9 cuts both DNA strands in the same location. This could be important, Zhang and colleagues write, because the staggered ends make it easier to insert a new gene after the old one is removed. That could help get around one of the hurdles of Cas9: Scientists say using Cas9 to replace an old gene with a new one has proven far more difficult than simply cutting out a gene.

—When Cpf1 homes in on a gene, it actually makes the cut off to the side, relatively speaking—farther down the DNA strand. (Imagine your friend holding a string in the exact location that needs snipping. You don't cut her finger; you cut off to the side.) Zhang and colleagues write that this could be a "potentially useful feature" because it preserves the target site for subsequent rounds of editing.

The off-setting of the splices is a significantly better method. It gives the "sticky" ends approach and tends to much fewer errors. This alone could make this much more attractive.

In a Nature discussion of these results they state^{8[4]}:

But now one of the technique's pioneers thinks that he has found a way to make CRISPR even simpler and more precise. In a paper published in Cell on 25 September, a team led by synthetic biologist Feng Zhang of the Broad Institute in Cambridge, Massachusetts, reports the discovery of a protein called Cpf1 that may overcome one of CRISPR-Cas9's few limitations; although

^{8[4]} <http://www.nature.com/news/alternative-crispr-system-could-improve-genome-editing-1.18432>

the system works well for disabling genes, it is often difficult to truly edit them by replacing one DNA sequence with another.

The CRISPR/Cas9 system evolved as a way for bacteria and archaea to defend themselves against invading viruses. It is found in a wide range of these organisms, and uses an enzyme called Cas9 to cut DNA at a site specified by 'guide' strands of RNA. Researchers have turned CRISPR/Cas9 into a molecular-biology powerhouse that can be used in other organisms. The cuts made by the enzyme are repaired by the cell's natural DNA-repair processes. Good, better, best?

CRISPR is much simpler than previous gene-editing methods, but Zhang thought there was still room for improvement.

*So he and his colleagues searched the bacterial kingdom to find an alternative to the Cas9 enzyme commonly used in laboratories. In April, they reported that they had discovered a smaller version of Cas9 in the bacterium *Staphylococcus aureus*. The small size makes the enzyme easier to shuttle into mature cells — a crucial destination for some potential therapies.*

The team was also intrigued by Cpf1, a protein that looks very different from Cas9, but is present in some bacteria with CRISPR. The scientists evaluated Cpf1 enzymes from 16 different bacteria, eventually finding two that could cut human DNA.

They also uncovered some curious differences between how Cpf1 and Cas9 work. Cas9 requires two RNA molecules to cut DNA; Cpf1 needs only one. The proteins also cut DNA at different places, offering researchers more options when selecting a site to edit. "This opens up a lot of possibilities for all the things we could not target before," says epigeneticist Luca Magnani of Imperial College London.

Cpf1 also cuts DNA in a different way. Cas9 cuts both strands in a DNA molecule at the same position, leaving behind what molecular biologists call 'blunt' ends. But Cpf1 leaves one strand longer than the other, creating a 'sticky' end. Blunt ends are not as easy to work with: a DNA sequence could be inserted in either end, for example, whereas a sticky end will only pair with a complementary sticky end.

"The sticky ends carry information that can direct the insertion of the DNA," says Zhang. "It makes the insertion much more controllable."

Zhang's team is now working to use these sticky ends to improve the frequency with which researchers can replace a natural DNA sequence. Cuts left by Cas9 tend to be repaired by sticking the two ends back together, in a relatively sloppy repair process that can leave errors. Although it is possible that the cell will instead insert a designated, new sequence at that site, that kind of repair occurs at a much lower frequency. Zhang hopes that the unique properties of how Cpf1 cuts may be harnessed to make such insertions more frequent.

In contrast we also have an article in The Economist which states^{9[5]}:

CRISPR-Cpf1 may also be better than CRISPR-Cas9 in other ways. Cpf1 is a smaller and simpler enzyme (known technically as an endonuclease) than Cas9, which means it will be easier to deliver to the cells whose genes need modifying. And its slightly offset cuts to double-stranded DNA will help researchers to insert genetic patches more efficiently and accurately.

Its discovery also raises the question of how many other endonuclease-based systems are out there in the world's bacteria. Viral infection is a serious threat to these microbes, and the natural job of both CRISPR-Cas9 and CRISPR-Cpf1 is to recognise viral genes and chop them up before they can do any harm. Conversely, viruses are constantly evolving to escape the antiviral systems' attentions, meaning bacteria need to generate new ones. The chances are good, therefore, that CRISPR-Cas9 and CRISPR-Cpf1 are not alone. ...

The tools to carry out that exploration now exist. CRISPR-Cpf1, for instance, was found not by searching in bacteria directly, but by scrutinising a published database of bacterial genetic sequences, which yielded two species that contain it. Further searches might be equally rewarding—and the more gene-editing systems are discovered, the harder it will be to monopolise their use.

Despite the optimism of those who think the new techniques may calm qualms about genetic engineering, however, some people are bound to have ethical worries—certainly when it comes to applying them to human beings. Earlier this year, for example, when Chinese scientists used CRISPR-Cas9 gene editing on a human embryo (albeit one that was unviable, and could not therefore have developed into a person) there was much brouhaha and several calls for a moratorium on this line of inquiry.

There may not only be ethical worries but as we have discussed previously there is a weaponization approach also readily available.

In a report in Nature World they state^{10[6]}:

The CRISPR/Cas9 system evolved as a way for bacteria and archaea to defend themselves against invading viruses. It is found in a wide range of these organisms, and uses an enzyme called Cas9 to cut DNA at a site specified by 'guide' strands of RNA. Researchers have turned CRISPR/Cas9 into a molecular-biology powerhouse that can be used in other organisms. The cuts made by the enzyme are repaired by the cell's natural DNA-repair processes...

The newly described Cpf1 system differs in several important ways from the previously described Cas9, with significant implications for research and therapeutics, as well as for business and intellectual property.

^{9[5]} <http://www.economist.com/news/science-and-technology/21668031-scientists-have-found-yet-another-way-edit-genomes-suggesting-such-technology-will>

^{10[6]} <http://www.natureworldreport.com/2015/09/cpf1-for-precise-genome-engineering/>

In its natural form, the DNA-cutting enzyme Cas9 forms a complex with two small RNAs, both of which are required for the cutting activity. The Cpf1 system is simpler in that it requires only a single RNA.

Cpf1 cuts DNA in a different manner than Cas9. When the Cas9 complex cuts DNA, it cuts both strands at the same place, leaving 'blunt ends' that often undergo mutations as they are rejoined. With the Cpf1 complex the cuts in the two strands are offset, leaving short overhangs on the exposed ends.

Cpf1 cuts far away from the recognition site, meaning that even if the targeted gene becomes mutated at the cut site, it can likely still be re-cut, allowing multiple opportunities for correct editing to occur.

The Cpf1 system provides new flexibility in choosing target sites. Like Cas9, the Cpf1 complex must first attach to a short sequence known as a PAM, and targets must be chosen that are adjacent to naturally occurring PAM sequences.

Finally, in a discussion in Wired the reporting is as follows^{11[7]}:

The discovery comes at a time when CRISPR/Cas9 is sweeping through biology labs. So revolutionary is this new genome editing technique that rival groups, who each claim to have been first to the tech, are bitterly fighting over the CRISPR/Cas9 patent. This new gene-editing protein called Cpf1—and maybe even others yet to be discovered—means that one patent may not be so powerful after all...

*Many different proteins are associated with CRISPR. But in the early 2010s, Emmanuelle Charpentier, who was studying the flesh-eating bacteria *Streptococcus pyogenes*, stumbled onto one with special powers. Her bacteria happen to carry Cas9 proteins, which have the remarkable ability to precisely cut DNA based on a RNA guide sequence. In 2012, Charpentier and UC Berkeley biologist Jennifer Doudna published a paper describing the CRISPR/Cas9 system and speculated about its genome editing capabilities. And they filed a patent application. Much more on that patent later.*

The patent issue is something we spoke about when the PTO pushed the Broad version through in less than six months, an unheard of process time.

While Cas9 has driven thousands of lab experiments and millions of dollars in funding for startups trying to capitalize on the technology, Cpf1 has remained relatively obscure. This study drags Cpf1 into the limelight. "It's a very comparable to Cas9 and it has a few different features which could be quite useful," says Dana Carroll, a biochemist at the University of Utah.

^{11[7]} <http://www.wired.com/2015/09/war-genome-editing-just-got-lot-interesting/>

That's because Cas9 isn't perfect, despite its hype as a laser-precise genome editing tool. Cpf1 offers some slight advantages. For example, when it cuts double-stranded DNA, it snips the two strands in slightly different locations, resulting in overhang that molecular biologists call "sticky ends." Sticky ends can make it easier to insert a snippet of new DNA—say, a different version of a gene—though the Cell paper does not actually show data directly comparing Cas9 and Cpf1 when inserting DNA.

Cpf1 is also physically a smaller protein, so it may be easier to put into human cells. It requires only one RNA molecule instead of two, with Cas9. But it's not a rival so much as a complementary tool: The two proteins favor binding to different locations in the genome, so together, they might allow more flexibility in where scientist want to cut.

The writer then returns to the patent issues:

Not long after Doudna and UC Berkeley filed a patent, the Broad Institute and MIT filed their own patent on behalf of Zhang for the CRISPR/Cas9 system. Zhang had been working on actually showing that CRISPR/Cas9 can edit mammalian genomes in mammalian cells, an application he published in 2013 and says he came up with independently. The Broad's and MIT's attorney paid a fee to accelerate their application. Ultimately, the US Patent and Trademark Office awarded the patent to Zhang, MIT, and the Broad Institute. The University of California, obviously unhappy with the decision, filed an application for an interference proceeding to get the USPTO to reconsider. That process is ongoing.

But biotech companies have raced ahead to develop therapeutics and techniques with the system. Feng and Doudna have since licensed their technology to rival companies, Editas and Caribou. Charpentier also cofounded Crispr Therapeutics in Switzerland. Whoever wins the patent dispute will have a monopoly on CRISPR/Cas9 technology, the hottest new thing in biotech.

But with Cfp1, the stakes of that specific patent dispute go down. A lab or company could use Cfp1 without infringing on the CRISPR/Cas9 patent. "It takes power away from whoever the winner is going to be," says Jacob Sherkow, a NYU law professor. (Zhang has indicated the rights to Cpf1 may not necessarily go to the company he cofounded, Editas.) Whether a CRISPR/Cfp1 system is patentable as a separate invention—Sherkow says it probably is—perhaps isn't even relevant because its very existence means Cas9 is no longer the only game in town.

This latter observation is of significant value. Namely Cpf1 if it is truly better makes Cas9 battles of less value.

It is of continuing interest to follow the dimensions of this new "tool box" available to those of us working on gene changes.

References

1. Zetsche, B., et al, Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System, Cell DOI: <http://dx.doi.org/10.1016/j.cell.2015.09.038>

2. Ledford, H., Alternative CRISPR system could improve genome editing, Nature News, 25 September 2015



Labels: [CRISPR](#)

THURSDAY, SEPTEMBER 24, 2015

[THE CANADIAN WALL](#)

One is always amused when reading the Canadian Press view of Americans. The [National Post](#) has an article speaking to the desire by some 40% of Americans to build a wall between the US and Canada.

They state:

Failed Republican presidential candidate Scott Walker may feel some vindication in this number: 41 per cent of Americans say that if a wall is built along the Mexican border, one should also be erected on the Canadian one. And yes, the same percentage favors a wall erected along the nation's southern border. The latest Bloomberg Politics poll that also shows that immigration, a flashpoint in the 2016 presidential campaign thanks in large part to the incendiary rhetoric of Republican front-runner Donald Trump, is an issue that stirs strong emotions among Americans, some of them contradictory.

Now I just returned from a business trip from my New Hampshire home to Laval in Quebec City. The return was via the NH Route 3 "Moose Alley" entry point. Now this is a single lane road in the northern most point in NH and it was empty going north and south. When you approach the border there is a gate on the Canadian side, open, but on the US side there is a multimillion dollar bunker. It is an enormous facility and out came two HS men with weapons. Here we were, two mid 70 year old in a 10 year old Caddy from New Jersey. Clearly a major threat.

We presented our passports. They had my wife remove her sunglasses, show her face in the sun. Then they inspected the underside of the car, all packages in the back seat, the trunk, the contents of our luggage. They asked where we went, why we returned this way, the "moose" dummy, everyone comes down here to see the moose!

Twenty minutes, no other vehicles in sight coming south or going north! I guess they were just bored. I have returned from Russia, Thailand, Bulgaria with less inspection.

Guess they heard I spoke French! Yes, also my wife's family is from Nova Scotia! Yikes.

Then about a mile south of the border is a massive sign just on the edge of the uninhabited forest, "Trump". I guess the moose vote!

Maybe the Canadians should build that border.



Labels: [Politics](#)

TUESDAY, SEPTEMBER 22, 2015

[WHY IT IS NOT STUPID](#)

[The Telegraph](#) lists 20 "stupid" questions asked by passengers. One is:

"Excuse me, what's in the ham and cheese sandwich?"

All you have to do is look and see it is already more than "ham and cheese". That is the problem. Culturally say in New York, ask for "ham and cheese" and get just that, you want bread, ask for the bread, "stupid". In California when you ask for "ham and cheese" on rye, you get some amalgam of fruits, nuts, plants, and who knows what that the cook, owner or someone thinks you should have and never intends to inform you. Kind of like Republicans versus Democrats.

So to paraphrase Forest Gump, "Life is like a hand and cheese sandwich."



Labels: [Commentary](#)

SATURDAY, SEPTEMBER 19, 2015

[CTCS, PCA, AND WNT](#)

Circulating Tumor Cells, CTCs, are now capable of being extracted efficiently from patients. From Haber's Lab at Dana Farber his team has published a paper in [Science](#) describing the results. The results are worth examining.

They state in an earlier version on breast cancer:

Circulating tumor cells (CTCs) are present at low concentrations in the peripheral blood of patients with solid tumors. It has been proposed that the isolation, ex vivo culture, and characterization of CTCs may provide an opportunity to noninvasively monitor the changing patterns of drug susceptibility in individual patients as their tumors acquire new mutations. In a proof-of-concept study, we established CTC cultures from six patients with estrogen receptor-positive breast cancer. Three of five CTC lines tested were tumorigenic in mice. Genome sequencing of the CTC lines revealed preexisting mutations in the PIK3CA gene and newly acquired mutations in the estrogen receptor gene (ESR1), PIK3CA gene, and fibroblast growth factor receptor gene (FGFR2), among others. Drug sensitivity testing of CTC lines with multiple mutations revealed potential new therapeutic targets. With optimization of CTC culture conditions, this strategy may help identify the best therapies for individual cancer patients over the course of their disease.

We have examined the pathways above extensively in the past and WNT is a well known target.

I hear Haber talk this past week at NYAS and his talk was quite informative. I was especially impressed by the means used to extract CTCs, that alone is worth a look.

My general concern however is several fold:

1. CTCs can come from anywhere. As we have discussed before the work of Gundem et al demonstrated a complex proliferation of genetic profiles in AR PCa. Thus one may be able to gain some prognostic information but not localization.
2. There is always the issue of stem cells. Again what cells may get extravasated is not the same as what cells are proliferating.
3. Cell communication via exosomes is a concern as is the ECM issues of localized growth.

This is an extraordinary useful tool and definitely worth following. The current [Science](#) work on PCa states:

*Prostate cancer is initially responsive to androgen deprivation, but the effectiveness of androgen receptor (AR) inhibitors in recurrent disease is variable. Biopsy of bone metastases is challenging; hence, sampling circulating tumor cells (CTCs) may reveal drug-resistance mechanisms. We established single-cell RNA-sequencing (RNA-Seq) profiles of 77 intact CTCs isolated from 13 patients (mean six CTCs per patient), by using microfluidic enrichment. Single CTCs from each individual display considerable heterogeneity, including expression of AR gene mutations and splicing variants. Retrospective analysis of CTCs from patients progressing under treatment with an AR inhibitor, compared with untreated cases, indicates activation of noncanonical Wnt signaling ($P = 0.0064$). Ectopic expression of *Wnt5a* in prostate cancer cells attenuates the antiproliferative effect of AR inhibition, whereas its suppression in drug-resistant cells restores partial sensitivity, a correlation also evident in an established mouse model. Thus, single-cell analysis of prostate CTCs reveals heterogeneity in signaling pathways that could contribute to treatment failure.*

The last sentence is the most powerful and disturbingly consistent observation. PCa is just "too sneaky". It does not follow simple lines of development. It is not a BRAF V600 melanoma, it is not a Vogelstein colon cancer progression.

Frankly, it is for this reason alone that the USPTF recommendations on PSA testing are cruel and unusual. It is clear that PCa is a highly complex cancer and one that lends itself to multiple parallel paths resulting in some significantly high mortality rates. The very thought of taking the only tool and refusing to use it may, in my opinion, almost border on the criminal.



Labels: [Cancer](#)

THURSDAY, SEPTEMBER 17, 2015

WHERE IS MUSSOLINI WHEN HE IS NEEDED?



Getting the trains to run on time into and out of Penn Station, or anywhere in New York these days, needs a strong hand. Amtrak seems never to be on time. When at Penn Station I rarely see a on time departure, it seems 50 minutes is de rigueur.

But now we have power losses in the tunnel almost daily. What are we waiting for? Possible disasters. There is not a single politician addressing the issue. However this is what happens when Government runs something, anything, except Defense it appears.

I feel for the poor folks who try to use Public Transport only to be deceived by those who "provide" the service.

Let us see what Friday delivers. As of now they are still stumbling along. At least NJ Transit posts updates. If one looks at Amtrak; all is well.....Pity.

Oh yes, and that low carbon stuff, won't work this way folks!



Labels: [Commentary](#)

WEDNESDAY, SEPTEMBER 16, 2015

PROGRAMMING, COMPUTER SCIENCE, OR WHAT?

The [NY Times](#) recounts the current Mayor's intent to introduce Computer Science into the Grammar and Secondary School programs.

They state:

To ensure that every child can learn the skills required to work in New York City's fast-growing technology sector, Mayor Bill de Blasio will announce on Wednesday that within 10 years all of the city's public schools will be required to offer computer science to all students. Meeting that goal will present major challenges, mostly in training enough teachers. There is no state teacher

certification in computer science, and no pipeline of computer science teachers coming out of college. Fewer than 10 percent of city schools currently offer any form of computer science education, and only 1 percent of students receive it, according to estimates by the city's Department of Education.

Now this raises several questions.

First, does he understand what Computer Science means? Doubt it but lets continue.

Second, I think he means programming. Computer Science is a much broader discipline, from architecture to language structures.

Third, and this is a key point, coding can be counter productive. Let me explain.

In 1962 I started teaching Fortran on an IBM 709 computer to students. I first had to learn some, FAP, Fortran Assembly Programming. Recently I came up to speed with Python on an MIT MOOC. What I noticed was that the focus was on using Python to "manipulate" the solution. The underlying mathematics was not even discussed. When I did Apollo guidance calculations we used an assembly program and that was only after we had done the mathematical analyses and reduced the steps to a minimum, after all we only had 64K memory!

Over the years I have picked up probably a couple of dozen languages, depending what I needed them for. Pascal for an options trading station, C for a communications protocol, Python for DNA string analysis, SNOBOL for modelling switching networks, FORTRAN for scientific stuff, BASIC to run my old Atari, and the list goes on. More than two dozen languages, each to solve a specific set of problems. Programming is implementing a logical set of commands to achieve a result from a potential complex mathematical problem. It is a means to an end, NOT an end in itself.

Learning a language is secondary to understanding the application and its related mathematics. Cluster analysis for genomic testing, or time series analysis for Kalman Filtering.

Thus the issue is that programming is a tool, and there are many tools available. So what are we trying to teach a student. If we had a spectrophotometer, we use it to help solve a chemical problem, not to know how to use a tool. Programming should be viewed first as a tool, not as an end.

Yet Computer Science is NOT programming. Hematologists are not Phlebotomists.

The final issue is who are the teachers? If good programming is a means to an end and if the end is the solution of some putatively complex mathematical problem, that we do a mass disservice to students in "teaching" them to code. We need to facilitate their thinking process. Not turn them into coders.



Labels: [Education](#)

TUESDAY, SEPTEMBER 15, 2015

MISBEHAVIOR AT MICROSOFT

Now I am no fan of Microsoft. They in my opinion exude an arrogance based upon an internally generated self image. Then there is Windows 10, which kind of works, and can almost be put back into an XP type OS where things are somewhat understood. I still cannot figure out how to effect the old cmd files but that is another story.

Yes, they have tried dozens of time to download w10 onto my office systems. Multiple times a day, I think I have blocked them. I have a W10 pad and it works kind of OK. It does not deal with Bluetooth well, wrong drivers, and try and get the right ones, and the WiFi is iffy at best. Again I suspect a driver problem.

Now [Inquirer](#) reports that they are actually loading W10 even if you did not ask for it. Imagine what that would do to a production machine! Bring it to a total halt. All drivers would be dead on arrival. They do NOT work on W10. It would almost in my opinion be a terrorist act. But they keep hitting my updates. The article states:

WHEN WE REVEALED last Thursday that Microsoft has started downloading Windows 10 indiscriminately to anyone who qualifies for an upgrade, whether they want one or not, we knew it was kind of a big deal. We're proud to be recognised as a credible news source and our articles are often cited and quoted. What we didn't expect was that this would be picked up first by the tech press, then the national press, then the world press in droves. To say that it struck a nerve is an understatement. It's like the keylogger story last year, but much, much, much bigger. There are several factors here. At a basic level, there's the privacy and intrusion aspect. After all, it's one thing to agree to receive updates to your operating system automatically, especially given that many of them relate to keeping the system locked down, but this isn't an update, it's a whole new operating system. Then there's the sneakiness. Microsoft offers an opt-in scheme to Windows 10. Remember all that stuff about reserving your copy? If you didn't reserve a copy and it just goes ahead and downloads it anyway, it's going directly against your wishes. And let's remember, it's going into a hidden folder that you actually have to change settings to be able to see. That says a lot.

I can see a great Class Action suit here! Where are the lawyers when you need them?

The damages could be astronomical! For example, let us say I have a time constraint on getting out a report of legal filing. Down comes W10, now I have to reassemble all my files, none of my software will work, bad drivers or incompatible, no peripherals and the list goes on. Not to mention getting rid of all the "nice" graphics to get the presentation back some where near what you were used to. Do any of the folks at Microsoft even think? Perhaps not.

Let's wait and see what happens next.



Labels: [Microsoft](#)

TURN AROUNDS AND POLITICS

Back in the 80s I did a few turn arounds. There was a simple formula:

1. Fire half the people. I used SSNs to make the decision, even numbers out. That reduced costs.
2. Raise the prices, that gave you some revenue for a short time.
3. Rush to find a buyer.

It works and private equity folks do it all the time. I left that when I did one in Memphis. I got to see what firing some of these folks meant. People with a spouse in the midst of cancer treatment, a child needing extensive care, etc. The stories were too many to take. They were real.

Now we have the tale of a couple of Private Equity folks taking companies like Kraft off the market. Guess what; they fired a ton of people and now are cutting off the health care plans for all the retirees. As reported in [insurancenewsnet](#) they state:

Global food giant Kraft Heinz Co. is going after retiree benefits as the recently merged company accelerates cost cutting to try to boost profitability. The company, which was created through the July combination of Kraft Foods Group and H.J. Heinz Co., is eliminating a group health insurance plan for about 15,000 Kraft retirees and will give them money to buy coverage on a private exchange. The company is also allowing some retirees to cash out their pension plans. Heinz retirees experienced similar cuts in 2013 and 2014. The moves are the latest efforts by Kraft Heinz and Highlight the belt-tightening that is typical of corporate shake-ups implemented by Brazilian investment firm 3G Capital, which partnered in 2013 with Warren Buffett's Berkshire Hathaway to buy Heinz. Berkshire and 3G engineered the merger of Kraft and Heinz to create the world's fifth largest food and beverage company, which is expected to have annual sales of about \$28 billion.

Yes indeed, one of the folks on the Private Equity side is that bastion of Liberal Democrat doctrine, the man from Nebraska. So what do we see? Tens of thousands of folks now scrambling to get coverage and many in the midst of life threatening situations. A quick calculation shows that these poor folks will go from a costs of approximately \$2,000 per year plus out of pocket per person to well over \$10,000 per year per person, assuming they can even get a plan. And what of that poor person in the midst of cancer therapy? I remembered that, I got the guy another job, and carried his plan. I guess I am just not cold enough for that business.

One is reminded of Tennessee Williams and "relying on the kindness of strangers". Blanche DuBois did not make it through so well. Thus one should think twice when some well heeled Private Equity person tells us how we should manage our lives; what of the impact they had on the lives of the many?

What could or should have been done? Tell the folks a year ahead of time, give them so room to maneuver, but don't drop it on them at the end of the year. Will one year cost that much? Especially if the tax rate for these guys is so low.



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

SATURDAY, SEPTEMBER 12, 2015

[CAVEAT EMPTOR](#)

The current President had some two years ago proposed that the Federal Government in its wisdom provide a list of some to be determined quality metrics and evaluations of the Nation's Universities. According to the [NY Times](#) the same folks have decided not to go with that idea.

The Times states:

(the President) on Saturday abandoned his two-year effort to have the government create a system that explicitly rates the quality of the nation's colleges and universities, a plan that was bitterly opposed by presidents at many of those institutions. Under the original idea, announced by (the President) with fanfare in 2013, all of the nation's 7,000 institutions of higher education would have been assigned a ranking by the government, with the aim of publicly shaming low-rated schools that saddle students with high debt and poor earning potential. Instead, the White House on Saturday unveiled a website that does not attempt to rate schools with any kind of grade, but provides information to prospective students and their parents about annual costs, graduation rates and salaries after graduation. (The President) praised the new website in his weekly address, saying that by using the new College Scorecard, "Americans will now have access to reliable data on every institution of higher education."

Now we thought it was a rather dumb idea at the outset. Imagine a group of GS-9s beholding to their politically appointed leaders deciding on how to rank say MIT, Stanford, and Cal Tech. You think they would understand the courses? How about what people do?

Now take MIT as an example. Frankly if some Junior drops out of school to do a start up which in turn changes the world for the better, is that drop out bad or good? By the way this happens all the time. So to the good old GS-9, who may have made it through a Community College somewhere, it would be bad.

Just think, the same folks who brought you the ACA wanted to drop a bomb on Higher Education!

But wait, look at the [Web Site](#). I looked for Engineering and ranked them by highest salary upon Graduation. What one was highest? SUNY Down State Medical School! Are you nuts! They are graduating MDs, in Medicine. Best I know MDs and Engineers are a bit different, been there done that. The The Merchant Marine Academy! That is not engineering, it is ship steering and maintenance. It is not Annapolis. Then fourth comes Harvard. What happened to Stanford, Cal Tech. Keep going and going!

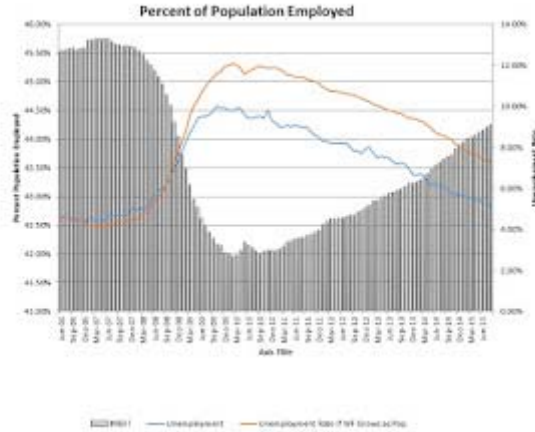
When one puts a list like this together one should try it out on real people to see if it makes sense. Not the Government! Who cares about reality!



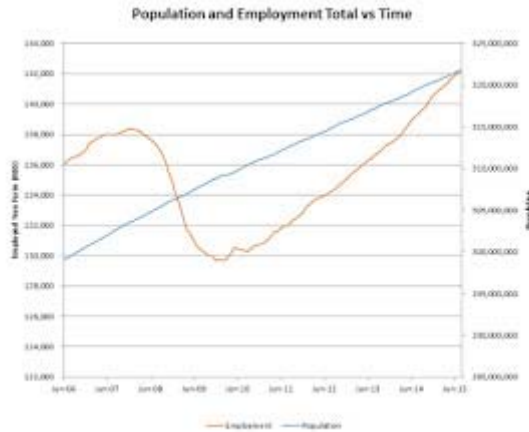
Labels: [Academy](#), [Government](#)

FRIDAY, SEPTEMBER 4, 2015

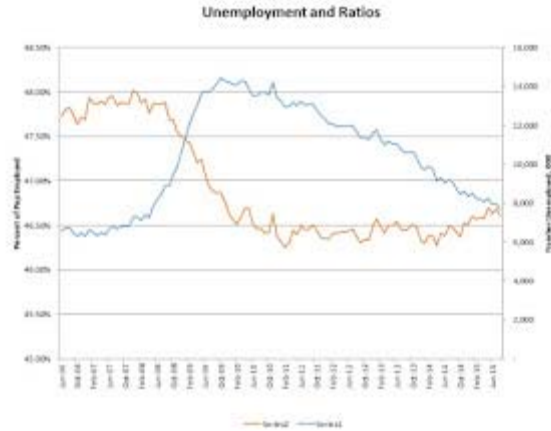
UNEMPLOYMENT: SEPTEMBER 2015



Some thoughts on employment. That chart above depicts the unemployment numbers with and without the change in participation rates. Clearly there is a sustained gap.



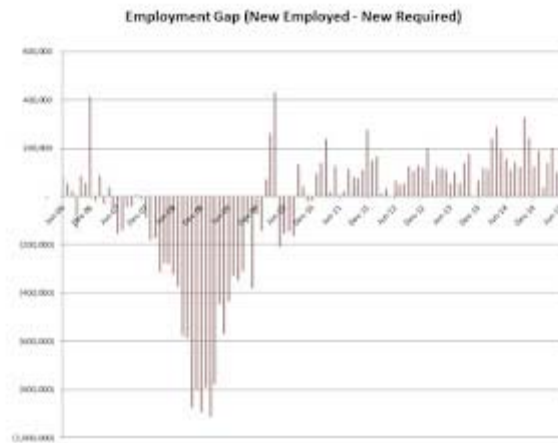
The above details this a bit more.



The above is the gap in some specific detail.



The above shows the gap per month from what it should be. There is a growing and systematic gap in employment. This means that we have more people on the dole and less taxes. Making things worse is that more employment is related to Government funded work; Government, Education, Health Care.



This is the actual gaps per month.

Overall people are being added to the payrolls but not at a large enough rate and not in value creating jobs.

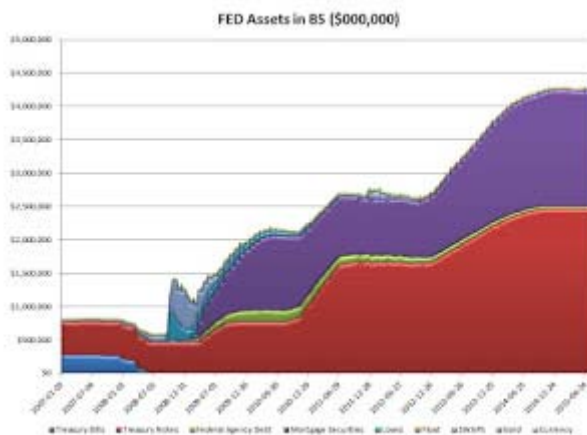
After the seven years we have been tracking these numbers we still see systemic weakness in the economy.



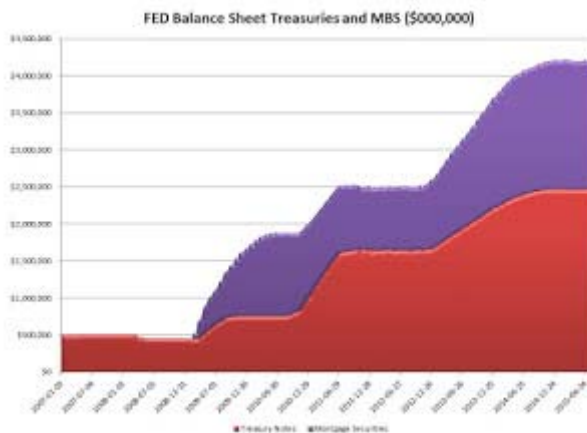
Labels: [Economy](#)

WEDNESDAY, SEPTEMBER 2, 2015

FED BALANCE SHEET



The above is the current Fed Balance Sheet. Note that it has remained constant somewhat since Q1. Specifically as shown below:



The two main components have remained with minimal change. This appears to be a significant factor and may be a key reason for increasing the rates.



Labels: [Economy](#)

[MIT WEIGHT LOSS?](#)

It appears that [MIT](#) had added a "weight loss" program to its ever growing list of advantages. The article states:

the program helps participants learn to love foods that support weight loss and maintain a healthy lifestyle. It includes meal plans, a high-fiber regime, and portion control. There is also a weekly online support group that provides nutrition education and helps dieters form new, healthy habits that promote weight loss sustainability. There is also weekly check-ins and weight tracking with various Web tools. Unlike many other weight-loss programs, iDiet requires daily weigh-ins — “an important and effective way to see and appreciate your success” according to the program’s website — but there are no set exercise requirements. Meal planning on the program is simple. You can buy the cookbook or find simple recipes online. Recipes include vegetarian options; others are designed to address special dietary concerns such as high blood pressure or cholesterol, diabetes, or gluten and lactose intolerance.

Well here is my take:

1. Get rid of the high carb fast food "food courts". They are everywhere. One could in the past walk over to Walker Memorial, sit at a large table and have a conversation while eating a reasonably priced balanced meal. You got exercise, reasonable food, low prices, and you actually met people. Now we have the solitary fast food outlets selling high carb and high priced food just a few steps away from one's computer, or they now actually have it on the table.
2. Get rid of the refrigerators and food storage units in all of the "labs" It appears that there is always someone bringing cookies from "mom" in Bangalore and a constant flow of consumption. In my old days in Building 20, the wooden remnants of the Rad Lab any loose food was consumed by the resident rodents. Perhaps we should bring back the rodents!
3. Watch out for those Chinese Restaurants. Now I like Chinese food but it is so high in calories that the almost daily routine of going out to eat with the team gets a bit much, as well as adding to the waist line.

Adding another costly program will not change the above. It will just shall we say "put lipstick on the pig".



Labels: [Health Care](#)

MONDAY, AUGUST 24, 2015

CHINA DOWN ANOTHER 5.5%

Shanghai is down 5.5% and dropping. This AM in US markets we saw an almost 1100 point drop. It was like watching the White Ford on the LA Freeway. Deer in the headlights.

Tuesday will be another round, possibly not as bad. We are going from a "Correction" to a massive down turn. And where are our glorious leaders? On the golf course, of course.

The key question is a two part question; (i) our exports are low as compared to imports so who cares, and if China drops values we get cheaper imports, (ii) what about the debt on the fracking companies now that oil is in the tank? The China issue may be secondary to another financial collapse hidden in low cost but un-payable debt, close to a trillion.

I guess that pipeline can wait?



But then again for China look at the past ten years. They collapsed in 2008-2009 but what we see is really a bubble bursting. So we are still on good growth if we take out the bubble. So possibly China is not a problem. Debt is however.



Labels: [China](#)

[MORE ON WINDOWS 10 AND BLUETOOTH](#)

Drivers can be the bane of any user. When I first did an OS some 40+ years ago the interfaces to external devices were through various drivers. Nothing much has changed.

Except there seems to be a mass of defective Bluetooth devices, due it appears to drivers.

An interesting tale can be put together by Googling w10 and Bluetooth. One of the better one is on [SuperSite](#).

Could you imagine what may have happened if one were inclined to update from W7 to W10 and now you have dozens of dead drivers!

Welcome to Microsoft! Thanks to Google!



Labels: [Microsoft](#)

[A CURRENT MINDSET: TERRIFYING](#)

It is always interesting to read comments on the Web, especially those in prominent sites. In a [Science](#) article discussing President Carter's illness a commentator writes:

You are wrong. The meaning of existence of private/public company/corporation is to serve critical needs of society at large and that's why it is allowed by the society to make reasonable, limited, profits for future investments and not for opulent spending. If company cease to serve the public interest is must be dismantled. And because of that monopolistic Big Pharma must be dismantled for the good of patients. But those principles have been corrupted and now so-called US company serves their management and also foreign oligarch ownership, not public.

The English is atrocious but the thought is terrifying. This goes beyond socialism, communism, into some communitarian extreme.

What drive this person to write in such a highly regarded journal. Well it was this paragraph:

Still, researchers have a lot to learn about pembrolizumab and other PD-1 therapies in development. Keytruda is also extremely expensive, at about \$150,000 a year. In clinical trials, PD-1 blockers generally work in less than half the participants. Research published earlier this year suggested PD-1 inhibitors may work best on tumors with lots of mutations, and a small clinical trial of pembrolizumab backed this up. It found that people with advanced cancer were far more likely to respond if they had so-called mismatch repair mutations in their tumors. This could also help explain why, so far, PD-1 inhibitors have produced the best outcomes in people with lung cancer and melanoma—both are often mutation-heavy tumors.

PD-1 inhibitors are the next step in immune therapy with MABs. There has been decades of R&D and hundreds of billions spent, not to mention trials which have exposed many patients to false hopes. But as [we have written before](#) this is now one of several paths to treating cancers.

But that is no excuse for the vitriolic comments by some of these readers. This same commenter states:

There is some other aspect of it however. President J. Carter recently stated that US is run by Oligarchic cabal and that democracy is no more. An that includes Big Pharma that grows like a cancer within the bodies of cancer patients and that's the problem in America. The Big Pharma is offering nothing but more pain, suffering, household financial collapse and plenty of false hopes. Mr. President I suggests you look seriously into massive, up to million mg intravenously a day dose of ascorbic acid aka Vitamin C in appropriate form, that has shown good results in clinical therapy but is dismissed by Big Pharma brainwashed medical professionals.

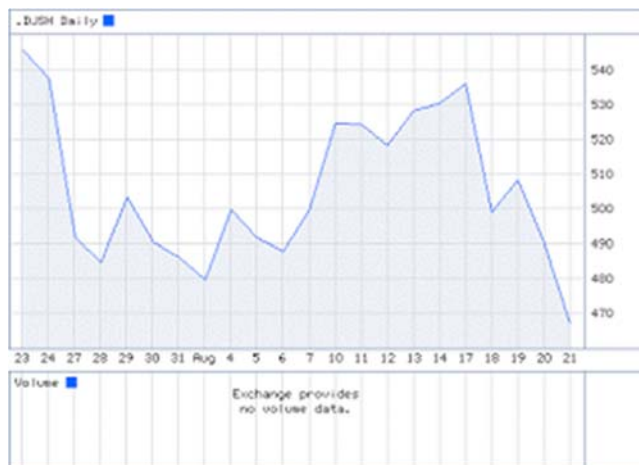
Perhaps this individual is some hidden genius we have just missed as a society. Perhaps not!



Labels: [Commentary](#)

SUNDAY, AUGUST 23, 2015

[CHINA DOWN 7.5% AT THE START](#)



There seems to be a total collapse in China. This was not fully expected but the ripples will be significant. Remember the China Sovereign Fund holds several trillion US Debt. This will be a very very bumpy week!



Labels: [China](#)

[WHY WINDOWS 10 IS LIKE A CALIFORNIA HAM SANDWICH](#)

Now a few years ago I wrote about my saga of getting a ham on rye sandwich in California. Some how in California no one listens to the customers, they all want to add something. I noticed Panera also acts that way but not as bad as California. You ask for a "ham on rye" and they ask if you want sprouts or onions, peppers or tomatoes, "you want chips or fries".

All I wanted was ham on rye! I then did the Jack Nicholson thing; hold the tomatoes, hold the

peppers, hold the fries!

Then I found someone who had experience. He said; "You from New York?" "Yeah!" then he said: "Two pieces of rye with ham in between, nothing else, yeas!" I answered, "got it!"

Now W10 is like a California sandwich. Instead of getting the computer you get their graphics, their placements, their way of doing things which when you try do not work.

Why not try like ham on rye. Let me decide what to add, lay out the condiments. Don't force me to figure out how to scrape off the avocado stuff, I hate avocados. I also hate mayonnaise on ham! I like mustard and I want to put on my own amount!

So W10 comes as Seattle would like you to consume it. I guess that is also why I hate Starbucks. Try and get a small regular black coffee!



Labels: [Microsoft](#)

SATURDAY, AUGUST 22, 2015

[MAKING WINDOWS 10 LOOK LIKE XP](#)

Microsoft is not very user friendly. Really not friendly. Well welcome to Windows 10. Just got a pad to use and it comes with 10. Now Dell makes a fantastic product. Then on to W10.

First thing I do is get rid of all the junk that some marketing guru, a true oxymoron for Microsoft, wants me to have. Change screen to classic blue and layout the files folders like my other 7 machines. That way no visual dissonance.

Then go to start and get rid of all the junk. Tons of junk, none of which I will ever use!

Then make a Recovery stub. No wait, it seems that no one has been able to do this yet. You have to Google this since Microsoft tells you they have too many questions and yours is not important.

But, there is a back door, a Windows 7 restore to a 1TB disk. Got that done.

Then try and get Bluetooth working! It connects, then drops, and then, well I have no idea what then. To see how bad Microsoft is one need look no further than the ["Support" pages](#). The Company in my opinion must really despise its customers. The poor customer had the same issues I did. Now bluetooth is really simple. I have it in my car, my GPS, dozens of other computers. But for Microsoft, taking a simple need and turning it into massive neuro surgery in the dark is common place!

Then there is your WiFi. For various reasons it drops you, sending you to Airplane mode. This happens randomly.

Yes, it can be made to look and almost act like XP. But given a clean install and the mess so far I could see no rational human upgrading from W7 to W10! Why upgrade to a system which the

users have not shaken down yet. Yes, that is Microsoft. Thank God Google still works, but I suspect they will also soon be going the way of Seattle. Pity.



Labels: [Microsoft](#)

FRIDAY, AUGUST 21, 2015

[OBESITY AND GENES; REDUX](#)



There seems to be a continuing search for the genes which "cause" obesity. To reiterate, independent of any gene;

Input - Output = Net Accumulation

Thus eat too much means you get fat. Of course the problem with the above is; how does one measure input and output. The classic manner is in food and Kcal. Thus:

3500 Kcal = 1 pound

That is for every 3500 Kcal one consumes above a Basal Metabolism burn rate one gains a pound.

However not all food is equal and not all people burn calories at the same rate. Thus perhaps there is a genetic factor on burn rates. That does not negate the above argument.

Into this fray is a new article in [NEJM](#). They state:

Our results point to a pathway for adipocyte thermogenesis regulation involving ARID5B, rs1421085, IRX3, and IRX5, which, when manipulated, had pronounced pro-obesity and anti-obesity effects.

This is 3 genes and a single SNV. But we must always ask; what is the cause? Again it appears that with these genes fat cells burn at a lower rate. Thus if a normal person, whatever that means, can deal with 1800 Kcal per day and not gain weight then a gene encumbered person may only burn 1200 Kcal per day and eating the same amount will thus gain weight. So eat less! The cause of obesity is consumption. If one has a lower set point then eat less.

Now in the [MIT write up](#) of this article the authors state:

But there may now be a new approach to prevent and even cure obesity, thanks to a study led by researchers at MIT and Harvard Medical School and published today in the New England Journal of Medicine. By analyzing the cellular circuitry underlying the strongest genetic association with obesity, the researchers have unveiled a new pathway that controls human metabolism by prompting our adipocytes, or fat cells, to store fat or burn it away. "Obesity has traditionally been seen as the result of an imbalance between the amount of food we eat and how much we exercise, but this view ignores the contribution of genetics to each individual's metabolism," says senior author Manolis Kellis, a professor of computer science and a member of MIT's Computer Science and Artificial Intelligence Laboratory (CSAIL) and of the Broad Institute.

Well frankly the CSAIL reference is wrong. It does not relate to exercise but cell burn rates. We always knew that. We further know that some people's cells burn at different rates and that obese people burn at a lower rate. The classic case is the Southwest Indian Tribes who most likely after generations have adapted to low caloric input due to the nature of their environment and thus have a lower conserving burn rate. We see this in many immigrants from countries where food was not readily available. The Irish and many Hispanics have a similar characteristic. (Also some early epigenetic studies demonstrated inheritable traits from WW II starvation in the Low Countries). They can maintain lower weight by not eating our high calorie foods. Don't blame the genes, in fact the genes have adapted to the harsh limited food environment which may be beneficial.

The NEJM article concludes:

Last, we found that direct manipulation of the ARID5B–rs1421085–IRX3/IRX5 regulatory axis in primary cell cultures of adipocytes from patients reversed the signatures of obesity. This indicates that in addition to changes in physical activity and nutrition, manipulation of mitochondrial thermogenesis offers a potential third pathway for shifting between energy storage and expenditure in a brain-independent and tissue-autonomous way in humans. In summary, our work elucidates a mechanistic basis for the strongest genetic association with obesity. Our results indicate that the SNV rs1421085 underlies the genetic association between the FTO locus and obesity. The SNV disrupts an evolutionarily conserved motif for the ARID5B repressor, which leads to loss of binding, derepression of a potent preadipocyte superenhancer, and activation of downstream targets IRX3 and IRX5 during early differentiation of mesenchymal progenitors into adipocyte subtypes. This results in a cell-autonomous shift from white adipocyte browning to lipid-storage gene expression programs and to repression of basal mitochondrial respiration, a decrease in thermogenesis in response to stimulus, and an increase in adipocyte size. Manipulation of the uncovered pathway, including knockdown or overexpression of the upstream regulator ARID5B, genome editing of the predicted causal variant rs1421085, and knockdown or overexpression of target genes IRX3 and IRX5, had a significant effect on obesity phenotypes.

Now the last thing we need is a new medication to control genetic pathways when the answer is just lower food consumption. That is free!

As an aside I found that the paper relied on murine samples. In addition they state:

To translate the results of genomewide association studies into mechanistic insights, we combined public resources (epigenomic annotations, chromosome conformation, and regulatory motif conservation), targeted experiments for risk and nonrisk haplotypes (enhancer tiling, gene expression, and cellular profiling), and directed perturbations in human primary cells and mouse models (regulator–target knockdown and overexpression and CRISPR–Cas9 genome editing).

Let's just hope we don't do CRISPR Cas9 editing on humans for obesity! Just a concern.

Oh and by the way, there is a very effective tool already in use. It is called the Scale. Cheap, lots of them around, and it provides a set point feedback loop. You get on it once a day and if it gets higher you stop eating, if it gets too low, then see a Doc!

And yes, one last thing, the MIT Stata Center where CSAIL is located has a "food court" I used to frequent, albeit carefully. The food there is carb rich, and more than likely will be the cause of later obesity issues. So one must always examine their own sand box, and not blame the genes for everything!



Labels: [Obesity](#)

THURSDAY, AUGUST 20, 2015

[IRAN, THE FRENCH REVOLUTION AND MANCHURIA](#)



In 1967 Noam Chomsky wrote a piece for Liberation entitled [On the Backgrounds of the Pacific War](#). This was what would become classic Chomsky. In my opinion is is excellent Sophistry, having a conclusion and fitting the facts to support the conclusion. Lawyers do it all the time and even some historians do so. Simply stated Chomsky rewrote his view of Japan' taking of China as driven by US Foreign Policy and then went on to link it to Viet Nam. It was my first time reading a powerful piece on the Viet Nam War. It too me almost 30 years to come back and

understand it, and fifty years almost to counter it. I was then a strong supporter of Chomsky, even seeing his way as the only way. It took those 50 years of seeing the world up close to understand it.

Then there is the [Kennan Telegram](#). Kennan saw Russia up close, as a diplomat. It would take me to the late 70s to see the Soviets up close in treaty negotiations and then from the mid 90s to mid 2000s to have them as business partners. The one thing I saw even in the 70s was that we and the Russians at core have the same values, our children. I recall talking with some Russians and we went to our children, we both wanted them to see a future, we both saw nuclear weapons as devastating. The RISOP scenarios I recalled lead to the elimination of not only humanity but nature. Kennan saw a middle way, that of delimiting Soviet reach, containment.

Now on the one hand we have the Chomsky view of seeing the US as the source of all international upheaval and the Kennan view of Soviet imperialism, a view which the US had to deal with, and was not the cause.

Now we have Iran, Persia to those of us who have long memories. Persia has for almost 3000 years tried to gain territory to the West, Xerxes, Darius, and the list goes on. Today they are not as strong, except through the power of a nuclear weapon. Do its leaders share the love of their children that we and the Russians do? That may be the only question worth asking. Nuclear weapons are not sending a plane into the World Trade Center. A nuclear event is devastating.

Now along comes some "expert" in [The Syndicate](#) to tell us what we should believe. He states:

Forget the French Revolution as a model: the so-called Thermidorian Reaction, when moderates ended Robespierre's Reign of Terror, was an exception to the pattern of modern revolutions. The typical pattern during our living memory is that the hardliners come after the moderates. In the Soviet Union, for example, it was hardliners after World War II who strove to export Marxist-Leninist revolution, condemning the world to decades of cold war.

Somehow Revolutions are not all the same. Many have studied the French Revolution and the rise of a Robespierre is a complex issue. The generalization the author makes in my opinion is totally without merit.

The author continues:

Worse was to follow for those hoping for better US-Iran relations. First, there was Bush's "axis of evil" speech in 2002. Then, in February 2005, just as the hardline Ahmadinejad was about to begin his first term as president, Bush formally rejected a nuclear deal that had been painstakingly negotiated by Rouhani (then Khamenei's representative in Iran's Supreme National Security Council) and signed in late 2004 by France, Germany, and Britain. As Iran scanned the strategic horizon, it seemed obvious that the US had invaded Iraq because Saddam did not have any weapons of mass destruction. This made Ahmadinejad's insistence on Iran's nuclear "rights" popular with the Iranian masses and the middle class alike.

Enough already with the Bush bashing. It is a poor Chomsky like way to blame others for Iran's actions. Even the Soviets did not chant "death to America". Should we take such chants

seriously? If one would in my opinion follow Chomsky we must ask ourselves "what have WE done to make them do this?". If we were to follow Kennan we would seek "containment".

The author concludes:

For Iran, what counts now is no longer ideology but national interest and realpolitik. That is why it finds itself currently backing the opponents of revolutionary Islam: Bashar al-Assad against the Islamists in Syria and the Houthis against al-Qaeda in Yemen. And it is why it finds itself not only signing a nuclear accord with the Great Satan but also tacitly cooperating with it against the Islamic State, their common enemy. Now that the revolution is over, cooperation in other areas is likely to become equally appealing.

The conclusions in my opinion lacks any touch of reality. Iran backs the Syrian regime for religious reasons. It does so for the other mentioned enemies. There is no realpolitik. There is a collection of funds and sellers of arms, Russia and China.

Thus how should the US react. Again I would go back to Kennan. We can bemoan whatever Chomskique actions taken but that will not control the future. What will and only will is a strong policy of containment. There is an inevitability of them attaining nuclear weapons, a clear and present danger to humanity. Yet Pakistan and India are in the same club. The US strategic nuclear policy covers only China and Russia. We somehow neglect Pakistan and India. We must add all three to this containment strategy and pray that they like the Russians value their children.



Labels: [Nuclear Weapons](#)

WEDNESDAY, AUGUST 19, 2015

[TEXT BOOKS, TUITION AND HARVARD](#)

In an interesting post [Mankiw](#) has a bit on the ratio of text book prices to annual tuition. Now there is quite a bit of apples and oranges here. But it is worth the study.

1. Text books have expanded in complexity and useless fill in the last 150+ years. For example I gave my granddaughter an 1880 algebra book, she is going into 7th grade and completing that course. You see algebra has not changed a great deal. In fact current texts contain more confusing extraneous materials that a good old 1880 version is just fine. I used an 1895 Geometry one for grandsons and that was sufficient. And yes they all cost less than \$5.00.
2. The production of text books, on the printer's side have dropped dramatically. The promotion costs have expanded. Getting someone to use the latest version of Calculus, and yes Macroeconomics, just pushes up the price, and the cost falls on sales not production. Nothing is new in Calculus, at least for the past 100 years. So get an old book for a couple of dollars and you are set.
3. Tuition reflects a lost more over head now than 150 years ago. Just think, there was no Title IX, and all the other mandated Government stuff. Text books did not do that.

4. Production efficiency in pedagogy seems to have been negative, less teaching student-hours and more other stuff.

It is a worthwhile observation but worthy of a great deal more insight.



Labels: [Academy](#)

MONDAY, AUGUST 17, 2015

[AN ALTERNATIVE TUNNEL](#)

The [NY Times](#) is advocating for a new tunnel under the Hudson. As they state:

The only long-term solution is the construction of a new tunnel complex, as proposed by Amtrak in its Gateway Program. Without a new tunnel and new rail tracks, a massive storm or some other disaster could sever a critical link in the Northeast rail corridor that serves more than 750,000 people a day on 2,000 intercity and commuter trains. For commuters and rail passengers crossing the Hudson River who are already complaining about delays, it can only get worse.

That is giving Amtrak from the Feds and States the money to build the tunnel. But I remember the first time I took a cab from the new Hong Kong airport through the new tunnel, a privately owned and financed tunnel. It was built in a very short time period, cost the Hong Kong taxpayers nothing, and was paid by those who used it.

Why not try that one. I use the train to Penn Station whenever I get to the city. The old facilities are rally falling apart and need replacement. But Government does not seem to work, especially Amtrak. So why not emulate the Chinese, it works.



Labels: [Commentary](#)

[MORE THOUGHTS OF KENNAN: RUSSIA AND/OR IRAN](#)

George Kennan in his lecture on American Diplomacy articulated a path to dealing with the USSR, in fact Russia. The following summarizes his view:

But we have seen that the Kremlin is under no ideological compulsion to accomplish its purposes in a hurry. Like the Church, it is dealing in ideological concepts which are of long term validity, and it can afford to be patient. It has no right to risk the existing achievements of the revolution for the sake of vain baubles of the future. The very teachings of Lenin himself require great caution and flexibility in the pursuit of Communist purposes. Again, these precepts are fortified by the lessons of Russian history: of centuries of obscure battles between nomadic forces over the stretches of a vast unfortified plan. Here caution, circumspection, flexibility and deception are the valuable qualms; and their value finds natural appreciation in the Russian or the oriental mind. Thus the Kremlin has no compunction about retreating in the face of superior force. And being under the compulsion of no timetable, it does not get panicky under the necessity for such

retreat. Its political action is a fluid stream which moves constantly, wherever it is permitted to move, toward a given goal. Its main concern is to make sure that it has filled every nook and cranny available to it in the basin of world power. But if it finds unassailable barriers in its path, it accepts these philosophically and accommodates itself to them. The main thing is that there_ should always be pressure, increasing constant pressure, toward the desired goal. There is no trace of any feeling in Soviet psychology that that goal must be reached at any given time.

These considerations make Soviet diplomacy at once easier and more difficult to deal with than the diplomacy of individual aggressive leaders like Napoleon and Hitler. On the one hand it is more sensitive to contrary force, more ready to yield on individual sectors of the diplomatic front when that force is felt to be too strong, and thus more rational in the logic and rhetoric of power. On the other hand it cannot be easily defeated or discouraged by a single victory on the part of its opponents. And the patient persistence by which it is animated means that it can be effectively countered not by sporadic acts which represent the momentary whims of democratic opinion but only by intelligent long-range policies on the part of Russia's adversaries policies no less steady in their purpose, and no less variegated and resourceful in their application, than those of the Soviet Union itself.

In these circumstances it is clear that the main element of any United States policy toward the Soviet Union must be that of a long-term, patient but firm and 'vigilant containment of Russian expansive tendencies. It is important to note, however, that such a policy has nothing to do with' outward histrionics: with threats or blustering or superfluous gestures of outward "toughness." While the Kremlin is basically flexible in its reaction to political realities, it is by no means unamenable to considerations of prestige. Like almost any other government, it can be placed by tactless and threatening gestures in a position where it cannot afford to yield even though this might be dictated by its sense of realism. The Russian leaders are keen judges of human psychology, and as such they are highly conscious that loss of temper and of self-control is never a source of strength in political affairs. They are quick to exploit such evidences of weakness. For these reasons, it is a sine qua non of successful dealing with Russia that the foreign government in question should remain at all times cool and collected and that its demands on Russian policy should be put forward in such a manner as to leave the way open for compliance not too detrimental to Russian prestige.

The key elements are that the Russians have a different view of time and we must let them preserve their prestige. Nothing has changed. Yet does this in any way apply to Iran, Persia in a historical context. The true issue is; does the United States today have a diplomatic core capable of having this discussion or have we politicized the extreme political tendencies of the State Department even further.

The US State Department has not always been the bastion of clever strategic thinking. Hay and the Open Door policy may have very well set the stage for Pearl Harbor. The State Department closed the doors to the Jews in the 30s. The list goes on. The problem now is that Executive Agreements can be cut that are not Treaties yet have significant influence. One wonders if we have any more Kennans.



Labels: [Russia](#)

[OCKHAM VERSUS THE SCHOLASTICS](#)

[Friedman's book, *Medieval Trinitarian Thought*](#), is an exceptionally accessible work discussing the complex issue of the Christian concept of the Trinity. Many of the early heresies in the Christian Church dealt with what was interpreted as false views on what the Trinity was. The complexity of the Trinity is driven by the acceptance of Jesus as God but also man and the incorporation of the Holy Spirit as a separate manifestation of God. The former was a result of the acceptance of the four Gospels, especially that of John and the latter the acceptance of the Acts of Paul. The complexity was further complicated by the inclusion of Greek philosophical thought and terms of philosophical understanding that became the tools to make this interpretation.

It was left to Augustine to lay for the Western Church a foundation that lasted almost a millennium until Aquinas delved into the process again in the 13th Century. To some degree the development ends as so many of these pursuits with Ockham. Ockham rejects the Academics and states that one can accept the Trinity *sola fide*, on faith alone. It is Ockham who introduces the concepts of Nominalism, the importance and criticality of the individual, the ability to rely on faith, and of course his accusation of heresy to the Pope in Avignon.

The Aquinas versus Ockham debate is first framed as the Dominican versus Franciscan debate. In Chapter 1 the author in the clearest of terms describes the debate. Here we have the Dominicans trying to rely on Aristotelean constructs and speak of the Trinity as a familiar set of relationships. The Franciscans take a more ethereal approach and lay out the emanation approach. It is Ockham, a Franciscan, who takes the ultimate extreme of rejecting both and stating that faith alone carries the day. This is a brilliantly written Chapter, one of the best I have seen addressing this debate. It may have been improved if it has a preface discussing Augustine a bit more and also the early Church debates, but that in no way detracts from the presentation.

Chapter 2 discusses the Psychological Model, or as the author states on pp 50-51 that the Son is literally the Concept of the Father and the Holy Spirit is the Love produced by the will shared by the Father and the Son. The author clearly explains the evolution of this approach via John's Gospel and the use of the term logos. In Latin the term is verbum and yet there may be a slight but material difference between the two terms. There is a brief integration of the Augustine thought on this approach.

Chapter 3 discusses the Trinity and Metaphysical thought. Chapter 4 is a key chapter; it introduces Ockham and *sola fide*. This is an especially clear and well written presentation. The author examines Gilson, the French Neo-Scholastic, and presents a well-structured Gilsonian analysis and contrasts it to Ockham. Whereas Gilson is a Thomist, and Thomism has persevered in classic Catholicism, the Ockham school does lend itself to a bifurcation of Scholastic approach into one that faith exists and can play a vital role to that attempt to use reason to explain all the nuances introduced in the New Testament.

Overall I would highly recommend this exceptional book. Although it deals with a highly complex and specialized issued, it does so fairly and in a quite readable manner. It is not a classic

heavy tome of Scholastic formalism but a clearly articulated discussion of a core principle of Christin belief.



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

SUNDAY, AUGUST 16, 2015

[LET THE SALES BEGIN!](#)

[China Daily](#) reports that it is negotiating sales of an F 16 knockoff to Iran in anticipation of the deal.

As they state:

The China-made J-10 multi-role fighter jet is a suitable choice for Iran if the Middle East power decides to upgrade its aging military aircraft fleet, Chinese aviation experts said. "Once the sanctions against Iran are completely lifted, the country will definitely renovate its civilian and military aircraft fleets. The J-10 is a good option for the Iranians because it can fulfill all operations they want to conduct," said Wang Ya'nan, deputy editor-in-chief of Aerospace Knowledge magazine. "In addition to air combat, our J-10 is also capable of performing air-to-surface strikes and anti-ship operations," he added. "Moreover, the Iranians must have known that China, among other major weapon exporters, is the most reliable supplier when it comes to arms deals. China is also very flexible in payment issues."

Thus the immediacy to see the market opportunity and arm Iran is at the top of the list of advantages of this deal. The idea of unintended consequences may not have been fully appreciated!

One should read and re-read Kennan's short work, American Diplomacy, and better understand all the mistakes the US has made over the years.

Having been a small part of the CTBT during the Carter period, verification of compliance is essential. Second is consequences to violations. Verification here appears to be near zero, since one could not tell until after an explosion.



Labels: [China](#)

[RUSSIA, THE TELEGRAM, KENNAN: THEN AND NOW](#)

From time to time it is worth re-reading Kennan's "Telegram" on Russia, then it was the Soviet Union, and ask what has changed; players or roles, or nothing?

On February 22, 1946 Kennan wrote:

At bottom of Kremlin's neurotic view of world affairs is traditional and instinctive Russian sense of insecurity. Originally, this was insecurity of a peaceful agricultural people trying to live on vast exposed plain in neighborhood of fierce nomadic peoples. To this was added, as Russia

*came into contact with economically advanced West, fear of more competent, more powerful, more highly organized societies in that area. But this latter type of insecurity was one which afflicted rather Russian rulers than Russian people; **for Russian rulers have invariably sensed that their rule was relatively archaic in form fragile and artificial in its psychological foundation, unable to stand comparison or contact with political systems of Western countries.** For this reason they have always feared foreign penetration, feared direct contact between Western world and their own, feared what would happen if Russians learned truth about world without or if foreigners learned truth about world within. And they have learned to seek security only in patient but deadly struggle for total destruction of rival power, never in compacts and compromises with it.*

Perhaps this applies quite well today. Russia today, albeit becoming more main stream, is still stuck in a Czarist state of strong rulers and limited outwardness.

He continues:

*In international economic matters, Soviet policy will really be dominated by pursuit of autarchy for Soviet Union and Soviet-dominated adjacent areas taken together. That, however, will be underlying policy. As far as official line is concerned, position is not yet clear. Soviet Government has shown strange reticence since termination hostilities on subject foreign trade. If large scale long term credits should be forthcoming, **I believe Soviet Government may eventually again do lip service, as it did in 1930's to desirability of building up international economic exchanges in general.** Otherwise I think it possible Soviet foreign trade may be restricted largely to Soviet's own security sphere, including occupied areas in Germany, and that a cold official shoulder may be turned to principle of general economic collaboration among nations.*

Russia in order to prosper and move from a pure extraction economy must seek to open up and allow for the creation of a full entrepreneurial society. It can adhere to many of its past ways but as to its relationship with the West it must seek trade related development.

The Kennan conclusion was:

*In summary, **we have here a political force committed fanatically to the belief that with US there can be no permanent modus vivendi that it is desirable and necessary that the internal harmony of our society be disrupted, our traditional way of life be destroyed, the international authority of our state be broken, if Soviet power is to be secure.** This political force has complete power of disposition over energies of one of world's greatest peoples and resources of world's richest national territory, and is borne along by deep and powerful currents of Russian nationalism. In addition, it has an elaborate and far flung apparatus for exertion of its influence in other countries, an apparatus of amazing flexibility and versatility, managed by people whose experience and skill in underground methods are presumably without parallel in history. Finally, it is seemingly inaccessible to considerations of reality in its basic reactions.*

Thus one wonders if Russia is going backwards or whether it will seek accommodations with the rest of the economic world. Perhaps we will only know when we see "Made in Russia" in Walmart.



Labels: [Russia](#)

[A MEASURE OF THE ECONOMY](#)



From time to time it is worth looking at some metrics to see if we are going anywhere. The above is the totality of Real Estate Loans. They are coming back to where we were at the time of the collapse. Also the annualized growth rate has been positive for quite a while but not too big, as compared to before the crash. This may be a good sign of returning stability. It is also amazing to see how bad we were before the crash!



Labels: [Economy](#)

[DID ANYONE EVER TAKE GEOGRAPHY?](#)



New Guinea was a major front during WW II. MacArthur landed on the northern side, I recalled from the exploits of my father's Destroyer records at the time. Today New Guinea is split down the middle. The West is Indonesia and the East is Papua. The interior is impenetrable. Abot 2 to 3 meters from the waterline one can no longer see the fingers on an out stretched hand, the growth of vegetation is so great.

Yet in all the news channels they indicate Papua as the West! Just check Google maps, please, someone! I am totally amazed at the general incompetence of the news media. Really guys! It is just Grammar School geography!

This is reflective of the general competence or lack thereof of both our media and our education system. I had this in the 5th grade with Sister Rosita. As did the Public School colleagues.

Why not try this one out on the Candidates, even the former Secretary of State!



Labels: [Commentary](#)

FRIDAY, AUGUST 14, 2015

[REINTERPRETING PEARL HARBOR](#)



I have to admit that being alive during WW II and with a father in the Pacific the position taken by Japan still rings loudly. Thus in reading Abe's somewhat self serving piece in [The Syndicate](#) I was a bit taken aback.

For example he states:

With the Manchurian Incident, followed by withdrawal from the League of Nations, Japan gradually transformed itself into a challenger to the new global order that the international community sought to establish after such tremendous sacrifices. Japan took the wrong course and advanced along the road to war.

The Manchurian Incident was a massive invasion and occupation by Japan of China's territory resulting in the massacre of thousands in Nanking.

Then he states:

More than one hundred years ago, vast colonies, possessed mainly by the Western powers, stretched across the world. With their overwhelming supremacy in technology, waves of Western colonial forces surged toward Asia in the nineteenth century. There is no doubt that the resulting

sense of crisis drove Japan to pursue modernization. Japan established a constitutional government earlier than any other country in Asia, and preserved its independence throughout. The Japan-Russia War gave encouragement to many people under colonial rule from Asia to Africa.

But was that an excuse for the assault on Pearl Harbor, for the Death Marches, for the abject slaughter?

Abe, in my opinion, writes a classic "on the one hand and on the other hand" piece. Japan had defeated Russia. Japan then occupied land mass after land mass, gathering up natural resources it needed in its attempt to defeat the United States.

Abe continues:

We will engrave in our hearts the past, when Japan attempted to break the deadlock it faced with force. Upon this reflection, Japan will continue to uphold firmly the principle that any disputes must be settled peacefully and diplomatically, based on respect for the rule of law, and to reach out to other countries in the world to do the same. As the only country to have ever suffered the devastation of atomic bombings during war, Japan will fulfill its responsibility within the international community, aiming at the non-proliferation and ultimate abolition of nuclear weapons.

I recall the [writing from my father's shipmate](#) which recorded today, as they prepared in the Aleutians for an invasion of Japan and sure death, that the men who had survived Japanese attack after Japanese attack and seen hundreds of their shipmates dismembered by Japanese shells, just sit in tears on the deck of their Destroyer, knowing that the end of the horror was near. Regrettably it was Hiroshima, and Nagasaki, but the end was quick, and the lives lost significantly attenuated.

Perhaps Japan may someday come to the point of recognizing that it really was not on the one hand and on the other, but that they made a terrible error. Yet it is this understanding that should be understood by all, for such errors, as can be self justified, can be repeated. The consequences of nuclear weapons are a horror mankind must avoid, and that means an acceptance of consequences, not an attempt to justify, no matter how slightly.

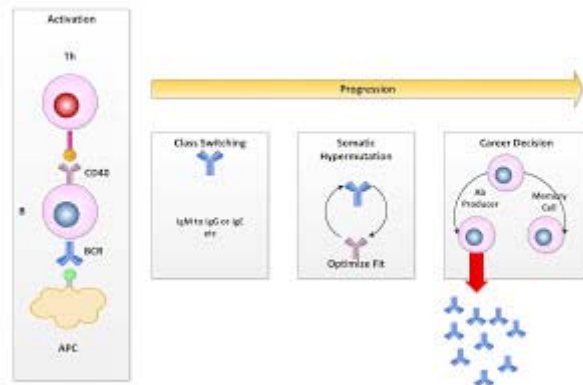


Labels: [Commentary](#), [Japan](#), [Nuclear Weapons](#)

THURSDAY, AUGUST 13, 2015

[INTERESTING WORK ON MABS](#)

Monoclonal antibodies are a class of antibodies which on the one hand reflect a response to a specific antigen and on the other hand can activate the immune system to respond to the cells presenting to that antigen and have them eliminated if possible.



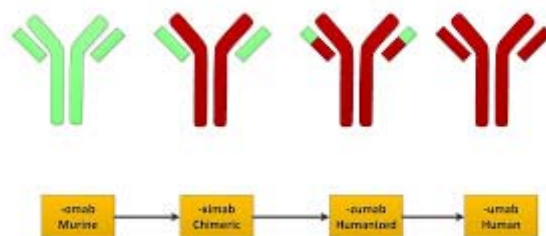
Back in the mid-1960s when I first came across the clinical use of antibodies what was frequently employed was gamma globulin, a massive amount of mixed IgG, immunoglobulin G, from many people and it was somewhat tried as another treatment for a variety of disorders including some cases of mumps. However the specificity of IgGs and the other immunoglobulins had not yet been ascertained.

As this identification progressed it became apparent that specificity of the antibodies could perhaps be a tool to attack certain disorders, including cancers. This then led to many examinations of ways to produce large volumes of specific antibodies. The result was the development of monoclonal antibodies. Simply this is the chimeric combination of antibodies developed to attack a specific target and a vehicle cell that had immortality to bind this product to so it became a small factory for production. From this came, after a significant amount of effort, the monoclonal antibody, and in turn the new therapeutics ending in –mab.

The work of Marks, *The Lock and Key of Medicine*, is an effort to tell this story. It starts with some of the early researchers in the UK who persevered to get some of the initial samples available and the ever changing dynamic of researchers and clinicians. As with so many efforts of this type, there is an ever challenging set of steps that the researchers and the clinicians go through, some winning and some losing. The early days of the late 1960s, when in the practice of medicine little was truly understood but the tools for the researchers were coming on quickly.

The author takes the reader through the many individuals and the many crises and victories as they progressed. The book focuses on the many individuals and their steps in developing MABs and the ultimate commercialization of them and their application to human therapeutics.

As we progress we have seen basically four classes of Mabs. They are: murine or mouse versions with therapeutics ending in –omab, chimeric murine and human Mabs with the ending –ximab, the humanized Mabs ending in –zumab, and finally all human Mabs ending in –umab. Mabs are now one of the arms in treating a variety of diseases from cancer to arthritis and colitis. At the same time they have become “big pharma” and the author takes the reader through this process in some detail.



Overall, the book and an excellent articulation of the people, the conflicts, the achievement, and the institutional progress. From that perspective is an excellent contribution.

On the other side it would have been more helpful to have provided some simpler introductions to Mabs and the immune system. For a well-educated reader this is an interesting tale of scientific and clinical development. It does lack a feeling of personal involvement. The description of the individuals is in my opinion quite arm's length and unlike other works of similar genre this is a discussion of facts and events and dates.

What I especially missed was the recent explosion of applications. For example in advanced melanoma there is the use of Mabs and pathway control therapeutics such as BRAF inhibitors and MEK inhibitors. This raises the issue of how does one see a blending of these two or are they not so complementary. On the other hand there are certain cancers such a prostate cancer which may be so complex and changing at such a rapid rate that Mabs would just not work. It would have been useful for the author to have contributed some substance to the debate.

Overall, again, this is an excellent book albeit for possibly a smaller community of engaged readers.



Labels: [Books](#)

THURSDAY, AUGUST 13, 2015

[MORE ON PCORI](#)

PCORI has now exceeded \$1 B in funding as a result of the ACA. One [should examine the projects](#). Its head recently stated in an email:

We've just marked a major milestone here at PCORI - topping \$1 billion in funding approved for research projects and other initiatives that will help patients and those who care for them make better-informed healthcare choices.

We're proud of these investments, all of which support our mandate to advance comparative clinical effectiveness research (CER), studies of what works best for whom under which circumstances. All of our awards are approved by our Board of Governors and reflect ongoing input from patients, family caregivers, clinicians, and other stakeholders from across the healthcare community. All directly fulfill our mission to both improve the quality and relevance of evidence available to clinical decision makers and the methods used to see that this evidence is reliable. And all ensure that we live up to our name by supporting research addressing the questions and concerns of patients and other stakeholders. Two-thirds of our awards to date, nearly \$680 million, support studies of the effectiveness of two or more approaches to care focusing on outcomes that matter to patients

However when one tries to examine what may actually have been accomplished it seems in my opinion to be fairly empty. Needless to say they will continue to burn \$500 M or more each year, a sum which frankly could be much better spent elsewhere.



Labels: [Health Care](#)

[CALORIES ARE CALORIES?](#)

In a recent [NIH study](#) there was an attempt to demonstrate that fat calories were more effective in adding body fat than carbohydrate calories.

The procedure was as follows:

The researchers studied 19 non-diabetic men and women with obesity in the Metabolic Clinical Research Unit at the NIH Participants stayed in the unit 24 hours per day for two extended visits, eating the same food and doing the same activities. For the first five days of each visit they ate a baseline balanced diet. Then for six days, they were fed diets containing 30 percent fewer calories, achieved by cutting either only total carbs or total fat from the baseline diet, while eating the same amount of protein. They switched diets during the second visit.

They conclude:

“Our data tell us that when it comes to body fat loss, not all diet calories are exactly equal,” “But the real world is more complicated than a research lab, and if you have obesity and want to lose weight, it may be more important to consider which type of diet you’ll be most likely to stick to over time.”

Now there are several issues here:

1. The sample is much too small
2. The duration time is much too short
3. The switching is in the middle of a metabolic change which takes possibly weeks, not hours to

adapt.

4. The key issue is the definition of a calorie. Namely if we measure 3500 Kcal = 1 pound, then how do we differentiate at all?

This is not in my opinion a study of any value for the above and many other reasons.



Labels: [Health Care](#)

WEDNESDAY, AUGUST 5, 2015

[GINKGO AND HIROSHIMA](#)



Seventy years ago Hiroshima was bombed. Some nearly 20KT yield uranium device fell some 30,000 feet and exploded several thousand feet above the city. The result was a massive ring of destruction. Surviving that was a few century old Ginkgo trees, trees which themselves had survived some 250 million years^{12[1]}. As a symbol of survival the Ginkgo has great standing. As we look backwards and then again look forward one thinks of these Ginkgos.

Some twenty five years ago I took a handful of Ginkgo nuts from the trees at the New York Botanical Garden. I placed them in my pocket, stink and all, and let them sit in my refrigerator to cold stratify over the winter and then planted them in my seed beds. Up they came and now twenty five years later I have one female tree filled with Ginkgo nuts. The legacy of 250 million years goes on. The hardy tree may survive us all, in some way shape or form, since its seeds will be transplanted elsewhere, to grow again.



Labels: [Commentary](#)

^{12[1]} <http://www.bbc.com/news/uk-england-manchester-29920359> and <http://kwanten.home.xs4all.nl/hiroshima.htm>

MONDAY, AUGUST 3, 2015

[WHY NOT TO USE WINDOWS 10](#)

When Microsoft does things they almost always, always in my opinion, do it for their sole benefit. One twist in W10 is the peer to peer updating. Yes indeed, you get to work for Microsoft FREE. No not really, you may actually have to pay!

[PCWorld](#) has a great piece describing what it does. Simply W10 has a peer to peer system. Kinda like BitTorrent, except for Microsoft. When you get an update, they then use you to send that update to many others. You suddenly become a peer or even a Tracker as in BitTorrent and you never know it. It is your bandwidth which is used and if your service is measured you are then paying for it.

Simply:

1. Microsoft W10 has a P2P system
2. Microsoft downloads an update
3. You then via the P2P send it to peers or lechers.
4. You pay for the up load BW
5. Microsoft has enlisted you in their business and you get to pay.

Beware W10, what else is there?

But also beware if the P2P can be hijacked and some third party now uses you to send God knows what! The Feds get your IP address and you without any knowledge may be thrown into a long painful process.

The PCWorld piece tells how to disable this. There surely are many more such traps. Beware of those folks bearing gifts. W10 may not be "free" after all!



Labels: [Microsoft](#)

SUNDAY, AUGUST 2, 2015

[CHINA AND PATENTS](#)

[China Daily](#) reports:

China recorded 928,000 invention patent applications in 2014, more than that of any other country, for the fourth consecutive year, according to data released by the State Intellectual Property Office on Monday.

The office found that about 663,000 inventions had high quality and market value. About 4.9 patents per 10,000 population were filed, according to the data. Enterprises have been pillars of research and the development of new technologies and products, according to the office. In 2014, about 485,000 invention patent applications were filed by enterprises, more than the number filed by individuals, academies or research institutes.

It is not clear just where those patents apply nor was there a breakdown by area. However this is a clear national goal and as with most things there is strong Chinese unity and drive. I always wonder why Russia is so far behind. The Russian have always had brilliant technologists but they are clearly way behind in biotech and other areas of focus in the 21st century.



Labels: [China](#)

SATURDAY, AUGUST 1, 2015

DUMB, DUMB, DUMB!

I took my annual trip to Seaside Park today. It is a ritual. I started in 1960 when I was first a Lifeguard in New York City. We would take our day off, a Wednesday and drive down in O'Neil's fathers white Lincoln Continental. It was beautiful, the water was clean, we could swim, and we could make fun of wimpy New Jersey Seaside Life Guards. We were after all from Coney Island, and other New York Beaches, we were all well over 6' and we walked with the confidence of having survived July 4th with over 1 million bathers!

Why Seaside, it was just because it was there, and far enough from New York that the Jersey Sewers did not deposit Jersey stuff on the sands. You see in those days Jersey had no sewer plants and they, well to be crude, dumped their stuff in the harbor. It would then wash onto our beaches! We refrained from swimming except under dire circumstances, and one of our guys was a 3rd year med student so we had all kinds of antibiotics.

But now it is a routine, down to Seaside, trying to support them after their multiple disasters. But this year, in my opinion, some Government entity decided to install electronic parking meters.



Now the screen for instructions faces the sun, is about 3" by 2", and the font looks like 4pt Arial. The font is almost the same color as the screen. Lines of dozens of people are waiting as each tries to read what to do, half leave in disgust!. I have never, in my opinion, seen a system so incompetently designed. I asked the local police if this was a common complaint, YES. It is clear to me, in my opinion, that the town may just not want any visitors! Only in New Jersey. Perhaps these were the same programmers who did ObamaCare web site? Not really, at least you could read that.



Oh Yes, this is politically correct, it is solar powered, but guys the sun is 90 degrees off, it shines on your screen! I guess they were educated in New Jersey Schools!

Let's see how the pig race turns out!

Oh by the way, I have been reminded that the candidate from Queens has used a similar tale to bemoan solar. Now this is not a solar rant, in fact our oldest is the solar guy for the NH Electrical Co-Op. We also have wind turbines in NH. The problem there is distribution. Namely we have a century old electrical distribution network and technology can do so much more. The problem here is design. Small letters, poor contrast, complex entry mechanisms, and facing the sun to make it unreadable, unworkable. So unlike the Candidate from Queens, my gripe as the "Voice from Staten Island" is if all else fails.... listen to the customer! But that is something Government entities fail to do, since there is no cost at messing up.



Labels: [Commentary](#)

FRIDAY, JULY 31, 2015

POLITICS AND PIGS



August is County Fair month. And County Fairs always have pig races. In a sense I look forward to next week's debate as an adjunct to the County Fair.

Which pig are you betting on?



Labels: [Commentary](#)

THURSDAY, JULY 30, 2015

THE PRESS AND THE PROSTATE

There are times when you have to say; "You cannot make this up!". In a [WAPO](#) piece today the reporter extols the work of [some Brits](#) who have on some work on a very small sample and have identified a few genes, mRNA, SNPs etc and from this have developed a staging type system. One should add this to the list of hundreds of others.

Now the researchers state:

We show the relative contributions of gene expression and copy number data on phenotype, and demonstrate the improved power gained from integrative analyses. We confirm alterations in six genes previously associated with prostate cancer (MAP3K7, MELK, RCBTB2, ELAC2, TPD52, ZBTB4), and also identify 94 genes not previously linked to prostate cancer progression that would not have been detected using either transcript or copy number data alone. We confirm a number of previously published molecular changes associated with high risk disease, including MYC amplification, and NKX3-1, RB1 and PTEN deletions, as well as over-expression of PCA3 and AMACR, and loss of MSMB in tumour tissue. A subset of the 100 genes outperforms established clinical predictors of poor prognosis (PSA, Gleason score), as well as previously published gene signatures ($p = 0.0001$). We further show how our molecular profiles can be used for the early detection of aggressive cases in a clinical setting, and inform treatment decisions.

Frankly much of the above was known in some way shape or form. There are also quite a few

commercial tests available already. Now WAPO states:

Through genomic profiling of 259 men with prostate cancer, scientists have identified five groups of prostate cancer with distinct DNA signatures. The discovery represents a major advance as researchers can now begin trying to tailor therapies to those subtypes. The approach has worked well in breast cancer and helped millions avoid the unnecessary cost, pain and time spent on treatments that are destined to fail. [Obama touts 'lifesaving' potential of personalized medicine] Such work is the backbone of President Obama's \$215 million precision medicine initiative announced in January, which aims to pioneer a new approach to how we treat disease by moving away from a "one-size-fits-all" approach to medicine to one that takes into account things like a person's genetic makeup, or the genetic profile of a tumor.

Now this is UK, Sweden, and Norway work. It also is at best personalized but not precise. One can be "precise" but inaccurate. I can tell you precisely where something is but it may not be there. But alas I guess English is no longer used "good" uh well.

Now if the WAPO author had understood where the work in this area is going perhaps they would have had a better view. In fact we have detailed work by [Gundem et al in Nature](#) just a short while back. They noted:

Using whole-genome sequencing, we characterized multiple metastases arising from prostate tumours in ten patients. Integrated analyses of subclonal architecture revealed the patterns of metastatic spread in unprecedented detail. Metastasis-to-metastasis spread was found to be common, either through de novo monoclonal seeding of daughter metastases or, in five cases, through the transfer of multiple tumour clones between metastatic sites. Lesions affecting tumour suppressor genes usually occur as single events, whereas mutations in genes involved in androgen receptor signalling commonly involve multiple, convergent events in different metastases. Our results elucidate in detail the complex patterns of metastatic spread and further our understanding of the development of resistance to androgen-deprivation therapy in prostate cancer.

Namely they noted that prostate metastatic cells in the body had a disparate set of genetic changes. In fact the profiles were quite complex. Thus any small sample as in this article is in my opinion suspect.

As [Cancer UK](#) notes:

First, the researchers looked at copy-number alterations in tumour samples from 156 men who had undergone surgery in Cambridge to remove their prostate after being diagnosed with cancer. They then analysed the levels of thousands of mRNAs in these same samples. Next, they compared the two sets of results. Could they find regions of genetic disruption that, by altering gene activity – the level at which they are switched on or off – could be driving the growth of tumours? The answer was yes – they spotted around 1,000 genes where changes in the copy-number – that is, they were deleted or repeated – also changed gene activity. The researchers then homed in on 100 genes with the greatest change compared with healthy samples and which seemed to be crucial to prostate cancer growth, and looked to see how their activities varied

*across the 156 men. They found that by using this group of 100 genes – or gene signature – prostate cancer patients who'd had surgery to remove their prostate could be divided into **five distinct sub-groups**.*

- *One group had lots of DNA deletions and consequently low activity of certain genes*
- *Another had high amounts of DNA repetition which resulted in increased activity of specific genes.*
- *Two more groups had very few copy-number alterations, or changes in activity.*
- *The fifth and final group had some – but not too many – copy-number alterations.*

But one may ask; how do these compare with all the others? Also the sample size is quite small. As [Science Daily](#) states:

"This research could be game-changing if the results hold up in larger clinical trials and could give us better information to guide each man's treatment -- even helping us to choose between treatments for men with aggressive cancers. Ultimately this could mean more effective treatment for the men who need it, helping to save more lives and improve the quality of life for many thousands of men with prostate cancer."

Namely the authors themselves seem to readily admit the small sample size issue.

But there are two points to be made:

1. All too frequently authors extend the significance of their results. This is the equivalent of "shingling the roof in the fog". Be careful.
2. The Press, especially WAPO, uses this as some adulation of the Obama Administration. It was NOT in the US and IT IS NOT CONCLUSIVE!

It is truly amazing in my opinion how political even basic medicine has become, especially in reporting.



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

WEDNESDAY, JULY 29, 2015

[MEDICARE AND TELEMEDICINE](#)

Telemedicine is a rather complicated issue. It can be quite helpful but then again it may be an added cost. The CBO is examining this to some degree and it is worth following.

As [CBO](#) states:

Whether expanding Medicare coverage for telemedicine services would increase or decrease federal spending is difficult to predict, but doing so depends on two main considerations:

- *The payment rates that would be established for those services, and*
- *Whether those services would substitute for (or reduce use of) other Medicare-covered services or would be used in addition to currently covered services.*

If all or most telemedicine services substituted for or prevented the use of more expensive services, coverage of telemedicine could reduce federal spending. If instead telemedicine services were mostly used in addition to currently covered services, coverage of telemedicine would tend to increase Medicare spending. Many proposals to expand coverage of telemedicine strive to facilitate enrollees' access to health care. Therefore, such proposals could increase spending by adding payments for new services instead of substituting for existing services.

Many Medicare patients are with chronic diseases such as Type 2 diabetes, COPD, congestive heart failure and the like. Even cancer patients just need monitoring, not face time. There development of methodologies to do this remotely is exploding.

However, this is with an elderly population. They generally are not adept at the use of the new technologies, especially ones requiring a modicum of expertise, or patience.

Thus there is both an opportunity and a challenge. It is worth following.



Labels: [Health Care](#)

TUESDAY, JULY 28, 2015

STAT3 AND PCA: OF MICE AND MEN

Signal transducer and activator of transcription (STAT) proteins are powerful controllers of gene expression. Recent work has involved them in Prostate Cancer along with the many other targets which have been identified. We examine this specific gene and its recently identified significance. The specific STAT is STAT3. Previously it has been linked to aggressive cancers. In fact attempts have been made to therapeutically target this pathway. The authors in a recent paper however contend that it is just the opposite. Namely STAT3 actually prevent metastatic behavior.

This discussion is a critical one as we examine further the targeting of genes and their behavior. The STAT3 issue seems to state that on one hand over-expression is bad, yet then on the other hand over-expression is good. This highlights the issue of cross talk between paths as well as the yet to be fully understood dynamics of pathways. Add to this is the fact that STAT3 is driven by IL-6 and this links in the immune system as well.

We begin the discussion with information in a Press Release in Science Daily which reports^{13[1]}:

^{13[1]} <http://www.sciencedaily.com/releases/2015/07/150722081410.htm>

A gene that is responsible for cancer growth plays a totally unexpected role in prostate cancer. The gene Stat3 is controlled by the immune modulator interleukin 6 and normally supports the growth of cancer cells. The international research team led by Prof. Lukas Kenner from the Medical University of Vienna, the Veterinary University of Vienna, and the Ludwig Boltzmann Institute for Cancer Research (LBI-CR) discovered a missing link for an essential role of Stat3 and IL-6 signalling in prostate cancer progression.

Interleukin 6 (IL-6) is an important cytokine that controls the cell survival and tumor growth. Hyperactive IL-6 may support cancer growth, particularly as it controls STAT3, which was shown to have an oncogenic role in most tumours. Many therapies are therefore designed to suppress IL-6 or STAT3. But the situation is different in prostate cancer. Lukas Kenner's research group has shown that, contrary to expectations; active STAT3 suppresses cell growth in prostate tumours. It activates the gene p14^{ARF}, which blocks cell division and thus inhibits tumour growth.

IL-6 is one of many interleukin cytokines, activating immune cells and leading to their proliferation. In a classic model for STAT3, it is activated by IL-6 and then it progresses via phosphorylation to act as a promoter or enhancer for a multiplicity of genes whose expression leads to cancerous growth. However there is an alternative pathway, the ARF-MDM2-p53 pathway the controls and may mitigate some of these processes. This paper focuses on this crossover effect.

The article continues:

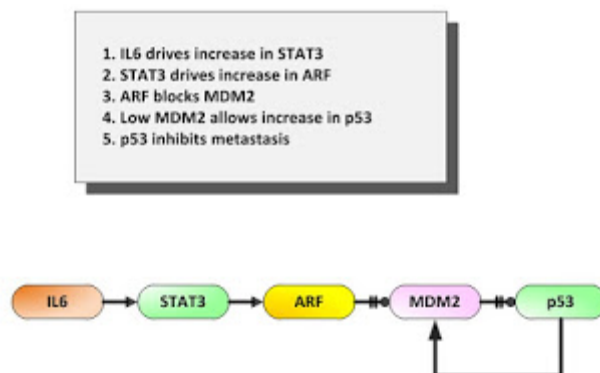
For this reason, STAT3 and p14^{ARF} are ideally suited to act as biomarkers for the prognosis of this disease. If these two factors are missing in tissue samples, the risk is massively increased that the tumour grows and forms metastases.

According to Lukas Kenner, this is important, as the predictive power of these proteins as biomarkers is twice as good as the previous gold standard. As only about 10 % of patients with prostate cancer die from the disease, this can help to prevent unnecessary therapeutic interventions with severe side effects such as incontinence and impotence. A non-invasive nuclear medical test based on these findings might soon be able to replace the painful removal of tissue samples to be examined.

The reversed role of interleukin 6 as an inhibitor of prostate cancer has an additional significance. Blockade of interleukin 6 is used to treat other diseases, such as rheumatoid arthritis. According to Kenner, this means that therapies that block the IL-6 pathway may enhance the growth of prostate cancer.

Thus, the drug that is used to treat inflammatory disease may exacerbate malignancies. "Applying IL-6/Stat3 blockers to clinical practice might be dangerous for patients with cancerous lesions, further studies are mandatory to assess the possibility of increased cancer risk right now," says coauthor of this study, Helmut Dolznig, also from the Medical University of Vienna. The study was financed mainly by the LBI-CR and the FWF. These results have just been published in the distinguished scientific journal Nature Communications.

The following is a generalized paradigmatic summary of Pencik et al. Namely; they observed that IL6 controls STAT3 which in turn controls the ARF-MDM2-p53 pathway, which is critical in the overall control of PCa metastasis.



Now it should also be noted that the above is not the complete presentation. For example in this pathway p53 actually drives MDM2. There are other linkages that should be considered as well. We shall discuss some of these later.

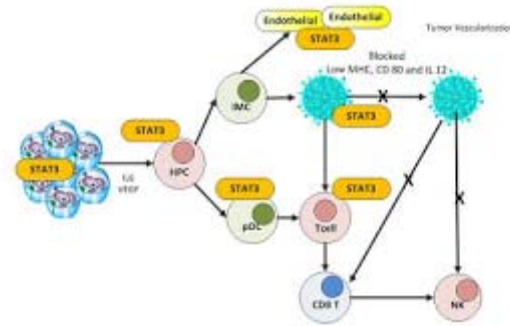
Now from the paper in question, namely Pencik et al, they conclude:

We have uncovered a paradigm shift in understanding the key function of STAT3 in tumorigenicity and metastatic progression in PCa. Therefore, our results call for cautious use of anti-IL-6- STAT3 signalling blockers in the treatment of PCa as this may turn low-grade tumours into highly malignant cancers by loss of senescence controlled by the STAT3–ARF axis. As IL-6/STAT3 signalling blockers are successful in the treatment of chronic inflammatory or autoimmune diseases, their influence on PCa development needs to be carefully evaluated in future studies.

Reactivating the IL-6/STAT3/ARF-dependent senescence pathway⁵⁷ might be a promising strategy for PCa therapy via downregulation of Mdm2 (ref. 58) or p53 induction⁵⁹. Alternatively, triggering ARF–p53-independent cellular senescence by a small molecule inhibitor could be beneficial for PCa patients in whom other therapies have failed.

Namely, they argue that the STAT3 control of the ARF-MDM2-p53 pathway should not be interfered with. That pathway actually enables control over metastatic behavior. We will discuss each element in some detail in what follows.

The classic understanding of STAT3 is that it acts to promote cancers. The figure below is a modification from Yu et al:



STAT3 signalling allows crosstalk between tumour cells and dendritic cells, forming an immunosuppressive network. Tumour-associated factors such as vascular endothelial growth factor (VEGF), IL-33 and IL-6 can not only be upregulated by signal transducer and activator of transcription 3 (STAT3), but are also STAT3 activators. Increased STAT3 activity in haematopoietic progenitor cells (HPCs) promotes the generation of immature myeloid cells (IMCs) and increases the numbers of both immature dendritic cells and plasmacytoid dendritic cells (pDCs), each of which promotes the accumulation of regulatory T (TReg) cells in the tumour microenvironment...preventing their maturation and compromising their ability to stimulate the anti-tumour effects of CD8+ T cells and natural killer (NK) cells.

As Yu et al state:

Immune cells in the tumour microenvironment not only fail to mount an effective anti-tumour immune response, but also interact intimately with the transformed cells to promote oncogenesis actively. Signal transducer and activator of transcription 3 (STAT3), which is a point of convergence for numerous oncogenic signalling pathways, is constitutively activated both in tumour cells and in immune cells in the tumour microenvironment.

Constitutively activated STAT3 inhibits the expression of mediators necessary for immune activation against tumour cells. Furthermore, STAT3 activity promotes the production of immunosuppressive factors that activate STAT3 in diverse immune-cell subsets, altering gene-expression programmes and, thereby, restraining anti-tumour immune responses. As such, STAT3 propagates several levels of crosstalk between tumour cells and their immunological microenvironment, leading to tumour-induced immunosuppression. Consequently, STAT3 has emerged as a promising target for cancer immunotherapy.

Thus the classic view is that STAT3 is an essential element in the pathology of tumorigenesis which as we indicated earlier is in contrast to the recent results. Thus do we block it or allow it? That is the question. Yu et al conclude:

The ability of STAT3 to broadly and profoundly affect tumour immunity strongly indicates that constitutively activated STAT3 both in tumour cells and in tumour stromal immune cells is an attractive target for cancer immunotherapy. Another unique and appealing aspect of targeting STAT3 for cancer immunotherapy is due to the crucial role of STAT3 in tumour-cell survival and tumour angiogenesis. Many experiments have shown that tumour rejection mediated by CD8+ T cells is always preceded by the inhibition of tumour-induced angiogenesis.

Because targeting STAT3 is expected to decrease the survival and angiogenic potential both of tumour cells and of the tumour stroma, targeting STAT3 could facilitate immune-cell-mediated anti-tumour effects at several levels. Although STAT3 is the first oncogenic target for cancer immunotherapy, other important onco proteins, such as MAPKs, might have similar roles. With the emergence of targeted delivery systems, and small molecule inhibitors or RNAi technology to

block STAT3 and other relevant oncogenic pathways, a new era of molecular targeting for cancer immunotherapy is on the horizon.

Yu et al are focusing on hematopoietic cells not prostate cells. There is no reason why one should expect the same effect in different cells. Yet from a therapeutic perspective if such a drastically different model is functioning, the results would be problematic at best.

As Niu et al have stated:

Loss of p53 function by mutation is common in cancer. However, most natural p53 mutations occur at a late stage in tumor development, and many clinically detectable cancers have reduced p53 expression but no p53 mutations.

It remains to be fully determined what mechanisms disable p53 during malignant initiation and in cancers without mutations that directly affect p53.

We show here that oncogenic signaling pathways inhibit the p53 gene transcription rate through a mechanism involving Stat3, which binds to the p53 promoter in vitro and in vivo.

Site-specific mutation of a Stat3 DNA-binding site in the p53 promoter partially abrogates Stat3-induced inhibition. Stat3 activity also influences p53 response genes and affects UV-induced cell growth arrest in normal cells. Furthermore, blocking Stat3 in cancer cells up-regulates expression of p53, leading to p53-mediated tumor cell apoptosis. As a point of convergence for many oncogenic signaling pathways, Stat3 is constitutively activated at high frequency in a wide diversity of cancers and is a promising molecular target for cancer therapy.

Thus, repression of p53 expression by Stat3 is likely to have an important role in development of tumors, and targeting Stat3 represents a novel therapeutic approach for p53 reactivation in many cancers lacking p53 mutations.

Thus, Niu et al also present a model for Stat3 inhibiting p53, again in contrast to the paper in question. Niu et al conclude:

1. Stat3 protein interacts with the p53 promoter.
2. Stat3 inhibits p53 expression at the transcription level.
3. Stat3 binds to the p53 promoter in vitro as determined by EMSA.
4. Interaction between Stat3 protein and the p53 promoter contributes to Stat3-mediated inhibition.
5. Stat3 activity inhibits the p53-responsive element and UV-induced p53-mediated growth arrest.
6. Blocking Stat3 activates p53 expression in human cancer cells.
7. Blocking Stat3 induces p53-mediated tumor cell apoptosis and facilitates UV-induced tumor cell growth inhibition.

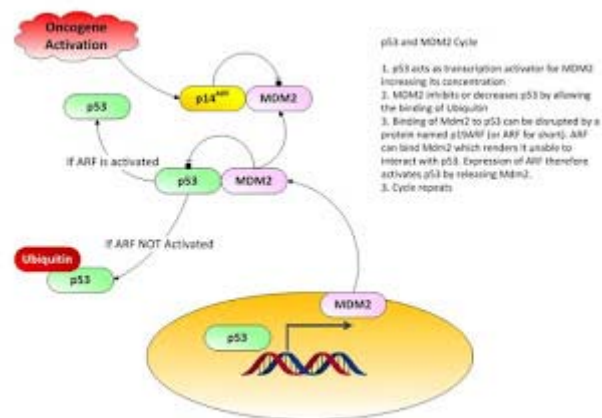
The results of these two studies seem fairly conclusive regarding Stat3. Namely it is oncogenic. But despite the study in question here seems to reverse that position. We will examine that in some detail.

Let us now review what is understood about the ARF-MDM2-p53 pathway. This will be necessary before linking this pathway to STAT3 and its functions.

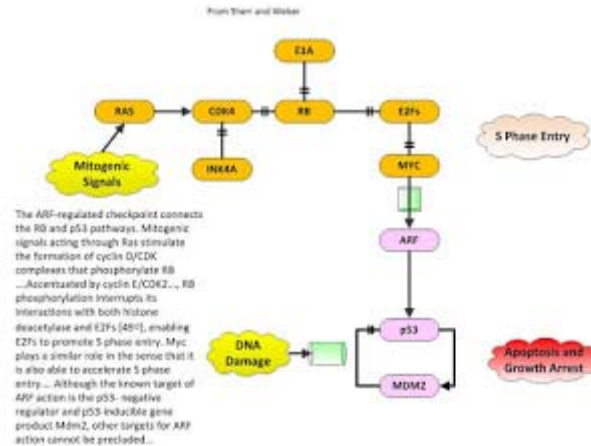
Now this is a classic pathway whose ultimate control mechanism is p53 expression. p53 is generally understood to be a control gene, keeping the cell in some homeostasis and preventing malignancy. As we will not later this may not always be the case but that will not apply to the current discussion.

The following Figure depicts the process of the three gene control mechanism. Simply:

1. p53 activates the production of MDM2
2. MDM2 can bind to p53 and result in its dissolution via an Ubiquitation
3. ARF can bind to MDM2 and allow the p53 to survive.
4. The process, albeit a bit complex, reaches a steady state for all three proteins.



From Sherr and Weber (as modified) we have the following details as well shown graphically:



Note in the above we have the cyclic MDM2 and p53 control as well as the cell instigators. Now Van Maerken, T., et al notes the following regarding the details of this feedback loop:

The p53-MDM2 autoregulatory feedback loop.

(a) *The p53 protein induces expression of MDM2, which negatively regulates the stability and activity of p53, providing a means to keep p53 levels and activity low in unstressed cells and to switch off p53 at the end of a stress response.*

(b) *The p53-mediated expression of MDM2 results from binding of p53 to response elements in the MDM2 gene and subsequent transactivation of MDM2. The domain structure of p53 is shown schematically:*

- i. *TAD, transactivation domain, amino acids;*
- ii. *PRD, proline-rich domain, amino acids; DBD, DNA-binding domain, amino acids;*
- iii. *TD, tetramerization domain, amino acids;*
- iv. *CTD, C-terminal regulatory domain, amino acids.*

(c) *The p53-inhibitory activity of MDM2 relies on multiple mechanisms. Binding of MDM2 to p53 conceals the TAD and consequently blocks the transcriptional activity of p53. MDM2 also recruits several corepressor proteins to p53, including HDAC1, CTBP2, YY1, and KAP1.*

The E3 ubiquitin ligase activity of MDM2 results in ubiquitination of lysine residues in the CTD of p53, preventing acetylation of p53, favoring nuclear export, and promoting proteasomal degradation (see text for details). Some of these lysine residues can also be neddylated by MDM2, resulting in inhibition of the transcriptional activity of p53. Finally, MDM2 may also serve as a p53-specific transcriptional silencer by binding and monoubiquitinating histone proteins in the proximity of p53-responsive promoters. Nd, NEDD8; Ub, ubiquitin. ...

They continue the discussion as follows:

The p14^{ARF} protein is predominantly localized to the nucleolus, in which it is stabilized by binding to nucleophosmin within maturing pre-ribosomal particles, pointing to a function in the regulation of ribosome biogenesis.

Nucleophosmin promotes the processing of ribosomal RNA precursors and the nuclear export of ribosomal subunits, whereas overexpression of p14^{ARF} or its murine homolog p19^{ARF} interferes with transcription and processing of ribosomal RNA, impedes nucleocytoplasmic shuttling of nucleophosmin, and inhibits ribosome nuclear export. However, the precise biological function of the nucleophosmin–p14^{ARF} complexes remains a subject of debate. Stress signals trigger the disruption of the interaction between p14^{ARF} and nucleophosmin, and induce translocation of p14^{ARF} to the nucleoplasm.

This redistribution enables p14^{ARF} to interact with p53-bound MDM2 and to antagonize MDM2 function by inhibiting its E3 ubiquitin ligase activity and by blocking nucleocytoplasmic shuttling of MDM2 and p53, resulting in p53 stabilization. The p53-inhibitory activity of MDM2 may also be neutralized by p14^{ARF}-mediated mobilization of MDM2 into the nucleolus, although this mechanism is not strictly required for the p53-dependent functions of p14^{ARF}.

This is clearly a highly complex mechanism. They continue:

Furthermore, the p14^{ARF} protein is capable of inhibiting the activity of another E3 ubiquitin ligase that targets p53 for degradation, ARF-BP1/Mule, and of counteracting the p53-antagonizing NF-kappaB pathway. It should be noted that p14^{ARF} also exerts a potent tumor suppressor activity independently of p53.

Various researchers have tried to model these systems using different techniques. One technique is the use of Petri Nets^{14[2]}. From CSML we have a Petri Net models describing the details of such a network and they state^{15[3]}:

Proteins p53, MDM2, and p19^{ARF} are proteins closely related to cancer. The protein p53 is a protein which suppresses the formation of tumors, and the protein MDM2 promotes the formation of tumors by decreasing the activity of the protein p53.

Understanding of control mechanism of these proteins connects to development of an effective medicine for suppressing the tumor. It is known that protein p53 works as a transcription factor for many genes and its transcriptional activity is controlled by a complex formed with proteins MDM2 and p19^{ARF}.

However, it is still unclear whether protein p53 keeps its transcriptional activity in the form of the trimer with proteins p53, MDM2 and p19^{ARF}. ... a hybrid functional Petri net (HFPN) model which has been constructed by compiling and interpreting the information of p53-MDM2

^{14[2]} See Reisig

^{15[3]} <http://www.csml.org/models/csml-models/p53-arf-dependent-stabilization-pathway/>

interactions... With our HFPN model, we have simulated mutual behaviors between genes p53, MDM2, p19^{ARF}, and their products. Through simulation, we discussed whether the complex p53-MDM2-p19^{ARF} has transcriptional activity for genes Bax and MDM2 or not.

It is worth examining these structures, namely the Petri Nets. We leave the examination to the reference. From Moll and Petrenko we have the following result:

Activation of the p53 protein protects the organism against the propagation of cells that carry damaged DNA with potentially oncogenic mutations. MDM2, a p53- specific E3 ubiquitin ligase, is the principal cellular antagonist of p53, acting to limit the p53 growthsuppressive function in unstressed cells. In unstressed cells, MDM2 constantly monoubiquitinates p53 and thus is the critical step in mediating its degradation by nuclear and cytoplasmic proteasomes.

The interaction between p53 and MDM2 is conformation-based and is tightly regulated on multiple levels. Disruption of the p53-MDM2 complex by multiple routes is the pivotal event for p53 activation, leading to p53 induction and its biological response. Because the p53-MDM2 interaction is structurally and biologically well understood, the design of small lipophilic molecules that disrupt or prevent it has become an important target for cancer therapy.

Let us go back and re-examine the functions of STAT3 and this time in the context of the paper in study. As NCBI states^{16[4]}:

The protein encoded by this gene is a member of the STAT protein family. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators.

This protein is activated through phosphorylation in response to various cytokines and growth factors including IFNs, EGF, IL5, IL6, HGF, LIF and BMP2. This protein mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis. The small GTPase Rac1 has been shown to bind and regulate the activity of this protein. PIAS3 protein is a specific inhibitor of this protein.

As Niu et al have noted:

Loss of p53 function by mutation is common in cancer.

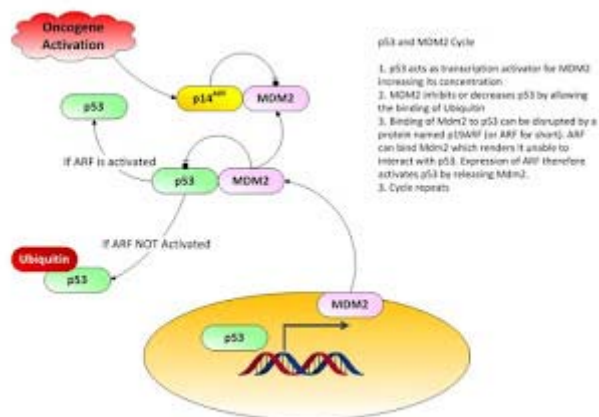
However, most natural p53 mutations occur at a late stage in tumor development, and many clinically detectable cancers have reduced p53 expression but no p53 mutations. It remains to be fully determined what mechanisms disable p53 during malignant initiation and in cancers without mutations that directly affect p53. We show here that oncogenic signaling pathways inhibit the p53 gene transcription rate through a mechanism involving Stat3, which binds to the p53 promoter in vitro and in vivo.

^{16[4]} <http://www.ncbi.nlm.nih.gov/gene/6774>

Site-specific mutation of a Stat3 DNA-binding site in the p53 promoter partially abrogates Stat3-induced inhibition. Stat3 activity also influences p53 response genes and affects UV-induced cell growth arrest in normal cells. Furthermore, blocking Stat3 in cancer cells up-regulates expression of p53, leading to p53-mediated tumor cell apoptosis. As a point of convergence for many oncogenic signaling pathways, Stat3 is constitutively activated at high frequency in a wide diversity of cancers and is a promising molecular target for cancer therapy.

Thus, repression of p53 expression by Stat3 is likely to have an important role in development of tumors, and targeting Stat3 represents a novel therapeutic approach for p53 reactivation in many cancers lacking p53 mutations.

Namely in many cancers the excess expression of STAT3 leads to an inactivation of p53 and thus an oncogenic state. The figure below is a depiction of this process.



However, Pencik, J., have recently noted the following as regards to PCa.

Prostate cancer (PCa) is the most prevalent cancer in men. Hyperactive STAT3 is thought to be oncogenic in PCa. However, targeting of the IL-6/STAT3 axis in PCa patients has failed to provide therapeutic benefit. Here we show that genetic inactivation of Stat3 or IL-6 signalling in a Pten-deficient PCa mouse model accelerates cancer progression leading to metastasis. Mechanistically, we identify p19ARF as a direct Stat3 target.

Loss of Stat3 signalling disrupts the ARF–Mdm2–p53 tumour suppressor axis bypassing senescence. Strikingly, we also identify STAT3 and CDKN2A mutations in primary human PCa. STAT3 and CDKN2A deletions co-occurred with high frequency in PCa metastases. In accordance, loss of STAT3 and p14ARF expression in patient tumours correlates with increased risk of disease recurrence and metastatic PCa. Thus, STAT3 and ARF may be prognostic markers to stratify high from low risk PCa patients. Our findings challenge the current discussion on therapeutic benefit or risk of IL-6/STAT3 inhibition.

But Pencik et al further note:

PTEN is one of the most frequently deleted or mutated tumour suppressors in PCa, with an estimated incidence of 70% in metastatic PCa, causing aberrant activation of the PI3K– AKT– mTOR signalling pathway

We have examined this extensively in our analyses of PCa.

Loss of Pten leads to senescence, which is critically regulated by the ARF–p53 pathway.

PTEN is a major controller of PI3K and its pathway. Loss of PTEN is common in most PCa. On the other hand we have the ARF-MDM2-p53 dynamic which we shall discuss later.

While the tumour suppressor ARF (p14^{ARF} in humans; p19^{ARF} in mice) is readily degraded in normal cells, it is stabilized to increase p53 function on loss of Pten. ARF was shown to augment p53 stability by promoting the degradation of Mdm2, a negative regulator of p53.

Concomitant inactivation of Pten and p53 leads to bypass of senescence and as a consequence to a malignant PCa phenotype.

Loss of PTEN and of p53 is potentially a universally catastrophic event. It is a loss of two of the most significant stabilization elements in any cell, especially the prostate.

Previous studies report PTEN–STAT3 signalling crosstalk in malignant glioblastoma, but the detailed molecular mechanisms in cancer progression and metastasis remain unresolved.

In this study, we show that loss of IL-6/Stat3 signalling in a Pten-deficient PCa model accelerates cancer progression leading to metastasis. Loss of IL-6/Stat3 signalling in PCa bypasses senescence via disrupting the ARF–Mdm2–p53 tumour suppressor axis.

We identify ARF as a novel direct Stat3 target. Notably, loss of STAT3 and p14ARF expression correlates with increased risk of recurrence in PCa patients. In addition, STAT3 and p14ARF expression was lost in metastasis compared with the primary tumours.

This is the nexus between the STAT3 pathway and the ARF-MDM2-p53 pathways. Namely the authors seem to argue that STAT3 targets ARF and it is through this “targeting” that the latter pathway becomes defective.

We identified STAT3 and CDKN2A mutations in primary PCa patients. Furthermore, PCa metastases show a high frequency of STAT3 and CDKN2A deletions.

We propose STAT3 and ARF as prognostic markers for high versus low risk PCa patient stratification.

Pencik et al also note the following inference:

Stat3 regulates the ARF–Mdm2–p53 pathway. Since loss of Pten triggers senescence thereby restricting cancer progression and metastasis [1], we next tested whether Stat3 exerts a tumour

suppressiveness function by activating senescence-inducing programmes in Ptenpc^{-/-}-PCa cells at an early stage of PCa development.

Senescence is generally characterized by upregulation of p53, cyclin-dependent kinase inhibitor 1 (Cdkn1, p21), promyelocytic leukaemia protein (PML) and elevated senescence-associated-β-galactosidase activity. Of note, Ptenpc^{-/-}-Stat3^{-/-} tumours lacked p21 expression, displayed reduced numbers of PML nuclear bodies and decreased SA-β-Gal activity compared with Ptenpc^{-/-} tumours, suggesting Stat3 as a novel mediator of senescence in response to loss of Pten.

Again the statement is “suggesting” and there is no definitive well defined mechanism.

Senescence associated with loss of Pten was shown to be bypassed by deletion of p53 leading to early lethality¹¹. We show here that loss of Stat3 and Pten revealed a phenotype strikingly similar to that of p53 and Pten loss¹¹. Intriguingly, Stat3 and Pten deletion resulted in downregulation of p53 expression in the prostate epithelium, which was accompanied by the loss of p19ARF

The authors make the following statement:

The p53 expression in the tumour stromal cells remained unchanged. Since p19^{ARF} is a critical regulator of Mdm2 degradation, our results suggest that the tumour suppressive capacity of Stat3 in senescent tumour cells may rely on the p19ARF–Mdm2–p53 tumour suppressor axis.

The conclusion is still a bit tentative. Just what the mechanism is may not be well understood.

Now Yu et al state:

The Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) proteins, particularly STAT3, are among the most promising new targets for cancer therapy. In addition to interleukin-6 (IL-6) and its family members, multiple pathways, including G-protein-coupled receptors (GPCRs), Toll-like receptors (TLRs) and microRNAs were recently identified to regulate JAK–STAT signalling in cancer.

Well known for its role in tumour cell proliferation, survival, invasion and immunosuppression, JAK–STAT3 signalling also promotes cancer through inflammation, obesity, stem cells and the pre-metastatic niche. In addition to its established role as a transcription factor in cancer, STAT3 regulates mitochondrion functions, as well as gene expression through epigenetic mechanisms. Newly identified regulators and functions of JAK–STAT3 in tumours are important targets for potential therapeutic strategies in the treatment of cancer.

Huang, et al state that STAT3 is a preferred target for cancer therapy. Specifically:

Numerous cytokines, growth factors, and oncogenic proteins activate signal transducer and activator of transcription 3 (Stat3), which has been recognized as one of the common pathways

in cancer cells. Stat3 signaling affects the expression and function of a variety of genes that are critical to cell survival, cell proliferation, invasion, angiogenesis, and immune evasion.

Evidently, the Stat3 signaling pathway regulates cancer metastasis and constitutes a potential preventive and therapeutic target for cancer metastasis. .

Furthermore Huang et al outline the reasons for this:

Contribution of Stat3 signaling pathway to cancer metastasis.

Stat3 in the cytoplasm of unstimulated cells becomes activated by recruitment to phosphotyrosine motifs within complexes of growth factor receptors (e.g., epidermal growth factor receptor), cytokine receptors (e.g., IL-6 receptor), or non-receptor tyrosine kinases (e.g., Src and BCR-ABL) through their SH2 domain. Stat3 is then phosphorylated on a tyrosine residue by activated tyrosine kinases in receptor complexes.

Phosphorylated Stat3 forms homodimers and heterodimers and translocates to the nucleus. In the nucleus, Stat3 dimers bind to specific promoter elements of target genes and regulate gene expression. The Stat3 signaling pathway regulates cancer metastasis by regulating the expression of genes that are critical to cell survival, cell proliferation, invasion, angiogenesis, and tumor immune evasion.

It would be useful if somehow these conflicting views could be brought into alignment. In addition we have the work Marcias, E., et al, who state:

Pathways associated with Stat3 activation. Stat3 is activated downstream of receptor tyrosine kinases (e.g., EGFR), cytokine receptors via associated Janus family kinases (JAKs) (e.g., IL-6 receptor), and nonreceptor-associated tyrosine kinases (e.g., c-src). Tumor promoters such as TPA and UVB activate Stat3 in keratinocytes primarily via the EGFR.

Activation of PKCs by tumor promoters leads to the processing of membrane-bound preforms of EGFR ligands such as heparin-binding EGF (HB-EGF) by matrix metalloproteinases (MMPs). In addition, PKCs associate with and phosphorylate Stat3 at Ser727, which is necessary for maximal Stat3 transcriptional activity. Furthermore, transcriptional induction of cytokines and EGF ligands can lead to autocrine stimulation and sustained Stat3 phosphorylation.

After phosphorylation, STAT3 dimerizes and translocates to the nucleus, where Stat3 dimers directly regulate gene expression of transcriptional targets including Bcl-xL, cyclin D1, c-myc, Twist and Survivin. STAT3-mediated regulation of target gene expression is involved in various cellular functions including cell differentiation, proliferation, survival, and oncogenesis. Stat3 can also act through noncanonical signaling pathways. In this regard, unphosphorylated Stat3 (U-Stat3) can drive gene expression of a subset of genes that are different from p-Stat3 dimers in an NF- κ B-dependent and independent manner.

In addition, p-Stat3 Ser727 can translocate into the mitochondria and influence mitochondrial respiratory chain activity. These noncanonical Stat3 signaling pathways have protumorigenic

roles in certain cell/tissue types; however their role in epithelial carcinogenesis has not been evaluated.

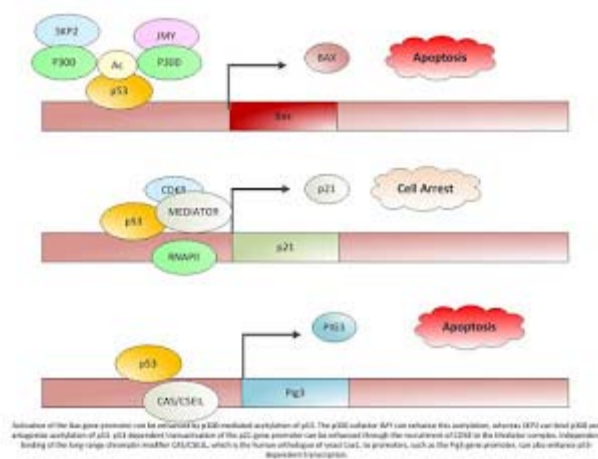
Thus the nature of STAT3 and its importance must be better investigated.

This paper by Pencik et al presents an interesting challenge to the ability to identify genetic markers for various cancers. What may at one time seem to be a problem may later be understood in a more complete fashion to be a necessary control element. To some degree we have observed this with BRAF inhibitors in melanoma, which lead to SCC and thus require a MEK inhibitor. In some sense unless a full dynamic understanding of pathways is established one may continue to see this “whack a mole” approach to therapeutics.

To reiterate the Pencik et al observations:

1. *Co-deletion of Stat3 and Pten triggers PCa*: We know that PTEN loss is found in PCa and we also know that active Stat3 is a significant factor in many malignancies. Yet the loss of both may appear as being of significance.
2. *Stat3 regulates the ARF–Mdm2–p53 pathway*: This is the key observation which they articulate and stress and the main divergence from standard thought.
3. *Loss of IL-6 and Pten leads to cancer and metastasis*: We know that IL-6 drives Stat3 and that loss of IL-6 would most likely lead to a loss of Stat3 expression. As noted above loss of both Pten and Stat3 would lead to a malignant state.
4. *Loss of STAT3 and ARF in PCa is associated with metastases*: ARF is key to the ARF-MDM2 – p53 pathway. MDM2 inhibits p53. Thus the association of Stat3 being the “driver” of the ARF process is essential.

We reiterate the p53 processes as shown below. The three lead to either apoptosis or cell arrest as one would expect. In all cases p53 plays a key role but it is also clear that other proteins are required in some cases.



Pencik et al finally note:

Interestingly, loss of PTEN expression in primary human PCa did not correlate with overall survival and could not predict PCa-specific death. Moreover, heterozygous PTEN deletions far outnumber homozygous deletions in primary human PCa and we show here that PTEN is mutated or lost only in a small subset (4.7%) of a large cohort of patients with primary PCa.

However, PTEN is lost in >50% of human PCa metastases suggesting an important role for PTEN in this process. Finally, we show in our study that STAT3 is co-deleted with PTEN in 66% of human PCa metastases in two independent data sets.

Since PTEN is mutated or lost in only a minor fraction of primary PCa, other aberrations must occur (oncogene induction or loss of tumour suppressor function) to activate STAT3 and ARF to induce senescence in human cancers. Indeed, several studies indicate that different aberrations can lead to induction of senescence in human cancers

From Soissi and Wiman:

The standard classification used to define the various cancer genes confines tumor protein p53 (TP53) to the role of a tumor suppressor gene. However, it is now an indisputable fact that many p53 mutants act as oncogenic proteins.

This statement is based on multiple arguments including the mutation signature of the TP53 gene in human cancer, the various gains-of-function (GOFs) of the different p53 mutants and the heterogeneous phenotypes developed by knock-in mouse strains modeling several human TP53 mutations.

In this review, we will shatter the classical and traditional image of tumor protein p53 (TP53) as a tumor suppressor gene by emphasizing its multiple oncogenic properties that make it a potential therapeutic target that should not be underestimated.

Analysis of the data generated by the various cancer genome projects highlights the high frequency of TP53 mutations and reveals that several p53 hotspot mutants are the most common oncoprotein variants expressed in several types of tumors.

The use of Muller's classical definition of mutations based on quantitative and qualitative consequences on the protein product, such as 'amorph', 'hypomorph', 'hypermorph' 'neomorph' or 'antimorph', allows a more meaningful assessment of the consequences of cancer gene modifications, their potential clinical significance, and clearly demonstrates that the TP53 gene is an atypical cancer gene.

There is an interesting paper from CSHL on progress on cancer classification. Linnaeus some 300 years ago came up with a classification system for various species. Aristotle was driven by his desire to classify, and ever since we have people trying their best to do that task. Patients always want to know what they have, and that is a form of classification.

We classify cancers based upon organs. We may modify it based on cell types or based on cell markers such as immunological markers. I remember back in the 60s that Leukemias were

simple; acute or chronic, you died now or later. Now we have a plethora of subtypes and a multiplicity of therapeutics.

But we also know genomic data. Perhaps then we should classify cancers based upon genes, not upon organs, binding proteins, or the like,

As the authors state:

Classification is an everyday instinct as well as a full-fledged scientific discipline. Throughout the history of medicine, disease classification is central to how we organize knowledge, obtain diagnosis, and assign treatment. Here we discuss the classification of cancer, the process of categorizing cancers based on their observed clinical and biological features. Traditionally, cancer nomenclature is primarily based on organ location, e.g., "lung cancer" designates a tumor originating in lung structures. Within each organ-specific major type, further subgroups can be defined based on patient age, cell type, histological grades, and sometimes molecular markers, e.g., hormonal receptor status in breast cancer, or microsatellite instability in colorectal cancer. In the past 15+ years, high-throughput technologies have generated rich new data for somatic variations in DNA, RNA, protein, or epigenomic features for many cancers. These data, representing increasingly large tumor collections, have provided not only new insights into the biological diversity of human cancers, but also exciting opportunities for discovery of new cancer subtypes.

They continue:

An ever finer classification system has many potential benefits. It is needed to capture the full spectrum of biological diversity—the "endless forms" that Darwin spoke of. It could lead to a better recognition of patient-specific disease mechanisms, and importantly, could suggest treatment options that are more accurately matched to the patient's tumor. Precision medicine, at its very foundation, relies on valid and continuously optimized disease classification that reflects the underlying mechanisms. However, a fine-grained classification system also has many potential drawbacks. The newly proposed splits may not be technically robust. Even when the finer categories are robustly supported by statistical significance and by replication, they may still lack a clear biological meaning, or have little impact on treatment options (#3 below) if it turns out that some subtypes share the same clinical endpoint, or if treatment options are limited.

Indeed, we may find it much more powerful to have a new Linnaeus type look at classification. Classifying genomically, via genes, RNA, and epigenetic factors, may help stratify and focus on therapeutics. This article raises an interesting dialog.

Overall we can make some summary observations:

1. Perhaps one should be cautious as regards to murine and human models. All too often what we see in mouse models does not pan out in human. The reasons may very well be the complexity of the signally paths.

2. Signalling paths are complex and dynamic. What may work at one instant may not at another? The question then is: how critical are realistic repeatable and predictive models in assisting in both prognostic evaluation and therapeutic approaches?

3. Cells are not the same everywhere. Thus when we perform a prostate biopsy we may get one profile but when that cell metastasizes to other organs we get dramatically different cells. As we have discussed before the paper by Gundem et al presnts a compelling picture of the complexity of gene expression in PCa. Namely each cell cluster may have complex and disparate genes expressed. If that is the case then we would also be concerned that we look at similar expression when performing biopsies.

References

1. Gundem et al, The evolutionary history of lethal metastatic prostate cancer, Nature 2015. doi:10.1038/nature14347
2. Hao, Q., W. Cho, Battle Against Cancer: An Everlasting Saga of p53, Int. J. Mol. Sci. 2014, 15(12), 22109-22127
3. Hart, J., et al, Essential role of Stat3 in PI3K-induced oncogenic transformation, PNAS, August 9, 2011, vol. 108, no. 32, 13247–13252 MEDICAL SCIENCES
4. Huang, S., Regulation of Metastases by Signal Transducer and Activator of Transcription 3 Signaling Pathway: Clinical Implications, Clin Cancer Res March 1, 2007 13; 1362.
5. Marcias, E., et al, Role of Stat3 in Skin Carcinogenesis: Insights Gained from Relevant Mouse Models, Journal of Skin Cancer Volume 2013 (2013), Article ID 684050, 10 pages
6. Moll, U., O., Petrenko, The MDM2-p53 Interaction, Molecular Cancer Research , Vol. 1, 1001–1008, December 2003.
7. Murray-Zmijewski, F., et al A complex barcode underlies the heterogeneous response of p53 to stress, Nature Reviews Molecular Cell Biology 9, 702-712 (September 2008)
8. Niu, et al, Role of Stat3 in Regulating p53 Expression and Function, MOLECULAR AND CELLULAR BIOLOGY, Sept. 2005, p. 7432–7440
9. O’Shea, et al, JAKs and STATs in Immunity, Immunodeficiency, and Cancer, NEJM, 368;2 nejm.org January 10, 2013
10. Pencik, J., et al, STAT3 regulated ARF expression suppresses prostate cancer metastasis, Nature Communications, 22 Jul 2015.
11. Pestell, R., M., Nevalainen, Prostate Cancer, Humana (Totowa NJ) 2008.
12. Reisig, W., Understanding Petri Nets, Springer (Berlin) 2013.
13. Sherr, C., J. Weber, The ARF/p53 pathway, Current Opinion in Genetics & Development 2000, 10:94–99
14. Song, J, et al, Cancer classification in the genomic era: five contemporary problems, <http://biorxiv.org/content/early/2015/07/23/023127?rss=1>
15. Soussi, T., K. Wiman, TP53: an oncogene in disguise, Cell Death and Differentiation (2015) 22, 1239–1249
16. Thiagalingam, S., Systems Biology of Cancer, Cambridge (New York), 2015.
17. Van Maerken, T., et al, Escape from p53-mediated tumor surveillance in neuroblastoma: switching off the p14ARF-MDM2-p53 axis, Cell Death and Differentiation (2009) 16, 1563–1572

18. Yu, H., et al, Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment, NATURE REVIEWS, IMMUNOLOGY, VOLUME 7, JANUARY 2007, p| 41
19. Yu, H., et al, Revisiting STAT3 signalling in cancer: new and unexpected biological functions, Nature Reviews Cancer, 14, 736–746, 2014.



Labels: [Cancer](#)

SUNDAY, JULY 26, 2015

[THE EHR AND WASHINGTON](#)

There is nothing better than a pediatrician who is an administrator, who wants to run for Governor and who in the process goes to Washington to specify how all physicians must in the future prepare their medical records. In fact in any real world one would find such a tale absurd, yet it is the truth. We now have the "meaningful use" standard, where did that come from, for the management of patient records. I thought this was stupid seven years ago, and yes even in 1992 when I first wrote of this, and still do.

Patient records are important, and part of the reason we never really got the problem solved is because it is really hard. Sometimes hard problems are hard for a reason.

At a recent AMA meeting as reported by [Medpage](#) the writer notes:

Almost immediately, physicians gave voice to the barriers to care they say are caused by electronic health records systems. Over the course of the 90-minute meeting they raised concerns over reduced productivity, the security of private patient medical records, interoperability, and government regulation. "We're removing the science from medicine," said one physician who described having to check "yes" and "no" boxes rather than being able to note subtle nuances his patients reported. "Thank God I learned to type in high school -- I never thought I'd use it," said another, explaining that she now has to make sure every employee she hires can type, regardless of the job for which they are hired.

It frankly is the arrogance of many who go to Washington who think that they know all there is to know...then again perhaps not.



Labels: [Electronic Medical Records](#)

FRIDAY, JULY 24, 2015

CANCER CLASSIFICATION

There is an interesting paper from [CSHL](#) on progress on cancer classification. Linnaeus some 300 years ago came up with a classification system for various species. Aristotle was driven by his desire to classify, and ever since we have people trying their best to do that task. Patients always want to know what they have, and that is a form of classification.

We classify cancers based upon organs. We may modify it based on cell types or based on cell markers such as immunological markers. I remember back in the 60s that Leukemias were simple; acute or chronic, you died now or later. Now we have a plethora of subtypes and a multiplicity of therapeutics.

But we also now genomic data. Perhaps then we should classify cancers based upon genes, not upon organs, binding proteins, or the like,

As the authors state:

Classification is an everyday instinct as well as a full-fledged scientific discipline. Throughout the history of medicine, disease classification is central to how we organize knowledge, obtain diagnosis, and assign treatment. Here we discuss the classification of cancer, the process of categorizing cancers based on their observed clinical and biological features. Traditionally, cancer nomenclature is primarily based on organ location, e.g., "lung cancer" designates a tumor originating in lung structures. Within each organ-specific major type, further subgroups can be defined based on patient age, cell type, histological grades, and sometimes molecular markers, e.g., hormonal receptor status in breast cancer, or microsatellite instability in colorectal cancer. In the past 15+ years, high-throughput technologies have generated rich new data for somatic variations in DNA, RNA, protein, or epigenomic features for many cancers. These data, representing increasingly large tumor collections, have provided not only new insights into the biological diversity of human cancers, but also exciting opportunities for discovery of new cancer subtypes.

They continue:

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Indeed, we may find it much more powerful to have a new Linnaeus type look at classification.

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Labels: [Cancer](#)

MONDAY, JULY 20, 2015

WINDOWS 10?

Are you out of your mind! Next Monday Microsoft releases Windows 10. Now I have Windows 7 and it works just fine. Even have a few XP systems for lab work so who cares since they are not even networked. But, updating to Windows 10 would be akin to inserting hot peppers into my eyes. Total agony.

Would anyone allow Microsoft to change their computer? The chance that all your data, all your software, all your drivers, all your security, all your connectivity, would just vanish! A Microsoft hot line? The IRS is easier to deal with.

So for those folks happily upgrading next Monday, I remind you of Dante and the Inferno and the sign above the door to Hell, "Abandon all hope you who enter!"

That's right, when you all find out that, oops, Microsoft had a few glitches, that Democrat speak for massive screw up, and you are now back to pencil and legal pads, you did it to yourself! Keep the XP machines, Microsoft no longer updates them, that means they are stable.



Labels: [Microsoft](#)

FRIDAY, JULY 17, 2015

PLUTO



From the [NASA web site](#), Pluton and its "moon". Interesting set of photos. But a note: In the old days we had to wear our own clothes. Today NASA seems to get everyone dressed up in matching polo shirts.



Labels: [NASA](#)

[THE NEO MARXISTS](#)

In the [Guardian](#) is an interesting piece if you can wade through it. The author wanders endlessly and argue for the destruction of capitalism, another revolution of the proletariat.

He says:

During and right after the second world war, economists viewed information simply as a “public good”. The US government even decreed that no profit should be made out of patents, only from the production process itself. Then we began to understand intellectual property. In 1962, Kenneth Arrow, the guru of mainstream economics, said that in a free market economy the purpose of inventing things is to create intellectual property rights. He noted: “precisely to the extent that it is successful there is an underutilisation of information.” You can observe the truth of this in every e-business model ever constructed: monopolise and protect data, capture the free social data generated by user interaction, push commercial forces into areas of data production that were non-commercial before, mine the existing data for predictive value – always and everywhere ensuring nobody but the corporation can utilise the results.

If we restate Arrow’s principle in reverse, its revolutionary implications are obvious: if a free market economy plus intellectual property leads to the “underutilisation of information”, then an economy based on the full utilisation of information cannot tolerate the free market or absolute intellectual property rights. The business models of all our modern digital giants are designed to prevent the abundance of information.

Intellectual property rights or property rights of any time will in his mind fall away as we see the proliferation of more and free information.

He continues:

There is, alongside the world of monopolised information and surveillance created by corporations and governments, a different dynamic growing up around information: information as a social good, free at the point of use, incapable of being owned or exploited or priced. I’ve surveyed the attempts by economists and business gurus to build a framework to understand the dynamics of an economy based on abundant, socially-held information. But it was actually imagined by one 19th-century economist in the era of the telegraph and the steam engine. His name? Karl Marx.

Yes, Marx comes back again. Just like Marx, this piece is an endless rant against capitalism and its pending demise. All because of Wikipedia. After all Wikipedia did away with encyclopedias! What did away with encyclopedias was the cost and size, and frankly the useless nature of an encyclopedia.

It is always worth reading those Marxist writers and impending doom. Well back out to my garden, it is a nice summer day!



Labels: [Commentary](#)

WHAT IS REAL PROGRESS?

I read the article about [Reddit](#) in the [NY Times](#). The article opens with:

The return of a founder to a company is a well-worn story line in Silicon Valley. In Apple's darkest hour, Steve Jobs came back, eventually turning the computer maker into the world's most valuable corporation. In April, Mark Pincus stepped back into the chief executive role at Zynga. And Jack Dorsey, a co-founder of Twitter, has twice returned to help right the social media company's ship. Now Steve Huffman, who co-founded Reddit in 2005, may have one of the toughest returns of all. After being away for six years, Mr. Huffman reappeared last Friday as chief executive to pull off a turnaround of the online message board, which has grappled with a series of missteps and is embroiled in a battle to win back the confidence of its users.

Now I have dropped my Twitter and Facebook accounts. Never figured what to do with Twitter other than get into trouble with some stupid remark and Facebook became watching friends of friends making inane comments about their lives. I have looked at Facebook for "advertising" one's company but it is such a linear time sequenced medium that finding something is a problem. One can find Facebook adds but content is another thing.

Along comes Reddit. Never saw it until yesterday. It appears to be a never ending set of nasty comments. At least from a first view. This is what has become of Silicon Valley. Formerly a center for high tech, now the center for high touch.

Then I walk around MIT and Kendall square and look up. Building after building with "smoke stacks" if HEPA filters. Each of these massive "factories" are "making" change, real change. It is what Pittsburgh was to steel a century or more ago. One measure is the parking fees. Five years ago it was \$11.00. Now it is \$42.00. No poor folks here! Senator Warren should try to get a parking spot...

But the point is simple. Jobs and Apple started by making something, computers. Google had a search engine, it was a breakthrough akin to a word processor. Facebook, Twitter, Reddit, Linked In et al facilitate something, but do they in any way create value? How would one measure value? In Cambridge I look at CRISPR Cas9 and see tremendous value. As in the Graduate the new thing was "plastics". in this generation it is CRISPR. It is not Twitter or even Reddit.



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

TUESDAY, JULY 14, 2015

TOO MUCH MONEY

In a recent piece in [Science](#), the author seems to bemoan the reduction of budgets for [AHRQ](#). The writer states:

Those who want to trim or eliminate AHRQ argue that its work overlaps with NIH research. To make his point, Representative Andy Harris (R-MD) points to the \$1.37 billion that NIH spends

each year on health services research and \$1 billion for studies of patient safety Others say AHRQ overlaps with the Patient-Centered Outcomes Research Institute (PCORI), a nonprofit supported by a trust fund that was created by the 2010 Affordable Care Act. PCORI now spends about \$500 million a year on studies looking at which of two treatments works better, an area known as comparative effectiveness research.

The real issue is not AHRQ, which Congress can control, but PCORI which lies outside of Congressional control. PCORI was setup by the Democrats as a patient input entity funded by the fees imposed in the ACA. PCORI is another of those unregulated by Presidentially appointed rogue entities whose value is highly questionable. Thus Congress targets AHRQ since it cannot do so to PCORI. The real question is; what value is PCORI? Its funding expires in 2018 so Congress believes if it reduces AHRQ, laudable because of putative duplication, then it can just let PCORI die on its own.

The author continues:

AHRQ has attracted critics in the past because its work can threaten the financial interests of some groups. In the 1990s, Republicans tried to shut down the agency after spine surgeons objected to a report that found rest and pain medications worked as well as surgery for back pain, notes one commentator. Simpson says it's important to have a U.S. agency that keeps a close eye on health care quality, noting a 2011 Institute of Medicine report that found 30% of the \$2.5 trillion the United States spends annually on health care is wasted on unnecessary services and other needless costs. "With that amount of waste, it's shocking that people talk about duplication of AHRQ research," she says.

This is really a red herring. The issue of lower back pain has been examined in multiple venues and this is in my opinion merely an attempt to justify AHRQ. The real issue is; how can anyone justify PCORI?



Labels: [Health Care](#)

WEDNESDAY, JULY 8, 2015

THE GLITCH

It seems that the term "glitch" has entered the US vocabulary with full force. Years ago we would have called it gross incompetence. The ACA web site had glitches. Frankly it was typical Government incompetence. A surgeon removing the wrong leg is not making a glitch, he should be hanged!

The NYSE collapsing from a glitch is likewise cause for massive rearrangement of management. Maybe it would include the Board as well. You see this is not new. When one fields a new Software release there is always a Plan B, namely if it collapses we just switch back to the previous release. But that seems not to be the case any longer. Microsoft sends out updates that crash computers. God knows what is in our autos. Then there is the EHR stuff mandated by the Government under the management of a pediatrician! Watch that puppy run wild.

When we did the software for Apollo missions we had a plan B and C and D. I guess I got D. The manual return method, assuming the computers and software dies. It was the sextant. It worked for centuries so stick one on just in case. And then Apollo XIII! Took the guys home after the Plan A thru C got blown up.

But the NYSE, United, the ACA folks never even had a Plan B.



Labels: [Commentary](#)

TUESDAY, JULY 7, 2015

THE EHR AND BIG DATA

In a recent study by [MIT staff](#) there is a result that claims to have the ability to gain significant insight from EHR data.

They state:

The results are quite interesting: This is one of the first analyses of large data you get from using electronic health records, and it just became available. This is a big amount of data we got from General Electric. What we tried to look at is, when you go to see the doctor, you've got a certain [medical] history, and you're perhaps looking at a [medical] problem. When you look at that problem, is there any predictive power in the history that comes before? We looked at that from a pure computer science point of view — and it turns out there is predictive power....At the level of the individual, this allows you to compare the medical history to other people, and give additional information to the doctor. Doctors can get additional input from this analysis of the medical history. Of course this is what doctors already do — they look at the past in order to understand what might be the problem. But it's a mathematical way that guides you, gives you more [than] than you might get by going through [one patient's medical history].

Now there are several concerns here.

1. The EHR has become a cut and paste system. EHR records have become extensive restatements by rote of what may be patient complaints or conditions. Physicians all too often just sit and "take" a patient history of a chronic disease such as Type 2 Diabetes by cutting and pasting what they did the last several visits. Perhaps the HbA1c data is changed but otherwise the rest is the same.
2. EHRs for the most part do not provide or encourage a key element in medical analysis; namely examining changes. Patient health all too often is determined by something that has changed. Did the patient gain or lose weight, gain or lose endurance, gain or lose sleep. Simple issues, some of which are quantitative and many subjective.
3. EHRs are distributed and dissonant. Namely a patient may be seeing several physicians. Take the Type 2 Diabetic patient. The ophthalmologist for retinal deterioration, while seeking a dermatologist for follow ups on a melanoma excision. Does the ophthalmologist look for ocular melanomas as well?
4. Images and imaging are frequently left out. This includes both classic imaging as well as pathology images. It may also include genetic results.

Thus the data may be very noisy, may be inaccurate, may contain the wrong results, and thus may be misleading. Moreover the data may become a baseline for policy, such as the PSA test. And the data like the PSA may be all wrong. One should remember the recent SEER data disaster!



Labels: [Health Care](#)

MONDAY, JULY 6, 2015

[DOES ANYONE TEACH HISTORY IN TODAY'S WORLD?](#)

In a piece in the web blog [Vox](#) I ran across one that seems to be disconnected from reality. Namely the author suggests we would have been better off having stayed with England.

The author states:

But I'm reasonably confident a world where the revolution never happened would be better than the one we live in now, for three main reasons: slavery would've been abolished earlier, American Indians would've faced rampant persecution but not the outright ethnic cleansing Andrew Jackson and other American leaders perpetrated, and America would have a parliamentary system of government that makes policymaking easier and lessens the risk of democratic collapse.

Perhaps the authors has missed a few facts. First in the English Parliamentary system only member of the Church of England can become Prime Minister. The Head of State is also the Head of the Church. How would that one fly in today's world!

Second, has the author somehow forgot Ireland. Read de Tocqueville. In his account of Ireland one sees a people not allowed to own land, forced to work for wages not enough to eat on, land taken away from the, religious persecution, not allowed to be educated, and the list goes on. If you think this relates to Ireland only ask any one from India. The Brits were brutal!

Then there is the "Class" system. One's family heritage counts more than anything else. Try that one on in this author's America cum England. Immigrants would not be second class, they would be no class.

I guess it is helpful to live in ignorant bliss and create one's own history.



Labels: [Commentary](#)

[PSA AWARENESS AND THE ACA](#)

For a few decades the routine annual measurement of PSA was common. Then along came the USPTF and the use of faulty studies on PSA to justify assigning PSA measurements a low grade, namely being considered as useless. One may reasonably see this as a means to get rid of the old men as fast as one can. Really.

Now in today's [NY Times](#) a NY physician reiterates what [I had written a few years ago](#), before the USPTF nonsense. The author states:

But men should not wait for a government agency to tell them what's best. My own strongest recommendation is that men insist on a baseline PSA test while in their 40s. From this baseline, a personalized screening regimen that considers risk factors and other indicators can be developed. Men must understand that screening does not commit them to further testing or treatment, even if abnormalities are found. Screening, followed up with today's sophisticated tools, simply provides information that helps them and their doctors make sound decisions — which could prolong their lives, or leave them reassured that they have little to fear from an indolent tumor.

Yes, men should not pay attention to the rantings of morbidly obese GS9 whose sole purpose is to "reduce costs".

PSA testing is complex. It requires a history, and the baseline must reflect prostate size as well. However death from PCa is rather painful as it moves into the bones and your spine collapses.

Perhaps this added awareness may help some men. One should also contrast this to the response to the USPTF attempt to curtail breast exams. Men should become more aware, and more responsive.



Labels: [Cancer](#)

SUNDAY, JULY 5, 2015

[SOME THOUGHTS ON GREECE](#)



I know Greece. I speak Greek, a little, I have had a company in Greece, my best man is Greek, my Godfather was Greek. I have spent time in parts of Greece that most non-Greeks never go to. The Greeks who are outside of Greece are all successful. Those in Greece are successful with their projects outside of Greece.

But Greece is a mess. There is an overload of Government employees, direct and indirect. Greek political overhead is almost as great as a US Hospital or Academic University. Our Government is rapidly moving to the Greek model. New Jersey is a bit like Greece. Political types have three or four State jobs, each entitling them to a pension and health care. So one can say we have our own clusters of Greece here at home.

Ireland got its act together, and is now rebounding. Yet Ireland never had the Greek disease, namely overstuffed Government employees. Iceland got its act together, and Iceland is not the Disney World of Europe, at best it has rocky hot baths.

So what is Greece to do. I have seen dozens if not hundreds of analyses. None will tell the true tale. Greek politicians are grand manipulators, but the drachma will return. It will again cost 5,000 drachma for a cup of coffee. I still have drachmas, but not enough for that cup of coffee.



Labels: [Commentary](#)

TUESDAY, JUNE 30, 2015

VERIZON AND FIBER

I am always amazed by some people who seem to miss the point, a simple technical and economic fact. Namely that wireless is getting better and better and fiber is just plain expensive, especially in New York. Verizon is slowly becoming a wireless carrier. I saw that in the late 80s and early 90s when I was the COO of the wireless company. I pushed CDMA and Qualcomm over AT&T soon to be Lucent and soon to be dead. Good choice. I saw wireless as a growing capacity and in the past 10 years we have seen with LTE and 4th generation (4G) some of that dream come true and with the 5th generation (5G) on the way this is a reality along with expanded WiFi.

Now just how much capacity do we need? Good question. But 25 Mbps is real good for most things. 1 Gbps is great if you have massive imaging data and real time needs. Not every home is going real time multi patient multi location functional MRI analyses.

Then along comes the lawyers, with some chip on their shoulders. One in particular has a desire to get that 100 Gbps service for what appears to be free. Publishing in [Backchannel](#) she states:

But I have a suggestion. Here's a plan for New York City, one that has the potential to be a win for everyone concerned: Cut a different deal with Verizon. Make Verizon into the operator of a passive, neutral fiber network that (as in Seoul and Stockholm) is connected to every single home and business. Release Verizon from the shackles of serving customers and acquiring programming. Let other ISPs emerge that will actually have the relationships with customers (who will probably be pretty happy never to negotiate Verizon's voice mail again). Set a reasonable price for provision of wholesale fiber access that Verizon must charge to any ISP.

This is like demanding we have Ford provide a million horses and carriages to be certain that everyone can have a ride in old technology any time they want.

Fiber has a niche market. That niche deems it quite valuable whereas most people can and should be served by an amalgam of wireless services.

It is real tough when you just can't seem to understand the basic technology and you demand the world fit your view. Add on top the demand that you tell people how to allocate their resources. I think someone tried that. It was the old 5 Year Plan. It did not work then and will not now.



Labels: [Broadband](#)

FRIDAY, JUNE 26, 2015

THE ECONOMY AND REAL ESTATE

From time to time it is worth a look at how well we may be doing. The above is an interesting chart. It is the total real estate loans issued by month and the annualized growth rate by month. One can see the collapse period but for the last eighteen months we have been doing quite well. This may be one of the best signs of late, of course unless you live in San Francisco!



Labels: [Economy](#)

MIT AND MITES

In the summer of 1974 while at MIT I got a group of local minority students to help on a radar problem at Logan Airport. We were to examine the issue of airport surface traffic control and my group of students were what I had to help me out. They were sharp, dedicated and hard workers. The following summer, 1975, MIT formalized a program called [MITES](#). It is not in its 40th year.

In the late 80s and early 90s I worked again with MITES bringing a half dozen or more students down to New York to work with me at NYNEX (now Verizon). They were great! They went on to Medicine, Investment Banking and Entrepreneurial start ups.

This is an amazing program and I am happy to have played a small role along the way. I still see the former students and from time to time get together. I have seen families grow and careers

expand. Of all the programs at MIT this is clearly one of the most productive.

So Happy 40th to MITES!



Labels: [MIT](#)

[INTERNET AND HUMAN RIGHTS](#)

I just read a piece which discussed the Internet as being a human right. Rousseau would even be surprised. Human rights do change with time, for example we do have "free" telephone service to those who cannot afford it. But Internet access is a bit more complex. It is available at your local library, if you have one, and at all Starbucks I would guess. Most hotel lobbies have it as well. But you have to possess a device which can access the Internet. Is that part of the right.

In [ArsTechnica](#) they state:

FCC Chairman Tom Wheeler said in a speech today that "broadband should be available to everyone everywhere." Wheeler: If slow speeds are enough, why do you heavily promote faster service? The FCC was created in 1934 with the mandate to ensure universal access to telephone service at reasonable prices. Today there is a "Universal Service Fund" to subsidize access to Internet and other communications services but no strict requirement that everyone in the US be offered broadband. Availability varies widely throughout the country, with many rural customers lacking fast, reliable Internet service.

I wrote extensively on [Universal Service](#) some twenty years ago, as the FCC was considering expanding it to wireless.

A United Nations report in 2011 said disconnecting people from the Internet is a human rights violation. Vint Cerf, who co-created the networking technology that made the Internet possible, wrote that Internet access is not a human right, arguing that "technology is an enabler of rights, not a right itself... at one time if you didn't have a horse it was hard to make a living. But the important right in that case was the right to make a living, not the right to a horse. Today, if I were granted a right to have a horse, I'm not sure where I would put it."

Universal Service was focused on a survival issue, the poor and elderly needing access to emergency care. Internet access is dramatically different. It is Facebook and Twitter, the benefit to humanity being marginal at best.

Thus one should ask why we should pay for this service, what is the societal benefit? My position of some twenty years ago seems to remain the same.



Labels: [Internet](#)

[CHINA AND THE US](#)



There are two contrasting media outlets which discuss their country's interests. China Daily is for China and RT for Russia. RT seems always to find the most extreme example of US actions and always finds a way to condemn the US. China Daily on the other hand is a window to China and is somewhat even handed.

A recent piece by [China Daily](#) is worthy of reading. It describes actions by the US with China during WW II. The article states:

Top-secret military documents from World War II have revealed the depth and strength of the alliance between China and the United States against Imperial Japan, as well as joint efforts to rescue downed US pilots. The cache of intelligence documents, detailing a number of daring missions, is on display at Jianchuan Museum in Anren, Sichuan province. More than 1,100 documents and other artifacts were donated by the family of Major Richard Hill (1908-92), a US military intelligence officer who coordinated the rescue of 46 US pilots shot down over occupied China. Fan Jianchuan, who owns the museum, said he is passionate about bringing the largely forgotten story of US-China collaboration to life for a new generation, and that the path to future peace and friendship lies in these wartime ties.

The fact was that the US and China did cooperate greatly during WW II and this was an added dimension that we all too often forget.

On the other hand we should always re-read Mahan as well as Bywater to best understand the Pacific as a region of potential military conflict. China is unlike Japan, it is economically self sufficient and has access to resources that it deems necessary. However control of the seas is as critical to China as it was to Japan.



Labels: [China](#)

WEDNESDAY, JUNE 24, 2015

SQUIRREL SUMMER

Just hanging out! Summer is here and so the guys are resting!



Labels: [Commentary](#)

WEDNESDAY, JUNE 24, 2015

BROADBAND AND POLITICS

In a recent article in [Backchannel](#) an attorney whose opinions in my opinion lack any insight into fundamental technical and operational factors opines on broadband in NH. Some ten years ago I spent a few years trying to do broadband in over 20 towns in New Hampshire. I have a home in New Hampshire and I got to know every street in these towns. All one has to do is examine some cases we presented on [our web site](#). We did years of work examining every street and every market. More than likely we got to know the state better than most Presidential candidates. From Nashua to Colebrook.

Now the author states:

Why? Because New Hampshire, our nation's 42nd most populous state, has lousy connectivity. The FCC defines high-speed Internet access to be 25 Mbps down/3 Mbps up these days, and

more than a third of the rural population in New Hampshire (most of which votes Republican, by the way) can't buy that kind of connection at any price. Fewer than one out of every six urban New Hampshire residents can buy that connection even if they want it: the wire just doesn't exist in their town.

Why the poor connectivity. All you have to do is look at the [paper](#) I wrote after the attempt to build out fiber. I stated:

This paper presents one of the most significant costs of implementing a broadband service but at the same time one of the least analyzed component in that process, franchising. Simply stated, for a town as small as a few thousand households, the time it takes to obtain a franchise under the best of circumstances is often well in excess of one year and the amount of labor includes often two or more people dedicated to that effort plus other costs such as legal, engineering and other costs. If the incumbent decides to fight, the process may take longer. The municipalities always want to increase their returns so the process becomes an escalation of demands and delays. For towns of say 2,000 households, as the author demonstrates by specific case studies, costs of \$400,000 to \$500,000 are not unrealistic. This means readily an additional cost of \$250 per HH or at 25% penetration, \$1,000 per HH. In contrast the capital required to deliver broadband in such a community is \$1,500 per HH. Thus the franchise costs are approaching the capital costs per HH in many communities. This clearly becomes a dramatic if hidden element but also becomes a real but avoidable barrier to entry for any and all new broadband entrants. This paper details these costs and others and makes suggestions to remedy them.

Namely, the towns themselves, in my experience and my opinion, were one of the greatest road blocks. Add to that was the influence the cable companies had in trying to stop any fiber build.

Overall the piece fails in my opinion to understand the complexity of New Hampshire politics. The towns may want fiber but the way they go about it is the most significant obstacle. It would really help to understand the record and not make statements which serve a political agenda.

Unfortunately I have the distinct disadvantage of experience. Politics does not.



Labels: [Broadband](#)

TUESDAY, JUNE 23, 2015

[GOVERNMENT DATA](#)

In the dark old days of on-line searching, such as with Dialog, one had a few databases which were searched by a complex string of commands. The result was a paper title or abstract at best. Then you selected the desired paper and waited until a copy arrived to only find that it did not contain what you really sought.

A holdover from that era is the [NTIS](#), a depository for all Government non-classified studies. Hidden deep within some cave somewhere are all these records. In this depository one must carefully craft a search strategy using the proper phrases and symbols. For example I entered "radar" and got but 2 replies! Do that in google and you get 370 million! So which is better? Not

hard to see.

Along comes a few senators and they see that perhaps they can save a buck. Novel thought. In an [NHPR](#) piece they state:

New Hampshire Sen. Kelly Ayotte is joining with three fellow Republicans to introduce legislation to eliminate what they view as an outdated and duplicative government agency. The bill, dubbed the "Just Google It Act," would eliminate the National Technical Information Services. Ayotte and her co-sponsors say the agency prints and sells copies of government documents that can be found for free online through a simple search. The other sponsors are Sen. Mark Kirk of Illinois, Tom Cotton of Arkansas and David Perdue of Georgia. Ayotte previously introduced similar legislation with Democratic Sen. Claire McCaskill of Missouri. Ayotte says there's no justification for funding an agency whose mission is no longer necessary. The Department of Commerce estimates the agency will have an operating cost of \$170 million this year.

Now \$170 million may not be much, 5 cents per citizen, but it is a start.



Labels: [Government](#)

MONDAY, JUNE 22, 2015

[USPTF AND ITS CONSEQUENCES](#)

Over the past few years as a direct result of the ACA we have seen positions taken by the USPTF on prostate and breast cancer. Women revolted and the USPTF was overturned. Men have just died.

Now in a recent article there are the quantitative results, assuming anyone can believe the Government records, remember the PSA data problem. In the [Journal of Urology](#) the author's state:

There was a 28% decline in incident diagnoses of prostate cancer in the year following the USPSTF draft recommendation against PSA screening. This study helps quantify the potential benefits (reduced harms of overdiagnosis and overtreatment of low risk disease and disease found in elderly men) and potential harms (missed opportunities to diagnose important cancers in men who may benefit from treatment) of this guideline.

The cause seems to be the following of the USPTF guidelines. Namely fewer diagnoses have been made because fewer tests have been performed but if we wait another few years we will see greater mortality.

Just to recall several facts:

1. The US and European studies in NEJM a while back were in our opinion flawed. The US study just looked at a PSA of 4 and did not account for velocity, percent free, age, size, and family history. The European study not only was faulty for those reasons but it samples once

every 2-3 years, much too long a period for aggressive PCa.

2. PSA is useful if and in our analysis and opinion only if its is done and recorded over time, accounts for the size of the prostate, measures velocity, and accounts for percent free PSA. Unfortunately despite all the pressure on EHRs the temporal statistics on patients is ignored.

Thus we see the results starting to appear. In [Science Daily](#) the writes notes:

The study identified a drop of 28.1 percent in diagnoses of intermediate-risk disease and 23.1 percent in high-risk prostate cancer one year after the draft guideline. The decline did not vary across age or comorbidity features. 'These findings suggest that reduced screening may result in missed opportunities to spare these men from progressive disease and cancer death,' said Barocas. While the observation period was too limited to determine the impact on the diagnosis of metastatic prostate cancer, which is associated with a high treatment burden, decrease in quality of life and increased mortality, the authors did observe a small upward trend in diagnoses of non-localized disease. 'The results raise concern that if this trend continues more men may be diagnosed at a point when their disease is advanced. Younger, healthier men with intermediate or high-risk disease would normally be candidates for aggressive local therapy and they may not be receiving a timely diagnosis under this policy,' said Barocas. The authors suggest that future research should focus on screening regimens that minimize harms and maximize potential benefits of screening, while also considering patient preferences.

It will be essential to continue to monitor this result but at the same time use what tools we have clinically to deal with those at higher risk, for example those with strong family histories. The USPTF in my opinion may very well have caused the demise of thousands in the long run.



Labels: [Cancer](#)

MONDAY, JUNE 15, 2015

[THE RATIONING BOARD](#)

Six years or so ago I wrote about my objections to the ACA as then structured and subsequently jammed into law. Now, slowly but forcefully, its reality is coming to the fore. One of the messes has been PCORI, spending almost a billion a year on projects of at best questionable merit. Then the quality parade of linking the elusive quality metrics to payments. Now the Independent Payment Advisory Board. Fortunately Congress is moving to stop this. They should do the same for PCORI, ICD-10, and the mass of other excess payments. Instead the IPDB will be the de facto rationing entity denying procedures that in its opinion are not necessary.

Let me give as an example the PSA test. For most, but not all men it is not a problem. But for those for whom aggressive PCa is the case it is a sine qua non. But IPAB will deny it to all. Remember that the Government has little demonstrated competence anywhere, other than the Military.

In a recent piece in [Bloomberg](#) one of the current Administration's mouthpieces states: but

forcefully

In the face of this pressure, it's crucial to move more forcefully away from fee-for-service payments and toward payments that reflect the value of care. Doing so will require a series of nimble adjustments based on evidence showing which incentives and other strategies work well. It would be foolish to bet the ranch on any one untested approach. The Independent Payment Advisory Board was created by the Affordable Care Act expressly to help with this. In particular, the IPAB is designed to provide a backstop if health costs grow beyond Congress's control. Presumably, Congress will be more likely to act if members know that failing to do so means the IPAB will step in. Those favoring repeal of the IPAB either oppose a shift away from fee-for-service payment, or believe that Congress is about to become much more adept at complicated payment reform than it has ever been in the past.

The reality is that the IPAB can and will control treatment. Physicians will be further loaded with a new set of restrictions and more than likely lives will be lost. This was the proverbial "death panel", a name which may very well have significance.

There are many elements of the ACA worth keeping and others requiring excision. This is one which should be dead on arrival, not the patients.



Labels: [Health Care](#)

[MAGNA CARTA](#)

Today marks the 800th anniversary of the signing of (the) Magna Carta. The [Guardian](#) reports on the current royal person in attendance. They state:

The site is now a National Trust park, but Runnymede was originally chosen as the agreed venue because the boggy ground prevented either the king or his barons from bringing their armies for battle. This time, the sovereign arrived without military backup but to a new fanfare, specially composed by John Rutter and sung by Temple church choir, whose London base served in 1215 as the London HQ for the beleaguered king. Her Majesty was invited to unveil a plaque by the master of the rolls, Lord Dyson, who has in the past described Magna Carta as "a curious hotch potch".

The document is in a sense an establishment of the English Class system. The Barron's wanted their "rights", as best they were understood at the time, and also they all despised King John, a man easily so despised. This was in no way a document for the people and the very concept of a "right" had a few centuries to mature.

Notwithstanding, it is always good to celebrate a day when one person rule gets a comeuppance.



Labels: [Law](#)

SUNDAY, JUNE 14, 2015

LAW OF WAR



The DoD has just issued the [Law of War Manual](#). It is almost 1300 pages and one doubts that many will read and understand it yet many will be judged by its words. It is worth examining to understand the complexity under which the US enters any combat situation. It is also interesting to note that it is a War Manual for the Department of Defense.



Labels: [War](#)

SUNDAY, JUNE 14, 2015

BUILDINGS AND CREATIVITY



The above is a view of Bell Labs in Holmdel. I spent the summer of 1965 there between my MIT work. I recall driving my little yellow VW into the complex the first time in 1964 when at NY Tel to coordinate with BTL on the introduction of the No1 ESS. My office in NY was a desk on some non-descript floor at 140 West Street. In NYC there was no air conditioning and you had to commute like all other New Yorkers, by bus, subway, ferry etc. Now Holmdel was the "future" Now of course it is trying to avoid the bull dozers and new homes. The tale is that buildings do not mean anything. Some of my most creative times were spent in Building 20 at MIT, the

wooden rat infested Rad Lab structures, now replaced by the Gehry monstrosity of the Stata building. What lent the most to creativity, wood and asbestos or glass and leaky windows?

Now the [New Yorker](#) has a piece on the Google building boom. The writer notes:

The idea of living not just near one's employer but in a world of its creation will sound horrifying to many workers: company towns were supposed to have vanished as an industrial-age perversion. But there are socially responsible reasons for holding employees in lavish corporate dorms. For one thing, it keeps them from messing with the local real estate. As I reported in the magazine last year, the greater Bay Area is in the throes of an acute housing crisis, exacerbated, if not caused, by forces attending tech's wild ascent. The value of employee housing, if built from the ground up, is one of the few points on which large tech companies and housing activists see eye to eye. For the companies, too, there's a promise of fruitful cohesion (the group that lives together grows together) and productivity (no trains to catch). It's less clear how tech giants are served by campuses that tune out the outside world. When organized monasticism took root with the Buddhists, in the fourth century B.C., it was the result not of religious insularity but of secular wealth. To shelter nomadic monks was thought to be admirable, so those with faith and money sought to institutionalize the practice. Twenty-five hundred years later, perhaps not too much has changed. To the extent that Google has done its business on the premises of enlightenment ("Universally accessible and useful") and virtue ("Don't be evil"), its research for the future shares a questing optimism—and a reverent isolationism—with the studious faiths of the past.

It is a truly monastic and insular approach. In old Building 20 we walked to many places just to get out of the cold and out of the heat. In Holmdel one went no further than your aisle. You never went to the adjacent aisle, no less the lower or upper floor. You were compartmentalized. My job was the cross point matrix driver for the No 1 ESS switch. Somewhere in the maze of a building was the software. No where was there a vision!

Buildings are a powerful mechanism for communications, or the destruction of such. The building should allow flow, not distract from itself, and facilitate what needs facilitating. My most creative spot was at the old MIT Instrumentation Lab looking out over the back window to the coffin factory, seeing the mahogany coming in and the finished products going out. It was a mix of Camus and Kafka, a vision of life that few have. Behind the coffin factory was the glue factory, with the remains of horses going in and little bottles of glue coming out to be sent to little children to draw their school picture cut outs.

Today in those same spots are multi story buildings all filled with biotech. small DNA segments running through machines. No more coffins. In fact few if any remember the coffin factory. Each day I sat there writing Stochastic Systems and State Estimation, no air conditioning, sweat dropping down my arm as I wrote pencil on yellow pads. No PC, no assistants, just the steady flow of wood to coffins and dead horse to glue bottles.

So perhaps Google may be making a colossal mistake. For McGarty's Law is "Anytime a company builds a massive new corporate headquarters, they soon go bankrupt!" Let's just wait. The again we may have to see what I meant by "soon", it took 20 years for Holmdel.



Labels: [Google](#)

MONDAY, JUNE 8, 2015

[OFF THE SHELF CRISPRS](#)



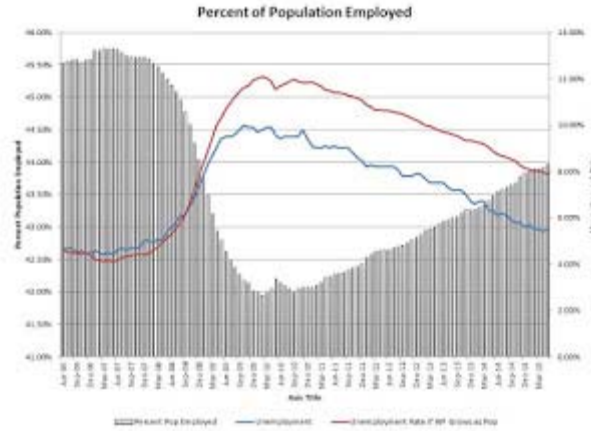
Ran across this for my CRISPR work! Really inexpensive and shelf stable!



Labels: [CRISPR](#)

[EMPLOYMENT NUMBERS MAY 2015](#)

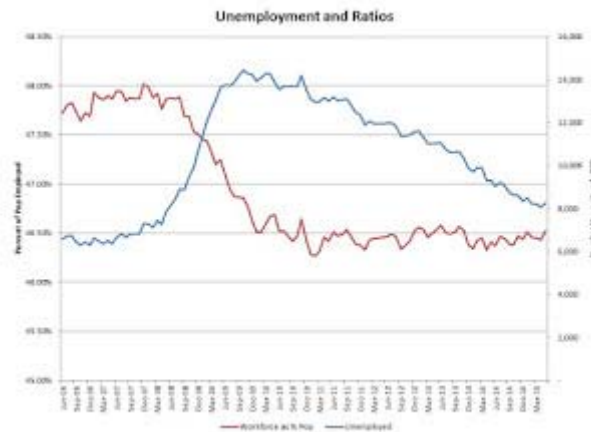
The following are some summaries of the employment data from last week.



First is the set of data on reported and actual using the projections on the 2006 data. We still see a substantial gap, namely using the 2006 participation rate we are near 8% unemployment.



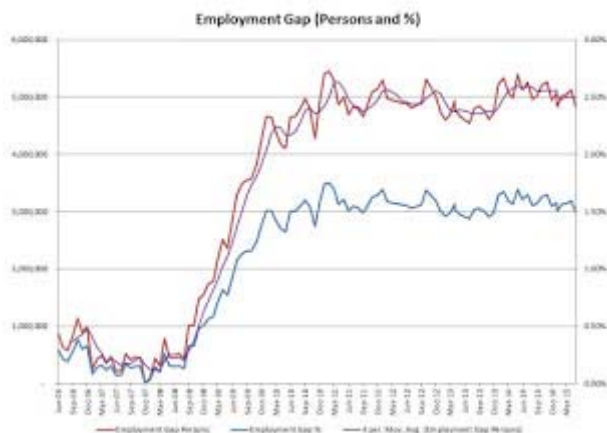
Employment is growing but it is not increasing at a rate commensurate with population growth.



The participation rate just will not climb back to where it was. This will mean a long term deficit, both in employment and in revenue. Also the unemployed will reap benefits independent of contributions.



This shows the incremental numbers. The gap is positive which is of some good news.



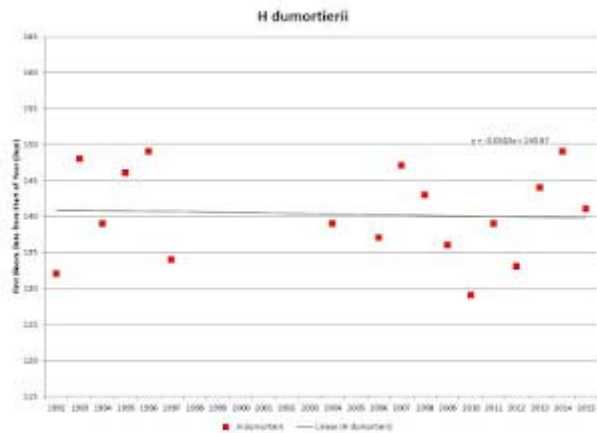
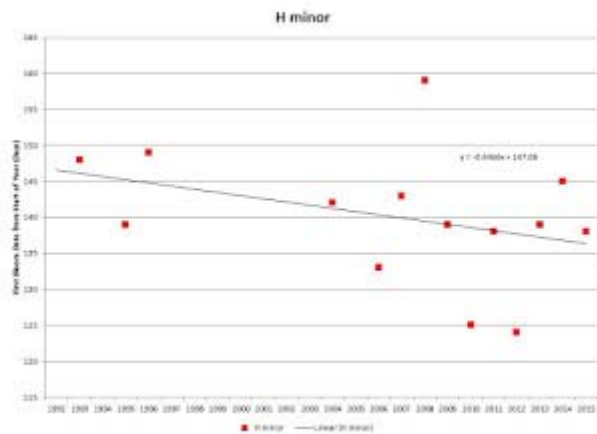
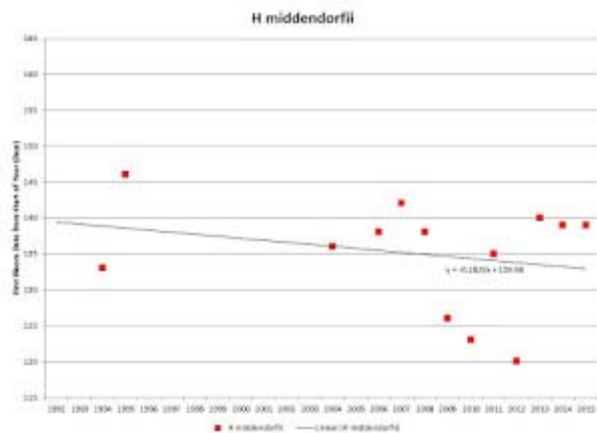
The gap is a measure of a lagging economy. It is not clear why this remains so stagnant.

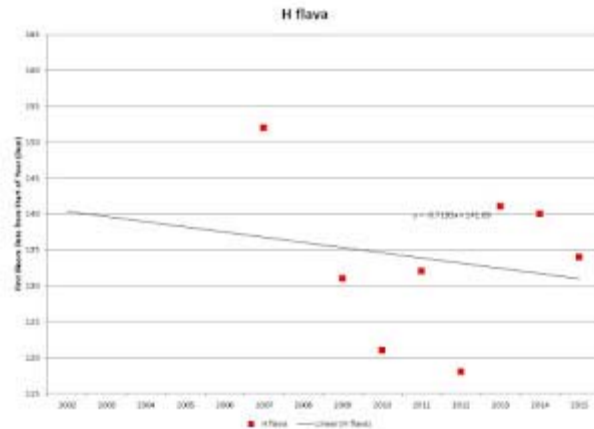


Labels: [Economy](#)

[GLOBAL WARMING AND DAYLILIES](#)

Each year for the past 25 we have monitored the date of first bloom measure as the day of the bloom from January 1 of that year. We present the results up to 2015 below.





There is a downward slope on all, meaning an earlier bloom date, and thus a trend of warming for the past 25 years. However there are micro-environment issues as well as "weather" versus climate issues as well. The trend is there however.



Labels: [Global Warming](#)

SATURDAY, JUNE 6, 2015

CRISPR AND RISKS

In a piece in [Nature](#) the author states:

By and large, researchers see these gaps as a minor price to pay for a powerful technique. But Doudna has begun to have more serious concerns about safety. Her worries began at a meeting in 2014, when she saw a postdoc present work in which a virus was engineered to carry the CRISPR components into mice. The mice breathed in the virus, allowing the CRISPR system to engineer mutations and create a model for human lung cancer. Doudna got a chill; a minor mistake in the design of the guide RNA could result in a CRISPR that worked in human lungs as well. "It seemed incredibly scary that you might have students who were working with such a thing," she says. "It's important for people to appreciate what this technology can do."

Indeed this presents a rather risky tool. Cheap, easy to get and with the right smarts one can target a specific person.

1. Cas9 can be programmed as well so the cells reproduce with Cas9..
2. sgRNA can do two things. Obviously cut a specific location but if we have a specific person's DNA we can program it for a specific person and specific cut.
3. We can then induce say a malignancy by just inhaling a virus which writes this in the target. Moreover we can do the same say with pollen by transcribing this into pollen.

Whether we target a person or mass attacks this can be a easily weaponized mechanism. Doudna

is right, but she may have just seen some of the horrors! One the one hand this is a magnificent tool, on the other and in the wrong hands one should be wary.

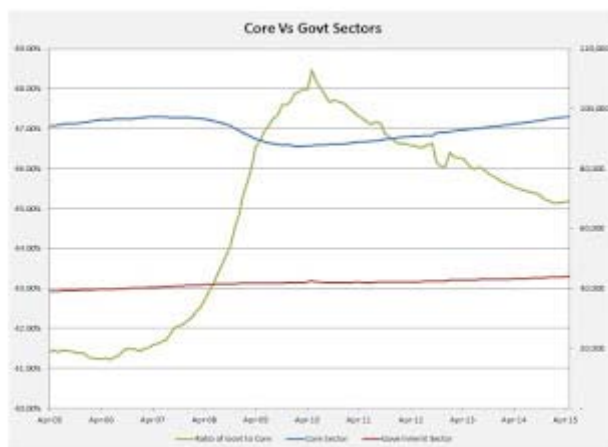
This is especially the case since we have essentially opened our bio labs to anyone coming here. If one thinks cyber terror is a problem, just wait!



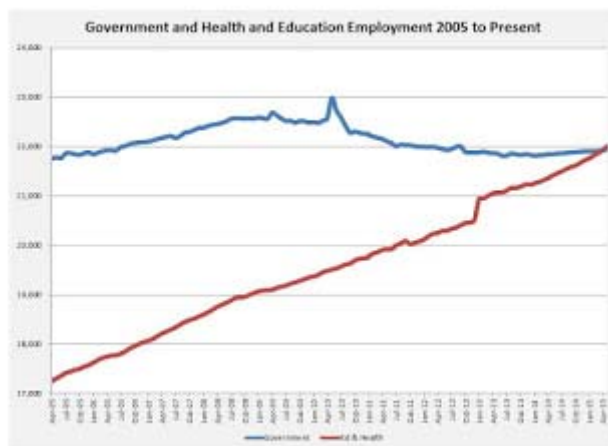
Labels: [CRISPR](#)

[EMPLOYMENT DETAILS MAY 2015](#)

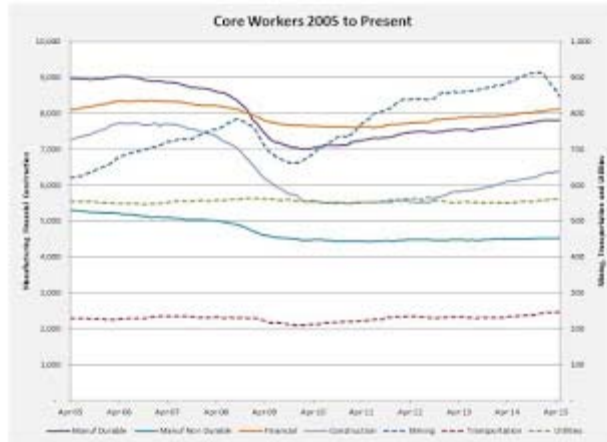
It is worth an analysis of the employment details. We have been doing this for almost seven years. Let us start with Government and related employment.



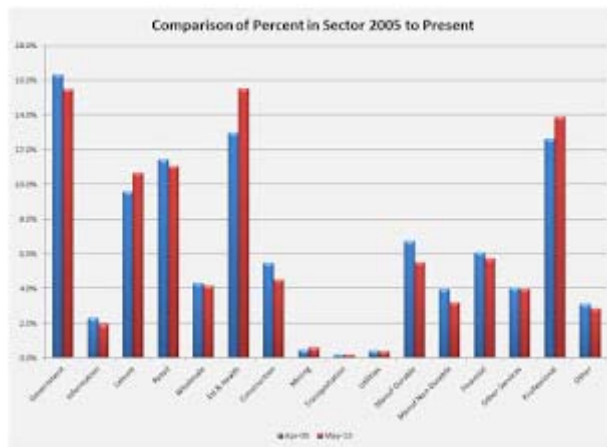
The above chart shows Government and Core, namely jobs that really do something and are not tax supported. The ratio of Government to Core exploded to a peak of 48% in 2010 and dropped but is increasing again. The Government related sector still grows.



The above shows core Government and Ed and Health, which we combine. Note core Government is steady but Health is exploding, from 17 M in 05' to over 22M in 15! That is almost a 35% increase.

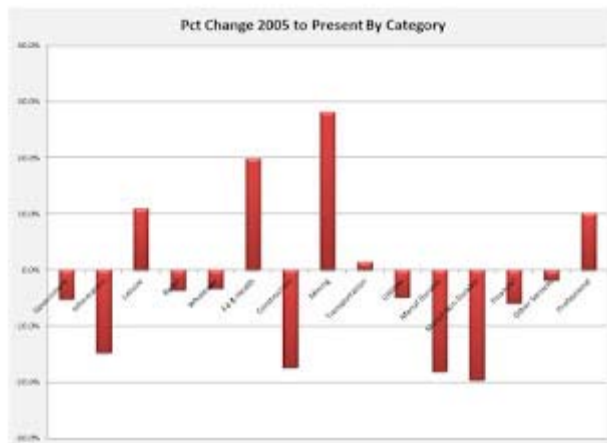


The above shows the Core sectors and their change. Durable Manufacturing has seen a slight increase. Mining has dropped. Construction is doing well again.



The above compares the percents of total in the two years noted. Ed and Health shows the growth as does professional. Manufacturing is down in all sectors.

We show the changes below.



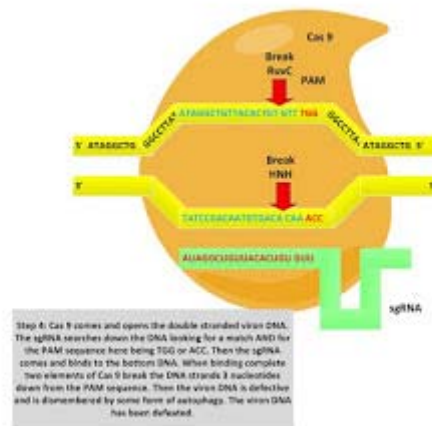


Labels: [Economy](#)

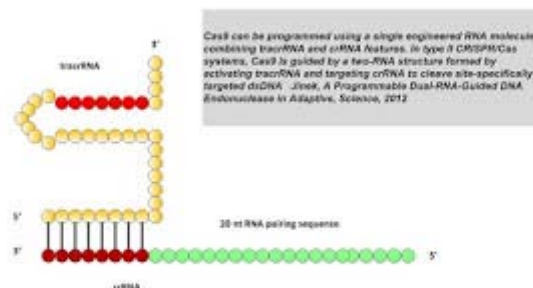
FRIDAY, JUNE 5, 2015

CRISPR ENGINEERING

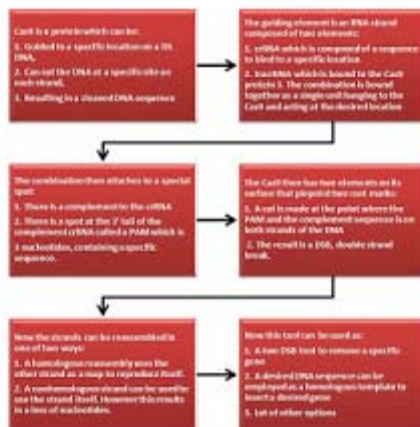
There is a current [Nature Reviews](#) article discussing CRISPR techniques. Just to review the CRISPR cas9 combo is a protein combined with an RNA piece that results in the precise slicing of a double stranded DNA. We demonstrate below:



The RNA is a chimeric combination of RNA which on the one hand attaches to a guides the Cas 9 protein and an RNA that finds the spot on the DS DNA.



The process is somewhat straightforward, albeit a few issues as to just "how" this tool works.



Finally the authors lay out a few applications which we detail below:

Process	sgRNA	DNA Donor	Annealing
Cut	2	X	HDR
Cut and Paste			
Loss of Function	1	X	NHEJ
Multiple Gene Knock Out	1	X	NHEJ
Multiple Gene KO	N	X	HDR
Gain of Function	2	Y	HDR
Generate endogenous alleles	3	Y	HDR
Tag endogenous alleles	N	Y	HDR
Interrogate non coding DNA	N	Y	HDR
Deletions	1	Y	HDR
Inversions	1	Y	HDR
Translocations	1	Y	HDR

I spent some time a few weeks back talking to my grand kids 6th grade class. My final remark was on CRISPRs. They got the point!



Labels: [CRISPR](#)

THURSDAY, JUNE 4, 2015

COMMENCEMENT SPEAKERS

[MIT](#) had an interesting list of its Commencement Speakers. I went back to my days and it was the MIT President. Missed 1970 where there was no speaker due to the Kent State Assassinations. That was a troubled time. But generally it was some content free discussion waiting to get diplomas.

Now we have a real collection of people who at times make no sense. The collection seems more reflection of the politics of the time rather than any academic content. It started with Ms Graham from WaPo. Strange for the time. This year it is the White House Techy, an MIT Grad, but clearly a political statement. Of the politicians they were all Democrats and even the Government Officials. Risky if the Republicans take over in 2016. Also boring if you are sitting

there waiting to get through the process to please your parents.

One must ask just who was your commencement speaker? Unless you had the list I bet not 1 of a hundred would remember. Better yet what did they say? No clue.

I would strongly suggest eliminating such a process. It is too political and content free. It also takes too much time! Just get to work!



Labels: [Academy](#)

THURSDAY, MAY 28, 2015

[AD HOC PROPITER HOC](#)

In a recent piece in [Vox](#) the authors state:

Compared to other developed countries, the US ranks high on income inequality and low on social mobility. This could be particularly concerning if such a trend is self-perpetuating. In this column, the authors argue that there is a causal relationship between income inequality and high school dropout rates among disadvantaged youth. In particular, moving from a low-inequality to a high-inequality state increases the likelihood that a male student from a low socioeconomic status drops out of high school by 4.1 percentage points. The lack of opportunity for disadvantaged students, therefore, may be self-perpetuating.

Perhaps they have never been to France or the UK. In the UK it is your birth family that all too often defines you. It defines your position in society and your outcome. In France it again is family and school. In Russia, well we all know that one.

In the US anyone has a chance despite the author's contentions. Moreover one should look at their own data to see that DC has the highest drop out rate the the highest income disparity! Why, the Government. Lobbyists get millions and the old time residents wallow in a failing school system, albeit supported by the taxpayers.

In my experience the US has the greatest social mobility of any country. Anyone can start anything and try to make a go of it. Failing to complete High School is all too often a failure of the local Government and its way to educate. One need just look at the Charter Schools and their success.



Labels: [Academy](#)

SUNDAY, MAY 24, 2015

[A BOOK ON THE GENOMICS OF PCA](#)

[Prostate Cancer by Stabiano](#) is a recent contribution to the field of literature discussing the genetic underpinnings of this disease. It is a multi-author work by those at the University of Naples and surrounding institutions. It consists of eighteen chapters and the focus is on describing the recent efforts on various elements of the genetic bases of prostate cancer. Each chapter is prepared by one or more of the authors and covers a somewhat specific topic.

Chapter 1 is a well written summary of pathological methods of current use in diagnosing PCa and its related presentations. The materials is well presented and sets the stage for the discussions regarding the genetic elements.

Chapter 2 sets the tone of the remaining Chapters. This Chapter discusses inflammation. Its style is carried through the remainder of the book. Namely the author presents briefly the importance of inflammation and then proceeds through the most recent literature on a topic by topic basis covered in one to two sentences. The presentation is more akin to a literature survey rather than an introduction or even detailed discussion of inflammation in PCa. Inflammation has always been a concern in PCa and its study has been spotty at best. To understand inflammation and its effects one must understand what genes may be affected as well as the impacts on methylation and miRNAs. This becomes a somewhat circular analysis and the authors set up each separately and on a somewhat standalone basis.

Chapter 3 is on apoptosis. This is a key element in almost and cancer. This is a well done chapter and does try to tie together some of the elements. The especially useful addition is the discussion on non-apoptotic elements which is fairly complete and of significant interest to those seeking an expansion of this work.

Chapter 4 discusses the AR, androgen receptor, dynamics and it again follows the style of reviewing and commenting upon the current literature. Chapter 5 does likewise for neuroendocrine issues.

Chapter 6 is an excellent chapter on metastasis. It covers a great deal of the current work including for example that on ALDH1A1 and potentially ALDH1A3. The graphics are generally good and useful. Chapters 7-11 continue the discussion of pathways and their interactions.

Chapter 12 is a discussion of epigenetic factors including methylation and miRNAs. This is a powerful area of research and it would be useful to have expanded the discussion. Whether or not SNP issues fit here as well is an open debate. However, epigenetic factors are becoming significant in understanding many cancers, since they can change expression while leaving DNA in its original form. Epigenetics blocks mRNA from converting into their operative proteins. This may then become a viable path for a therapeutic.

The remaining chapters cover a wide variety of related topics. All are written in the same manner

Overall the books is an excellent source of accessing the literature. It is, however, neither an introduction for those seeking to understand all of the elements, nor is it a standalone text useful for in depth understanding. I would strongly recommend it for those studying the genetic factors associated with PCa. It is an excellent addition and expands understanding the literature.

However it is not for the individual seeking a first exposure and it is not a document which attempts to provide unification of the topic.

I would like to have seen some detailed discussion on the issues associated with the loss of cell fixation by the breakdown of the extra-cellular matrix adhesion. I would also have like to see a more detailed discussion of the pathways and their interactions. So much of the book is a single sentence statement of third party work that the sense of cohesion is oftentimes missing.

Overall, however, this is definitely worth having as a reference source for those in the field.



Labels: [Cancer](#)

WHAT'S IN A NAME?

Names can mean something, should mean something. So I was surprised when I read a [WAPO](#) piece by a University President proposing some "innovative" way to monetize research.

The article states:

To create a new way of supporting the first stage — from idea to investment — a coalition of funders from the public, for-profit and not-for-profit sectors could work together to establish “innovation orchards.” These would provide what universities alone cannot: the physical space, mentorship and bridge-funding for entrepreneurs to turn new science into workable products, up to the point that they meet venture capital’s five-year threshold for the journey from investment to an impact on the market. This would make investing in tangible or tangible-digital hybrid innovations no riskier than investing in the purely digital.

It seems to propose that some group or groups "fund" the process of going from pure research to implementation with this "Orchard" concept. Frankly funding of all types seeks a return. The VC or similar funding entity has a lifetime associated with it. It does not go on forever and its returns have a discount factor. You can promise billions of dollars but if it is thousands of years from now one will have little to no interest.

One can suggest something but perhaps more meat on the bones would have been useful. There once was a time when University Presidents could suggest with some detail. This is throwing a name on the wall and hoping that others will fill in the gaps, there being many.

In my experience I am reminded by a comment made by a colleague, oft repeated, "A good idea does not a business make" It is quite unfair to researchers to let them think that the idea alone, even if it is embodied, has any merit other than its very existence. University research is a process of training, teaching a student how to accomplish a task. True research is just that, exploring the future. However one should not expect that every research result is productizeable. They are not.

The real issue is that in our current research the biotech world is soon to dominate. Unlike our past high tech adventures this world will be controlled by the Government, the FDA. It is that

process which will delimit what we can accomplish and it is that world which needs modification.



Labels: [Academy](#)

THURSDAY, MAY 21, 2015

[DIG A BIT DEEPER!](#)

In a recent [Nutrition and Diabetes](#) journal article the authors conclude:

Most studies examining the relationship of body mass index (BMI) with mortality in diabetic persons suggest a paradox: the BMI category with lowest associated mortality risk (overweight or obese) is higher than it is in non-diabetic persons (normal weight)

Let's try this in English. They seem to state that Type 2 Diabetics with lower BMI have higher mortality.

They continue:

In conclusion, in comparing physical and mental health status by BMI category in concurrent national samples of diabetic and non-diabetic persons, we found evidence of a physical (but not mental) health status paradox in diabetes. Physical health status was most optimal in the overweight category among diabetic persons, versus in the normal-weight category among non-diabetic persons. Given that physical health status influences mortality risk, the findings suggest possible pathways to a BMI mortality paradox in diabetes.

Now this article leaves several questions. They seem to mix Type 1 and Type 2 Diabetes. It is not really clear in reading.

Second, perhaps if one has Diabetes and has low BMI then one may have a totally different form of Diabetes.

Third, in examining anything like this one needs the history of each patient. Not just a single time sample. How heavy were they when the Diabetes started? Just to begin with.

The Tables state Diabetes, but what type?

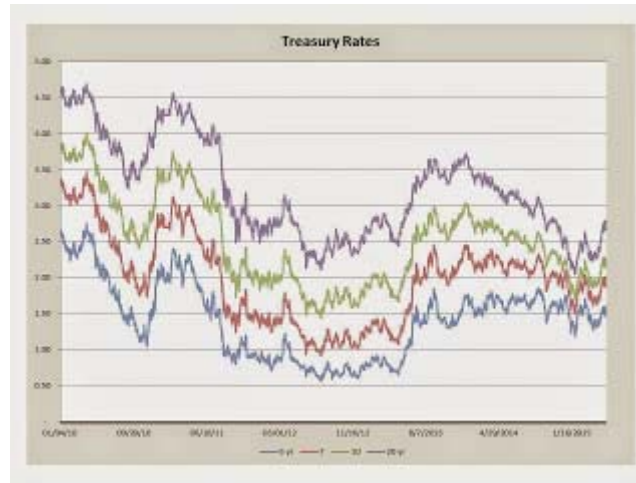
Type 2 Diabetes with BMI under 20? I find that amazing. One is on the verge of ketosis and yet they have Type 2 Diabetes. It makes no sense. Unless of course it is something else.

Perhaps we should have seen a picture of the authors? Just a thought.

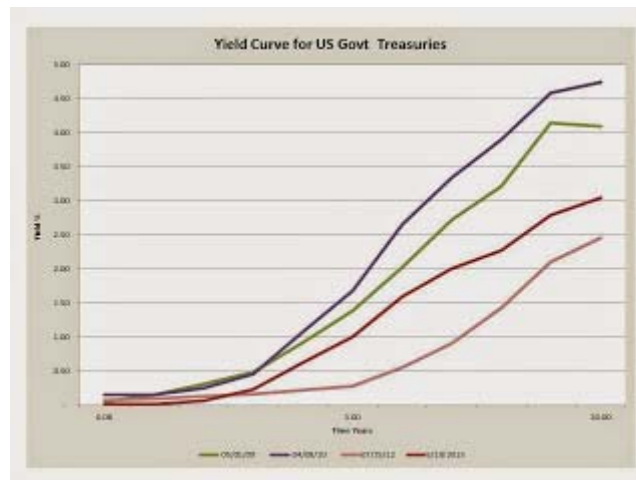


Labels: [Health Care](#)

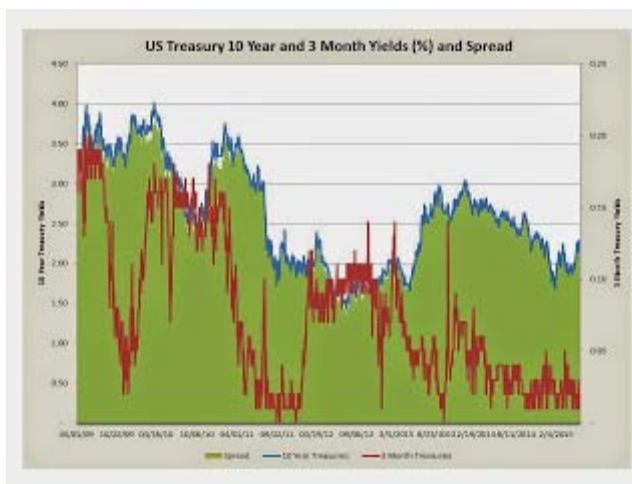
TUESDAY, MAY 19, 2015

YIELD CURVES MAY 2015

The Treasury Yield curves are shown above. They seem to have clumped and are now spreading out again



The above is an example show today's curves and lows and highs. The question is: what do these really reflect?



Finally the spreads, starting up again but not a great deal. In many ways this is still very artificial.



Labels: [Economy](#)

[FREE TUITION](#)



There is a movement to have free tuition at state universities funded by the Feds, aka the taxpayers. Is this a good idea?

Frankly if students who perform well and demonstrate their abilities, then in state tuition at their state schools is great. West Virginia already has it for high performers and New York used to have Regents scholarships before they did away with Regents. It makes sense for those who are doing well but not MIT or Harvard yet.

But one must beware of several factors:

1. It should be performance based. What performance? Class ranking, grades, even a competitive exam. There must be some clear demonstrable level of performance. It must also be blind to anything else. Otherwise it will be gamed.
2. The Feds must be hands off. We all know what the Feds do...drive up costs. How can this be done, block grants perhaps.
3. Avoid social engineering. If one wants people to perform then make the rules clear and play the game. We do not social engineer football, basketball, etc.
4. Promote productive studies. We really do not need too many fine art majors or French literature majors. We do need engineers. We don't need more lawyers, we do need competent physicians.
5. Reward performance and punish failure. Yes, if they fail then drop them. Give a second chance but do not let them linger.
6. Set standards, real standards for real life. The goal of education is to be productive. Productive in society. One can always study philosophy later. Or at the same time if one can fit it in.

Just some thoughts.



Labels: [Academy](#)

[PSA, TAX DOLLARS, AND THE GOVERNMENT](#)

From time to time one reads about the errors induced in Government programs. The recent report that NCI has removed all of the historical data due to data entry problems, that is about 45 years worth of data, is truly amazing. Here is what [NCI](#) states:

The results for this registry-based evaluation in two SEER registries confirmed that the PSA values were often incorrectly reported based on an implied decimal in that data field. Following current reporting guidelines for cancer registry data, PSA is coded in a 3-digit field with an implied decimal between the second and third digits. For example, a PSA of 4.0 ng/ml should be coded as 040. In both the study described above and in the SEER registry's evaluation of their data, it was noted that some registrars were confused with proper use of the implied decimal. For example, this resulted in coding a PSA of 4.0 ng/ml incorrectly as 004. The error rate for the SEER data was lower than that seen in the original study and was approximately 17%. The likely reason that the error rate was lower was a reflection of the ongoing quality activities that routinely occur at each of the SEER registries as data are submitted.

The core rule in entering data is to avoid ambiguity, yet expect it and check. Now we have many studies which have used this data and then make regulations based upon it. Perhaps the PSA rules mandated by the USPTF should be not only reconsidered but totally abandoned!

They conclude by stating:

We are currently developing a protocol that will be applied by all SEER registries to further assess the error rate and allow the registries to correct PSA values in recent years. As part of that protocol we will determine whether we can use statistical methodology to correct PSA from prior years. Once we have corrected the data, we will repost the PSA corrected values and make those available to researchers.

Anyone who has ever done a set of questions for a database knows the possibility of mis-interpretation. I see it all the time. Recently I examined a Columbia Medical Center set of questions that not only were ambiguous but flawed. They made no sense. But did that stop anyone, no!

Clearly the 040 or 4.0 could have been avoided by being clear, namely x.y, two fields, with an error check and a feedback in red restating the value. Frankly the required entry is truly confusing, and it probably costs us millions to design!



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

MONDAY, MAY 18, 2015

[NOW IT'S 5000+ AUTHORS](#)

In [Nature](#) there is a report of a paper having over 5,000 authors. As they state:

A physics paper with 5,154 authors has — as far as anyone knows — broken the record for the largest number of contributors to a single research article. Only the first nine pages in the 33-page article, published on 14 May in Physical Review Letters, describe the research itself — including references. The other 24 pages list the authors and their institutions.

This seems to be the trend.



Labels: [Academy](#)

SUNDAY, MAY 17, 2015

[INTERESTING BUT WORTH A CRITIQUE](#)



The [End of Ancient Christianity by Markus](#) is an enlightening presentation of the Church from Augustine to Gregory I, about 400 to 600. This is the post Constantine period, one where Christianity was no longer persecuted and managed to begin its establishment of elements of control over the lives of most people. At the time of Augustine, say 400, there were clouds on the horizon but not to the extent of those that Gregory had to contend with. Markus argues that there was in the West a change from the secular to the sacred, namely changes from classic Roman control to controls influenced and dominated by the Church.

One of the dominant changes was the move of the capitol city from Rome to Constantinople, Byzantium, and the remnants of control in the west being limited presence in Ravenna. Augustine in Hippo knew the old Rome, while Gregory in Rome saw a totally new reality. Markus presents his interpretation of how this change occurred and what were its elements.

On p 15 the author commences building his presentation of secular and sacred. He states “No one really doubts that in ways such as these Western Europe was being drained of the “secular”...” This in some ways is contradicted by the facts. The Franks, namely the Merovinginians, albeit Christian in calling, were anything but sacred in their actions. Gregory of Tours recounts their blatant brutality and even the letters between Gregory and Brunhilda, the former Queen, lay out the clear continuation of Frankish ways. Moreover the preponderance of Salic law had supplanted Roman law and the Code of Justinian never really made its way to the West. Add to that the Lombards who were Arians, and a continual burden to Gregory. Spain and its Visigoths had a similar situation. Thus the statement made by the author in my opinion is contradicted by both the record and the facts.

On pp 16-17 the author provides an outline. Part I is a discussion of the post Constantine changes. Part II discusses the forces that the author contends led to the changes from secular to sacred. Part III considers the ascetic norms which became part of the way of life going forward.

Chapter 2 is a discussion of the structure of the Christians in the beginning of the 5th century. They had become communities, open and were using the martyrs and their relics as a nexus to their past.

Chapter 4 is a discussion of Pelagius and Augustine. The key to understanding Augustine is his theory of grace and it is predicated on Paul’s letters in Romans. Grace was given, and acts were less important than grace. Pelagius in a simplistic sense saw acts as important if not more so than

grace. To this speculation Augustine responded with vitriol. On p 52 is an excellent interpretation of the development of Augustin and his battle on grace. He had sharpened his arguments on what he did with the Donatists. The Donatists position was that if you denied your faith you were not able to return to where you were when the cause for the denial was lifted. Augustine stated that once a priest always a priest and that if one recants one can return. This battle was the driver for sharpening the Augustine dialectic.

On p 55 is an interesting discussion on Augustine and the Pelagian view of sin. Namely the Pelagian view was that man could abstain from sin whereas Augustine saw man in a continually losing battle being saved only by grace. Further man never knew if God had given such grace.

Chapter 5 discusses the issue of; if grace is God's, then what is the worth of man trying? (p 63) This is followed by the Timothy statements by Paul on free will and the possible conflicts with grace. Many of these complex ideas led to the ascetic life and the separation from society of the hermits. Whereas the martyr was the sine qua non of the pre-Constantine period, the monk the author alleges is that in the post-Constantine period (p 69). The author then discusses the details of the monastic life as it developed over this period.

Chapter 7 discusses the martyrs. In particular it focuses upon the cult of the martyrs. The Church calendar became a continually celebration of martyr after martyr. There was a culture brought to the faithful centered on one martyr after another. The martyrs were in the past but they became the nexus to the present. On pp 98-99 the author discusses this in detail The calendar went from social to sacred, from the celebration of pagan events to the remembrances of the dead. Ironically as the times went by the calendar became not only sacred by the day but even by the hour, a time for one prayer after another. Chapter 8 then is a discussion of how secular festivals could be incorporated. On p 111 there is the Augustine dictum of "abstain as far as you can from worthless spectacles". Paganism slowly but then aggressively was persecuted. Chapter 9 is a discussion of the further Christianization of time. On p 131 there is a discussion of time being an element of the Christianization of all life.

Now the author contends that there is some universal acceptance of these principles across Western Europe. There does not seem to be evidence of this acceptance. Admittedly in Church controlled domains like monasteries and in Bishoprics, the religious times were practiced, yet as the population, in what would become France and even in Ireland, the people lived in ex-urban locations, and the monasteries were often segregated. England until Gregory I was even turning pagan. By the late 6th century the Irish monks like Columbanus had spread out across Gaul and down into Italy, such as at Bobbio, and their monasteries were open to all but distant from many. Thus it is questionable as to how universally acceptance and practice were.

In Chapter 10 there is a discussion of place. Christianity states the author abandoned place qua geography, and used place as worship. The discussion on pp 140-141 details some of this. The old Roman world was filled with holy places, albeit pagan. Christianity abandoned this, almost as a way to sever the tie to the old ways. On p 142 the author uses the martyrs as a bridge to the past during this period. It was a bridge that allowed them to connect the world of persecuted Christianity with the "new" world dominated now by Christianity. As he states on p 155 the places became locations of history and not holiness.

Chapters 11 and 12 discuss the isolation of the monasteries and the frontiers they created and then how these could be broken down. Chapter 13 adds the invasion of the ascetic into the daily lives.

Chapter 14 is a conclusion. It is here where I may have my greatest concerns. Here the author discusses Gregory I. Gregory was in a sense the last and in the sense the first of a generation of Bishops of Rome. Elected by the people, he looked westward. He befriended the Merovingians, especially the brutal Brunhilda. One must wonder how that was managed and as one reads his letters they are letters from a Bishop at once a religious leader and at once a true politician. He wanted to keep the Merovingians in the Church, albeit a brutal people. He managed the wife of the Lombard king, who eventually managed peace with the Lombards and Rome. He managed people in his lands, and he used some of the best of Roman management style to survive. At the same time he was the Bishop of Rome who truly severed the tie to Byzantium. On pp 224-225 the author commences on this discourse.

The last sentence of the book (p 228):

“The massive secularity of John Chrysostom’s and Augustine’s world had drained out of Gregory’s. There was little room for the secular in it. The Devil was close, always ready to swallow up the world and the flesh.”

I find this difficult to agree with. In reading Gregory’s letters, and there are many, one sees a man who balances the secular with the sacred. On the one hand he can write of Job and how to preach and on the other how to govern and how to handle complex situations. In the correspondence with Columbanus one sees a set of discussions on such issues as the true date of Easter but one sees an Irish monk, never dominated by Rome, and the Bishop of Rome respectfully but aggressively making their points. He was a politician and a political leader. He managed to keep invaders at arm’s length, discuss politics with barely civilized kings and queens and also managed to fear the people of Rome. Whether it is Gregory of Tours or Gregory of Rome, the devil often seemed a distant concern.

It could be argued that the Middle Ages in the West is the period from Gregory I to Ockham (400-1350). It was a period of Church dominance, sacred and secular. Gregory became the first Bishop of Rome to both sever the ties to Byzantium and at the same time establish political parallels with the emerging rulers of the developing nations. Ockham represents the first major denial of papal secular authority. Marsilius also parallels that effort but in many ways it is Ockham that introduces the individual, via both nominalism, as well as his papal analyses. In fact the very move from Rome to Avignon was a break from what the Bishop of Rome was to be, in Rome, not Avignon.

The author indicated he was starting with a biography of Gregory. That would be a worthy task by a highly worthy writer.

Overall this book is exceptionally well written and the author makes his arguments forcefully. I would strongly recommend this to anyone trying to understand this critical period not only in the history of the Church but the history of the West.



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

SATURDAY, MAY 16, 2015

1,000 AUTHORS

The explosion in the number of authors on papers has gone into the stratosphere. [Nature](#) reports on a recent paper on fruit flies:

*Author lists have grown lengthy in many fields of science, but when a *Drosophila* genomics paper was published with more than 1,000 authors, it sparked discussion online about the meaning of authorship. The paper, published in the journal *G3: Genes Genomes Genetics*, names 1,014 authors — with more than 900 undergraduate students among them.*

This really questions who does what. Why not include the cleaning crew, the folks who built the building, the manufacturing team on the sequencer.

The problem is that it is now impossible to determine who did what. Watson and Crick was enough. Nobel prizes are given to at most three people. This is akin to a new bumper sticker, "My Teenager is an author of a major research paper!" We seem to be going unstable.



Labels: [Academy](#)

TUESDAY, MAY 12, 2015

MY FATHER'S PARTNERS



In the late 50s and early 60s my father was in the NYPD Youth Division. During that time he had three partners, policewomen. They were:

Ruth Simon
Gertrude Schimmel
and
Felicia Shpritzer

Schimmel has just passed at 96! As the [NY Times](#) states:

Like all the female members of the department, Ms. Schimmel was assigned to the Bureau of Policewomen when she graduated from the Police Academy. In her early years with the department, her son said, she took part in undercover work breaking up gambling operations. She later joined the Youth Aid Division, which found temporary shelter for children whose parents were ill or otherwise unable to care for them. It was the type of assignment given to women to keep them from confrontations with criminals.

Frankly the Youth Division was in some ways more difficult than others. The pair would show up at apartments with butchered parents, picking up the terrified children and spending long hours finding homes. Tracking down wandering children, many who had fallen in with the bad set if you will, seeing lives not even started destroyed before a spark of adulthood. The damage done to children before their time could take a toll.

My father had been proud that his partners all managed to succeed in a profession that was male dominated. As the Times noted:

Police Commissioner Michael J. Murphy maintained that women lacked the physical strength and endurance to become sergeants, but the city lost the court battle.

As I recall my father saw these as equal colleagues, never as inferior weaklings. In fact the moral fiber was more critical than the physical, meaning that they had to help the children try to take first steps of regaining their lives, something that the rough and tumble men could not.

I remember all three, I recall the tales of their adventures, never a sharp word, always a team. The classic tale was when Ruthie finally admitted to my father many years latter that she never had bullets, she did not like guns!



WEDNESDAY, MAY 6, 2015

BATTERY WASTE?

Batteries have been useful but not the most efficient storage medium for energy. However with the introduction of lithium batteries this has improved. However lithium is hazardous waste. A rechargeable battery can go through a recharge cycle a few thousand times at best. If you do it every day, as in a home system, then you may get three to four years of use. Then you have a non-rechargeable toxic boat anchor. Where do you put it? Not as bad as nuclear waste but definitely not "green".

Along comes Tesla who announces a home battery (see the [CSM](#)):

All of the new batteries run on the same type of lithium-ion, software-equipped technology found in Tesla's cars, and can be mounted inside or outside of a building.

As [Computer World](#) notes:

Europeans have a dimmer view of landfilling lithium ion batteries. "There is always potential contamination to water because they contain metals," says Daniel Charet, general manager at Belgium-based Umicore Recycling Solutions. The bigger issue is a moral one: the products have a recycling value, so throwing away 2 billion batteries a year is just plain wasteful - especially when so many American landfills are running out of space. "It's a pity to landfill this material that you could recover," Charet says. He estimates that between 8,000 and 9,000 tons of cobalt is used in the manufacture of lithium ion batteries each year. Each battery contains 10 to 13% cobalt by weight. Umicore recycles all four metals used in lithium ion batteries.

As [Waste Management World](#) has noted, there is a recyclable option, albeit costly:

With lithium recycling in its infancy, there is currently no main recycling infrastructure in the world that treats only automotive Li-ion batteries. A few pilot plants, such as Umicore's Hoboken plant in Belgium that are at a demonstration stage exist. Lack of standardisation in battery chemistries and changing landscape with respect to different elements under research for battery production other than lithium have made evaluation of the recycled value of the components

uncertain for the recyclers.

Overall one should look at the full life cycle here. The "green" puffery is just that unless the plan to recycle safely is in place. Otherwise we will have mountains of un-usable trash!



Labels: [Energy](#)

TUESDAY, MAY 5, 2015

[WHY GO TO MARS?](#)

NASA has a continuing problem of laying out reasons for it to do things. The Mars mission is an example. Now we could always say that the Russians, Chinese, or whoever, is going there and we need to beat them to it, but perhaps a clearer head should prevail.

Scientific exploration is always good but a great deal can be accomplished with non-manned missions.

[NASA](#) now is seeking public input on setting up a manned base on Mars. As NASA states:

NASA Announces Journey to Mars Challenge, Seeks Public Input on Establishing Sustained Human Presence on Red Planet. What do you need to bring, and how do you minimize the need for delivery of future supplies in order to establish a sustained human presence on a planet 140 million miles away from Earth?

NASA is embarking on an ambitious journey to Mars and Tuesday announced a challenge inviting the public to write down their ideas, in detail, for developing the elements of space pioneering necessary to establish a continuous human presence on the Red Planet. This could include shelter, food, water, breathable air, communication, exercise, social interactions and medicine, but participants are encouraged to consider innovative and creative elements beyond these examples. Participants are asked to describe one or more Mars surface systems or capabilities and operations that are needed to achieve this goal and, to the greatest extent possible, are technically achievable, economically sustainable, and minimize reliance on support from Earth. NASA expects to make up to three awards at a minimum of \$5,000 each from a total award pool of \$15,000. NASA's efforts for sending humans to Mars is well underway today, with spacecraft monitoring Mars from orbit and rovers on the surface. The International Space Station is testing systems and is being used to learn more about the health impacts of extended space travel. NASA also is testing and developing its next generation of launch and crew vehicles -- the Space Launch System rocket and Orion crewed spacecraft.

It appears that NASA will award the public for their good ideas. Remember that it is taxable! And also if it does not work they will blame you!



Labels: [NASA](#)

[A NEW MALPRACTICE OPPORTUNITY?](#)

It appears that IBM will joining with an EMR entity to join their Watson diagnostic capabilities to the EMR.

As [Becker's](#) reports:

Epic plans to embed Watson's cognitive computing capabilities into its EHR using open standards, which will then allow patient data to be pulled from health records and delivered to Watson. The supercomputer will then analyze that data in comparison to its massive volumes of stored clinical data and produce medical literature and case studies most relevant to that patient's care to help inform clinical decisions in real time.

Now just think if you are a physician using this system and it "suggests" an alternative diagnosis or procedure and you over-ride it, then through discovery you may be found negligent, or IBM is brought into a claim for practicing without a license.

This is one of those nice ideas that sounded good when they first thought through it. It may not sound so great after a few trials.

One wonders if this is Press Release driven. Imagine suing the HAL 9000 or it cousin!



Labels: [Health Care](#)

[A BRILLIANT BOOK ON MEDIEVAL THOUGHT APPLICABLE FOR TODAY](#)



Shogimen's book on [Ockham and Political Discourse](#) is a highly readable and exceptionally insightful discussion of Ockham's view of political theory applicable not only to the Late Middle Ages but also to the current time. There have been a group of writers who have analyzed Ockham and his thought over the past century and Shogimen provides a new overview of his thought. It is logically presented and addresses not only Ockham's rejection of papal power over men's day to day lives but presents an excellent discussion of Ockham's views on individualism and constitutionalism. In a sense, Ockham in the readings of Shogimen is less a medieval political theorist and more the first contemporary examiner of republican structures.

Shogimen begins with a chapter examining others before him who have written on Ockham. From the brothers Carlyle through McGrade he provides an even handed summary of these other thinkers. This is an essential discussion for anyone studying Ockham. There are many views as to his thought and the true challenge is; how does one in the 21st century understand the mind of a person in the 14th century. That is always a hermeneutic challenge, the challenge to understand not only the use of words and ideas but also the motivation behind them. In Ockham's case the conflict with the Avignon Papacy and John XXII on the poverty led him to examine the heresy of the Avignon pope and then to examine the very powers exercised by the papacy as an institution. Having done this Ockham is drawn into examining political structure broadly.

Chapter 1 deals with the poverty issue which drew the attention of Ockham. The Franciscans were being attacked for their position on the poverty of Christ and in turn the belief that poverty is an essential element of Christianity. In turn John XXII attacked the Franciscans and it was this that drew Ockham to Avignon.

On p 39 the author quotes John XXII retort:

"Poverty is great but integrity is greater. Yet obedience is the greatest good."

In a sense it is this papal mandate to obey, not believe, not charity, not poverty, not even integrity, but pure abject blind faith obedience. The papacy speaks and all obey, a holdover from the Roman Empire days, albeit the papacy no longer a Bishop of Rome, but a resident of Avignon.

On p. 42 is a simple but well phrased summary of Ockham's argument. Namely if as Pope Nicholas' III statement accepting poverty were true, then John XXII is in heresy, if however it were not true than Nicholas was in heresy and had no true successor and there John XXII was in error. Either way the John XXII statement is false based upon heresy.

On p 57 the discussion of the Judas purse issue is well worth reading, it is clear and adds substantial light on counter arguments.

Chapter 2 is a discussion of heresy as examined by Ockham. On pp 81-83 is an excellent elucidation of the Ockham theory of heresy. Fundamentally heresy is deliberate and unrepentant articulation of beliefs contradicted by Scripture. It is not a result of papal interpretation but a conciliar interpretation as the early Councils of the Church had accomplished.

Chapter 3 is a discussion on papal heresy. This is a discussion of Ockham's elements of how the pope may commit heresy.

Chapter 4 is on papal power. Here we have a good discussion on papal power. Simply, for Ockham the papacy is not a power over men's lives but their spiritual well-being. Moreover he believes that the papacy as in Avignon has over extended itself in its control of the lives of people in dimensions where it has not authority, power or even knowledge.

Chapter 5 is on papal primacy. On pp 210-213 there is a discussion of the limits of papal primacy. Moreover on pp 226-230 there is a compelling discussion that basically argues; Scripture assigned primacy to Peter and since there is no mention of subsequent assignment then papal primacy is vacuous. Moreover the conciliar process has more merit as a successor to Petrine primacy than does papal primacy. It is interesting to ask why these arguments were not used as strongly during the Reformation period.

Chapter 6 is worth reading through multiple times. It discusses Ockham's view of human freedom and more importantly his view of individualism. On p 234 is an excellent discussion of individualism as self-autonomy. Such a concept one might have thought rare if not impossible during a time of evolving kingdoms and strong papal powers. However as suggested on p 239 it was the very interaction on papal power and authority that led Ockham there. Namely he saw that the spiritual and temporal should stay in their assigned quarters, and this left each individual responsible for their own lives.

Shogimen has written a timely and insightful book that has interest that well exceeds the corners of Late Middle Age political thought and philosophy. His analysis is worth examining in today's world as well see in many areas the confluence of religion on temporal lives.



Labels: [Political Analysis](#)

SUNDAY, MAY 3, 2015

[PQRS: MEDICARE, PAYMENTS, PENALTIES](#)

As we had indicated five to six years ago in this set of analyses, the ACA will be placing an unending set of costs and tasks upon physicians. PQRS is another example soon to hit the street.

The [details of PQRS](#) are:

The Physician Quality Reporting System (PQRS) is a quality reporting program that encourages individual eligible professionals (EPs) and group practices to report information on the quality of care to Medicare. PQRS gives participating EPs and group practices the opportunity to assess the quality of care they provide to their patients, helping to ensure that patients get the right care at the right time. By reporting on PQRS quality measures, individual EPs and group practices can also quantify how often they are meeting a particular quality metric. Beginning in 2015, the program will apply a negative payment adjustment to individual EPs and PQRS group practices who did not satisfactorily report data on quality measures for Medicare Part B Physician Fee Schedule (MPFS) covered professional services in 2013. Those who report satisfactorily for the 2015 program year will avoid the 2017 PQRS negative payment adjustment.

[A summary](#) for this program is on the CMS Site. Basically PQRS requires that CMR reimbursed physicians collect and report what they call "Quality" statistics. For example with Type 2 Diabetes the Quality metric would be:

Percentage of patients 18-75 years of age with diabetes who had hemoglobin A1c > 9.0% during the measurement period.

Frankly what that metric has to do with quality care one really wonders. If one is treating patients who are morbidly obese, say in a minority community, and you have tried everything up to and including insulin and the patients do nothing to try to do anything then why is this a quality metric? It is meaningless. You can tell a morbidly obese patient to reduce their weight but for many it is a hopeless task. Do physicians now get penalized for not doing what?

The [enabling law for PQRS](#) is stated as follows:

Affordable Care Act. The Affordable Care Act makes a number of changes to the Physician Quality Reporting System, including authorizing incentive payments through 2014 and requiring a penalty, beginning in 2015, for eligible professionals who do not satisfactorily report. The Affordable Care Act also authorizes an additional 0.5 percent incentive for 2011 through 2014 for eligible professionals who satisfactorily report and more frequently than is required to qualify for or maintain board certification status participates in a Maintenance of Certification Program for a year and successfully completes a qualified Maintenance of Certification Program practice assessment for such year.

This PQRS adds a tremendous reporting burden on the physician. Now they have EHR to do, billing, PQRS, and for what? Who will read all of this. Then there is compliance. What if one makes a mistake, audits can start and penalties apply.

The key question is what benefit to the patients results from this process. It is not at all clear to anyone at this stage. It just drives up costs and impairs care. That is not quality!



Labels: [Health Care](#)

SATURDAY, MAY 2, 2015

[PAPAL POWER: RELIGIOUS AND SECULAR](#)



The book [Political Thought](#) by Coleman is exceptionally well written and covers the main thinkers of the 13th and 14th centuries. She presents the ideas of Aquinas, John of Paris, Marsilius, Ockham, and Machiavelli. In a sense the many arguments discussed by her in the book, all exceptionally clearly presented, lay out the changes occurring at that period with Kings and countries evolving and the papacy in a growing position of power, following through the Avignon papacy of the Bishop of Rome, a bit of a contradiction in terms.

She starts with an overview of the key principles that had been some of the underpinnings of the political thought at the time. Two of them are The Donation of Constantine and the Two Swords theory. The Donation was an outright fabrication but it had been used by the papacy for establishing its primacy in all things. In essence the Donation alleged that Constantine had recognized and accepted the domination of the Church, which in a sense had become by this time the papacy. It was also based upon this false document that Henry II of England was “allowed” to give his son John kingdom over Ireland. The two swords principle is the belief that the papacy had both spiritual and temporal powers over people.

By the 13th century there clearly was an established power base with the papacy. The Pope had battles various Princes and had tried to hold his dominance over the Kings now emerging in the nations in formation. Thus there was a debate as to what was the role of the papacy and more importantly what were the principles related to governance. As would be argued that councils had primacy over the Pope, then too one could argue that people had primacy over Kings. The Council principle, Conciliar Theory, had re-emerged from centuries of dormancy. Popes had become Emperors in their own right, and in many ways this led to a breaking point, especially with John XXII in Avignon.

The discussion of Aquinas is standards but well done. Aquinas is a classic example of the Scholastic School, and he managed to explain Aristotle but to keep from exciting too great a Papal response.

John of Paris and especially Marsilius are key players in addressing the limited powers of the Papacy. They rejected the power of the Pope in civil matters and their arguments establish a base for what Ockham was to do next. The author’s presentation of Marsilius is one of the best I have seen. It is clear and delineates the details of his theory. Marsilius saw civil law as distinct from clerical rule and religious law. Marsilius, who is often less well known, set the path for much of what was to come in the 16th century.



The presentation on Ockham is clear and insightful. Ockham has many scholars who have examined his work. The recent work by Shogimen is an example. However the author lays out the brilliant arguments of Ockham especially targeted at John XXII in Avignon. Ockham saw the papacy as a purely religious arm. Ockham saw a separation between religion and politics and he was clear in his arguments for the papacy keeping to its own terrain. Ockham at this time was developing his ideas on individualism, one of the very first to articulate individual rights, individual presence, and an acceptance of individuals acting in groups, while retaining their individual character. Whether this is based upon his nominalism or not is still open for debate. Ockham is an interesting player in this area. Marsilius is often a footnote but one suspect that they in some way built upon one another. What drove Ockham was the opulence and arrogance of the Papacy, as exemplified by John XXII. The Papacy had become an interferer in all matters of daily life. It sensed supremacy over rulers and people, not only religious but in their daily actions. Ockham set the path that allowed this to fall apart, albeit over time.

Finally she deals with Machiavelli. This also is a well done section and is presents the almost natural transition from Aquinas, to Ockham and to Machiavelli. At this point we see the Aquinas nexus to Augustine and the old Roman way, to the individualism of Ockham and the brilliance of Machiavelli and the Prince.

This is a wonderful book and it is especially worth reading as we see a papacy becoming more involved in secular matters. Understanding its prior involvements may help in understanding the strengths and weaknesses of this effort.

Now what is especially prescient of this book is the application to the current Pope. As Ockham noted the focus of Papal power was limited to spiritual matters. The Pope had not authority over matters of state. The current Pope seems to be reverting to Avignon days and opining on matters that Ockham would have scowled upon. Thus to understand the Papacy, this is an excellent start.



Labels: [Politics](#)

FRIDAY, MAY 1, 2015

[HISTORY CAN BE NONLINEAR](#)

There is a wonderful piece in [Backchannel](#) describing the past and prognosticating the future of Silicon Valley. The author seems to state that Silicon Valley is unique and that it has a form of self perpetuation using its links to its past. The new entrepreneurs learn from the old.

The author concludes:

People around the world have tried to reproduce Silicon Valley. No one has succeeded. And no one will succeed because no place else—including Silicon Valley itself in its 2015 incarnation—could ever reproduce the unique concoction of academic research, technology, countercultural ideals and a California-specific type of Gold Rush reputation that attracts people with a high

tolerance for risk and very little to lose. Partially through the passage of time, partially through deliberate effort by some entrepreneurs who tried to “give back” and others who tried to make a buck, this culture has become self-perpetuating.

History is not linear. I suspect that the future will be less dependent upon micro circuits than upon micro RNA. Looking around Kendall Square one senses the future. Still assembling itself, but the sense of entrepreneurial drive, the true formative and life changing science and technology, and the amalgam of people is unique, and more life changing than silicon.

Carbon will beat silicon. The DNA circuitry and its decoding and re-engineering will be more world changing and world disturbing than anything we have yet seen in Silicon Valley. The difference is also one of style and scope. The ability of a tech company to start in a strip mall type office in the Valley is replaced by the need for a complex lab and a bunch of Illumina machines. Wet labs replace scopes and integrated circuits.

This is a form of abrupt creative destruction that all too often sets paths for new technology. The early entrepreneurs are starting to pop up in this market, and we will most likely see an explosion soon. Will Silicon Valley adapt, survive, enter this race. Just being able to program will be left behind, it will be the world of visionaries who understand biological systems and who can "engineer" them, not just research them.



Labels: [Commentary](#)

WASTED TAX DOLLARS? AGAIN?

Ever since the signing of the ACA, a massive number of new initiatives and overheads have been placed upon physicians with the stated intent of improving quality. Recent ones include the [PQRS](#) initiatives which demand at the penalty of loss of reimbursements the reporting of what is termed quality metrics. Frankly at first blush they are far from quality metrics and more just added costs to Health Care delivery.

But the worst offender still seems to be PCORI. In a great piece in [Modern Healthcare](#) the writer states:

The Affordable Care Act created an independent organization to support research that assesses which healthcare interventions are most effective. But three years after it started funding studies, there's no central repository of results or a clear strategy for making sure the knowledge reaches the clinicians it's intended to influence. The Patient-Centered Outcomes Research Institute distributed grants worth \$30 million to its inaugural round of 50 projects. About 30 are complete and more results are anticipated this summer, PCORI leaders told Modern Healthcare. It's not clear, however, when or where those results can be found. PCORI says grantees are expected to have a plan for sharing their findings but also that it does not set timelines for completing studies.

Frankly this is miled. PCORI gets \$500 million every year from a tax on our medical fees. Yes we are paying for them. They have handed out hundreds of millions of contracts to do studies

none of which have been made public. Since PCORI is not a Government entity, thanks to the Democrats, then it has no transparency, just a cost. It is easier to find out details about the CIA and NSA than it is about PCORI.

The author continues:

PCORI has now approved \$845 million in funding for nearly 400 projects, and the latest round came April 21. The organization announced \$120 million in funding for 34 comparative clinical-effectiveness research projects, including five pragmatic clinical studies.

But that is just the beginning. This will be an ongoing burden on the taxpayers but it will also be a burden on the practitioners who must comply with PCORI mandates.

The author continues:

The first study in that project, expected to begin this summer, will compare the effect of different doses of aspirin for the prevention of heart attack and stroke among people with heart disease. The early PCORnet projects will help "illustrate PCORnet's wide-ranging capabilities and pave the way for future research," the institute said.

What the author fails to note is that this study is from the patient perspective. The standards for standard clinical trials do not apply, it all too often is a study of "how do you feel about...?".

The costs and waste from such an agency are substantial. Yet Congress has no oversight capability since it was mandated as extra Governmental and funded through 2018.



Labels: [Health Care](#)

[WINDOWS 10, THE FUTURE?](#)

Microsoft is not known as a customer friendly company. That is an understatement. Just try to find help on the Microsoft site. You end up using Google to search Microsoft. One would think that they would have caught on by now. But why bemoan something you cannot do anything about? Simple, Windows 10.

The Microsoft Windows 10 strategy is to get everyone onto this new OS, from Windows 7 and 8, and then to change it to a subscription service, having each customer paying a monthly fee, like Cable! Yes, Microsoft has seen how people love Cable so much they want their products to be just like them. One wonders what is in the water in Seattle.

They should get a hint from all the folks still holding on to XP! In fact we still have a bunch of XP systems sitting there. Frankly they were XP because Vista was a disaster. Now Windows 7 is just fine. For our desk tops, those systems on which people do real things, not the walk around thumbing messages needlessly to each other, but real production devices, 7 is perfect.

[The Inquirer](#) notes:

WINDOWS 7 continues to dominate the battle of the operating systems with a rise of 0.35 percent to 58.39, while XP use takes the biggest dip to 15.93, down just over one percent. That's according to the latest figures from Net Applications. These show an almost flat line from last month, but we thought it would be more interesting to look at the year-on-year stats. We've included month-on-month at the bottom for your reference. So, one year after Windows XP reached its end of life its share of the market has dropped, but any hope Microsoft had of killing it stone dead has been quashed. It stands at 15.93, which is down 10.36 percent on its end-of-life standing, but shows that well under half of the holdouts have quit.

Imagine, if you will, what would happen if you "upgraded" your 7 system to Windows 10, and as expected it crashed. You are dead in the water. Microsoft believes that 1 billion users of will "upgrade". Are they out of their minds! If it is not broken then do play with it! Any computer users knows that.

In [PC World](#) they note:

Microsoft is setting a lofty goal for Windows 10 adoption as it tries to get app developers on board. Terry Myerson, Microsoft's executive vice president of operating systems, said at the company's Build conference that the goal is to get Windows 10 on 1 billion devices within the next two or three years. "Our goal for Windows 10 is to build the most attractive developer platform ever," Myerson said. Microsoft is counting on a mass upgrade of its existing base of 1.5 million (sic, I think he meant 1 billion) users to Windows 10. Unlike the separate app stores that currently exist for Windows 8 for PCs and tablet and Windows 8 for phone, Windows 10 will run across phones, tablets, PCs, and Xbox consoles, with a single storefront where developers can sell their apps. Myerson demonstrated how developers can tweak their apps to work with various screen sizes. For instance, USA Today will offer an Xbox One app, filtering its existing mobile news app to only show video feeds.

I get the point but one must be careful. The kernel of an OS may be quite different on a mobile device and on a workhorse PC. Trying to capture the world is a risky strategy, especially for a company and product that is often unstable.

Anyone who wants to see the weakness of a Microsoft OS just need look at the Registry. As a system is used the Registry becomes a patch quilt mess. That is a Microsoft OS. This may become a gift to Apple, if they ever want to address this users base again.



Labels: [Microsoft](#)

[THE BRITS AND MAY DAY](#)

I know the Brits like their gardening. I like mine also. Yet being a bit too much Celt I have to cover up at 40 degrees North Latitude, still too much sun. But for these Brits in [Manchester](#) newspaper:

A team of horticulturalists have donned their birthday suits to celebrate World Naked Gardening Day. The staff at Hulme Community Garden Centre got their kit off while the sun shines in preparation for the big day. The gardeners got in the buff ahead of the worldwide celebration of horticulture on Saturday May 2 and have been tending to plants and flowers unclothed as nature intended. Centre manager Rachel Summerscales said the team was inspired to try naked gardening during a quiet moment at the centre.

Yep, "Naked Gardening". I wonder what the French think of this one!

Just a light note for your Spring, whenever it gets here.



[HAPPY MAY DAY](#)

Just noticed a piece in [The Crimson](#):

Eighty-four percent of campaign contributions made by a group of 614 Harvard faculty, instructors, and researchers between 2011 and the third quarter of 2014 went to federal Democratic campaigns and political action committees, according to a Crimson analysis of Federal Election Commission filings. During the three years, the Harvard affiliates represented in analyzed public filings gave nearly \$3 million to federal campaigns and candidates. Each of Harvard's schools leaned to the left in the contributions made by their affiliates, many by wide margins. Ninety-six percent of donations in the data set from the Faculty of Arts and Sciences, which includes Harvard College, supported Democratic efforts. That figure was even higher—nearly 98 percent—at Harvard Law School. Harvard Business School was the most Republican, with 37 percent of its contributions supporting Republicans and 62 percent going to Democrats.

Why are we not surprised.



Labels: [Academy](#)

THURSDAY, APRIL 30, 2015

[MIDDLE CLASS ENTREPRENEURS](#)

I am always amazed by the economists who take something that works, albeit in a very select manner, and then argue to its generalization. A recent article by two such types in the left wing blog, [Project Syndicate](#), argues that what makes Silicon Valley work can be copied to create more middle class jobs.

They state:

The University of Virginia's Miller Center recently created a commission ... to identify strategies to support the creation of middle-class jobs through entrepreneurship. The ideas proposed in the commission's report include providing training and mentors for prospective entrepreneurs and startups, creating "ecosystems" of supporting infrastructure, and reducing regulatory

barriers. The report also highlights the importance of unlocking capital for “Main Street” entrepreneurs, who struggle to find the funding they need to launch, sustain, or scale up their operations, particularly as the recent recession drove out many of the community banks on which they had traditionally relied for credit. Silicon Valley startups, by contrast, enjoy the generous support of VC funds, having received 30-35% of all venture investment deployed in the US since the 1980s.

VC funding, and its like, which I have been doing for some 30 plus years, is a ruthless business, it is Creative Destruction real time. It requires motivated, intelligent, competent people. It is not a world for the reconstruction of the "middle class". We do not invest in a new candy store, at least I would not. We focus generally on game changing ideas that can be implemented with a dedicate team.

As I was once told, "A Good Idea Does Not a Business Make". It takes a team whose sole focus, not even their day job, is dedicated to. To this team, failure is no option, and there is no life other than the new business. One cannot go home for dinner at night.

Whose capital is being unlocked for Main Street? I suspect it is the taxpayers. That model just does not work. It never has. The Government is the worst entity to choose winners and losers. There is too much politics. Political favorites get taxpayer money and they most likely are good at getting political favors and not starting a business.

One must be wary of the advice rendered by these types of economists.



Labels: [Economics](#)

[INTERESTING MELANOMA THERAPEUTIC](#)

Melanoma is an aggressive malignancy and has been approached by pathway blockers, BRAF V600, and via immune therapy, including targeting PD-1. [As we had discussed](#) two years ago, T-VEC, a viral based therapeutic, had significant potential. The [FDA has approved](#) its use yesterday for melanoma. This means that we now have three axes to deal with melanoma; pathways, immunologic, and viral. All three are malignant cell specific and one suspects that a combination therapy may be best, one yet to be determined.

In [OneLive](#) states:

Although the current review is for single-agent use, multiple clinical trials are currently assessing T-VEC in combination with immune checkpoint inhibitors. A phase II randomized study is ongoing that will evaluate the safety and efficacy of T-VEC in combination with ipilimumab versus ipilimumab alone. Additionally, other ongoing clinical trials will investigate T-VEC in combination with immune checkpoint inhibiting antibodies, such as those targeting PD-1.

This tripartite approach is worth following.



Labels: [Cancer](#)

SUNDAY, APRIL 19, 2015

[ANTITRUST AND THE BRIT](#)

And now the Brit at the [Guardian](#) takes after Google. He states:

For all their promise of openness and equality, the technologies of the internet also promote the creation of giant companies. The question facing us as a society is what trade-offs we make: does the bigger danger lie in allowing the creation of unalloyed corporate power, or instead in curbing technology's potential to prevent it? The question could become moot: in practical terms, if Google trounces the EU on all counts after several years, few other competition authorities will want to take on the company, and they may even be deterred from pursuing other internet behemoths. A decade or so without a challenge may make a new normal near irreversible.

This is not a logical argument, it is a crie de coeur, French is always a good way to bemoan the Brits, especially those who appear to be totally ignorant of monopolies. Just because a company has a large market share does not make it a monopoly. Perhaps it is just better! And oh by the way it is free!

One could not do what one creates today without Google. Yahoo is a cacaphony of ads, nonsense, and useless blather. Bing is Microsoft, incomprehensible and insulting. Google, well it just works. So the Brits now want it dead! Yes, those same characters who, after the Danes, came and occupied the last vestige of intellectual acumen in the 11th century with the near imbecile of a King, John!

Perhaps we should return to a court with Henry VIII and the beheading of spouses, or perhaps they can take that out of the History books, except perhaps Wolf Hall, or whatever that is.



Labels: [Antitrust](#)

SATURDAY, APRIL 18, 2015

[ANTITRUST AND THE DANES](#)

The Irish can still recall the Danes invading in the 800s, driving up the Shannon, destroying and plundering, the monasteries and massive libraries of documents, driving the then both religious and educated into ever present terror. Then when Henry II arrived and he gave Ireland to his somewhat less than competent son John, it began a thousand year occupation which seems to continue to the present. Yet to a reasonable degree it was the Danes and their ships that destroyed what could have been a few hundred year leap on civilization.

Now to antitrust. This has always been a rather messy quagmire. [I have written](#) extensively on the topic and it may be worth an examination. One need look at just two cases; IBM and AT&T. At the time the dropping of IBM was totally correct. There was competition, just look at IBM today, going through another metamorphosis. On the other hand AT&T was also correct. It was a Government sanctioned monopoly that actually stifled any competition. [I examined](#) this in detail in 1990. Had DOJ not broken up AT&T we most likely would still have black rotary dial phones and would be leasing them for \$1,000 per month!

Now to the Dane and Google. In a sense Google is akin to the Irish monks, providing knowledge universally, along with some of their services, but it is the knowledge that counts. Then comes the Dane, not on a long boat this time but with the power of the EU, that mighty fortress that seem just two shakes from collapse.

As the [NY Times](#) notes:

Last year, as Ms. Vestager was leaving her job as Denmark's minister of the economy, she gave her successor a hand-knit toy elephant — she often works on them during staff meetings — noting that the animals “bear no grudge, but they remember well.”

Sounds like the Danes and their long boats! Off to the monasteries and their libraries, burn them down!

The Times continues:

In Brussels last Wednesday, she filed formal antitrust charges against the company, saying that the search engine giant had abused its market dominance by systematically favoring its own comparison shopping service over those of its rivals. If Google fails to refute the charges, the company could face a fine of more than 6 billion euros.

Google has competition. It is not an AT&T, perhaps it may become an IBM, but never an AT&T. Technology changes daily, regulators look backward, and project forward their worst visions. The Times continues:

That direction was filing formal charges, called a statement of objection, accusing Google of favoring its own comparison shopping service, called Google Shopping. In practical terms, the commission found that when a consumer used Google to search for shopping-related information, the site systematically displayed the company's own comparison product at the top of the search results — “irrespective of whether it is the most relevant response to the query,” Ms. Vestager said in a commission-issued statement about the charges.

The Dane does not seem to understand that the mechanism used is how Google pays for the service. It is a service, it costs money, and frankly anyone else can build their own such service. There is no monopoly, there is no barrier to entry, it is not AT&T preventing any competition. The Dane seems to be clueless about the world of business, but then most likely did her ancestors as they pillaged up the Shannon, past my ancestors. This may just be 21st Century pillage, again the Danes!



Labels: [Antitrust](#)

FRIDAY, APRIL 17, 2015

[THE EHR AND ITS PERFORMANCE](#)

The [NY Times](#) bemoans the status of the EHR. As it states:

The ability to transfer electronic medical records from one doctor or hospital to another is essential to the smooth functioning of the health care system and to providing the best possible care to patients. Yet all too often these transfers are being blocked by developers of health information technology or greedy medical centers that refuse to send records to rival providers. This will not be an easy problem to fix, but some possible approaches were detailed in a report to Congress last week from the Office of the National Coordinator for Health Information Technology, a unit of the Department of Health and Human Services.

The problem, as we have noted over the past several years is several fold:

1. First, the Government directed the process. The same group who did the portal for ACA. In addition in my opinion the management team were politically selected not professionally selected.
2. The system should have been patient centered and not practice centered. Namely the system should have take advantage of a secure cloud based approach minimizing physician costs and

overhead and allowing single points of collection and correlation. Unfortunately we have a plethora of systems which will be outdated and underused.

3. The system should be multimedia enabled. Now it is merely a text file system with some adjunct access for radiologists and perhaps pathologists. Other multimedia elements are piecemeal and unconnected.

4. The system should provide a customizable dashboard. If the patient is a Type 2 Diabetic one should see their BMI changes as well as HbA1c and others. If the patient has COPD the same.

The problem is NOT the vendors. The problem was in my opinion the very people who created this mess. We noted as such six years ago, but alas, it is this Administration.....And tens of billions of tax money has been spent and added costs to practices...not to mention physicians typing while not examining the patient!



Labels: [Electronic Medical Records](#)

[AD HOC PROPITER HOC](#)

It is always amazing to see what amounts to research. In a recent [MIT News](#) release there is a study that alleges to show that people raised in well off families are smarter than those in poor families because of the difference in income. At least that appears to be the gist, an academic study to justify income transfer and the elimination of income disparity. (This is funded by the Gate Foundation, somewhat ironic.)

The article states:

A new study led by researchers at MIT and Harvard University offers another dimension to this so-called “achievement gap”: After imaging the brains of high- and low-income students, they found that the higher-income students had thicker brain cortex in areas associated with visual perception and knowledge accumulation. Furthermore, these differences also correlated with one measure of academic achievement — performance on standardized tests. “Just as you would expect, there’s a real cost to not living in a supportive environment. We can see it not only in test scores, in educational attainment, but within the brains of these children,” says MIT’s ... Professor in Health Sciences and Technology, professor of brain and cognitive sciences, and one of the study’s authors. “To me, it’s a call to action. You want to boost the opportunities for those for whom it doesn’t come easily in their environment.”

Now I think of Faraday, orphaned and apprenticed as a bookbinder. His work was prolific and established the basis for our electromagnetic world today. One can go across MIT alumni and see all too many who came from what they would call less advantaged homes. In fact MIT was where one achieved from humble beginnings as compared to Harvard where one achieved from family pedigrees. I would hazard to say many MIT alums did more intellectually for society than Harvard. After all we had fewer politicians and that alone is an achievement.

But I suspect the facts belie the conclusions above. I think of the many MITES students I worked

with and befriended. Talk of hard times. Yet look at them now! Could they have done better? Frankly I believe that they did what they did because they had been challenged, not despite it. Probably the one of whom I am most proud went from a Mississippi rural area to heading a major investment fund in Africa!

Also one must remember all the well off kids that go nowhere. The "real cost" is in my opinion a political statement and lacks any factual reality.



Labels: [Academy](#)

FRIDAY, APRIL 17, 2015

[THE SELFIE](#)

There is an article in [The Guardian](#) discussing the Millennials and how they bemoan their situation in life. The rather self absorbed author writes:

Life is often referred to as a "highway", to borrow from Tom Cochrane, and for my generation that hasn't changed. "Adulthood today lacks a well-defined roadmap", writes Steven Mintz, in his forthcoming book The Prime of Life. "Today, individuals must define or negotiate their roles and relationships without clear rules or precedents to follow". This is especially true for us millennials, who are the product of a terrible economy that has required us to hit the emergency button in our lives. But it's becoming evident that we have been given a roadmap to a road that we are not even on and then are blamed for going in the wrong direction.

But this self absorbed statement is bettered by the photo atop the article, which is a collection of these individuals engaged in the Selfie. This in many ways defines them. They look inward, at themselves, and they see what they may not like. Albeit adoring themselves and their small worlds captured in this image or video, they are not looking outward.

Now they bemoan a "terrible economy". Are you nuts! My parents in the 30s had no economy to speak of, and survived on jobs at \$14 per week. You could not even pay you cell phone bill with that. How about Viet Nam and the 60s, for a male you had almost a 50:50 chance of going there as cannon fodder for Johnson. Equally you had the military say at Kent State killing innocent students and there was no justice for that event.

A [second article](#) bemoans the "following of your dream". It is some student whose life on food stamps as they go about following their dream is decried as not enough:

a twentysomething graduate student, knows something about trying to live on food stamps. One of the so-called millennials, ... took an unpaid internship fresh out of college in 2012 and had to rely on food stamps to help supplement her income. Currently enrolled in graduate school at Oregon State University, ... is making do with \$800 a month. "I was following my dreams, which I realized really quickly I could not afford to do. I was working as an intern at the Boston Review [during the week] and was unpaid. I was eating through my savings and applied [for food stamps] because I realized that I was not going to be able to continue pay rent and be able to

buy food at the same time," she said. It was actually Boston Review that had suggested she apply. "I guess other interns they had in the past had done it."

If you want to "follow your dream" then you have a price to pay. I should not have to pay your price, I did that when I ate rutabagas and drank powered milk. If you are willing to take an unpaid job then that economic choice has consequences.

Dreams do not an economically stable society make. It appears that the Selfie is a true metaphor for this group, inward focused and self absorbed. Talk of a "lost generation". Yet I look at many of those who have managed to squeak across our borders as at sunrise they line up looking for a days work and then applying themselves for fifteen or more hours and then doing it again and again. Never saw them take a Selfie.



Labels: [Commentary](#)

WEDNESDAY, APRIL 15, 2015

[CANCER AND OUTLIERS](#)

Decades ago I spent a considerable amount of time trying to logically develop a basis for rejecting outliers. When collecting data oftentimes most of the results look like the random variations one would expect, except for those few outliers.

At the time I noted:

When data are taken in many experiments there often are points which bear no resemblance to the actual experiment being performed but arise from other, possibly undefined, sources. These data points are called outliers and the data analyst seeks ways to identify them and accurately reject them from the data base. Statisticians have developed many techniques for recognizing and rejecting outliers, but their approaches have usually been centered upon techniques where time variations in the measurements were absent.

Namely I was concerned about rejection where we had some underlying but possibly uncertain dynamic process governing the system. Outliers can be viewed in many ways:

1. Just a bad data point.
2. A data point which is one of a kind.
3. A data point which represents a significant system underlying it.

Now consider the many new therapies for treating cancers; immunotherapy and pathway control therapy. We often see say 20% of the patients are "cured". The other 80% regress to normal status and do not survive. Are the 20% outliers, and should be rejected or are they representative of a different dynamic system and we should really try to identify that system. Forty years ago I felt the latter. Namely we observe data and if it divides into two distinct terminal states then we have two distinct underlying systems, pathways or immune responses, driving them there.

In [Nature](#) this week there is an interesting paper examining this issue. The authors note:

By definition, exceptional responses are rare, which makes them hard to study. Their anecdotal nature seems to contradict the teachings on statistically sound results in biomedical research. In a clinical trial, even if there are several exceptional responders, a drug will fail to achieve approval because it does not improve the health of the majority of patients. This means there has been little incentive for researchers or drug companies to investigate thoroughly why a few people respond so well.

This has typically been the result that these outliers are just bad data. In reality they are good data, great data, but for another reason. Find that reason, namely identify the system that allows the patient to respond. If something works for even one patient, then it is not a failure but a success. Yet the statistical approach to clinical trials means we declare the trial a failure. That was NOT my approach 40+ years ago, and it should not be the case now. Somehow we seem to reject success, small as it may be, rather than ask why.

The Nature article continues:

Vincent Miller, a former MSKCC oncologist, agrees that views about outliers are changing and thinks that many more such individuals might be found. Any oncologist has a handful of patients in whom cancer just melts away with no obvious explanation, says Miller, who is chief medical officer of Foundation Medicine in Cambridge, Massachusetts, a company that performs genomic analysis of samples from people with cancer. In January, the pharmaceutical company Roche, based in Basel, Switzerland, bought a majority stake in Foundation Medicine, which is also involved in the ERI.

Yes, physicians must learn to think differently. They must go beyond answering what and how, diagnosis and treatment, and start asking why. We now have means and methods to assist in attaining the answer, they are tools from systems identification and analysis.

Finally the article states:

For research on outliers to be of greatest help, the outlier cases must be rigorously selected. Only then can the analysis deliver sound results despite the fact that it remains a profile of only one person, says Friend. Taylor agrees, pointing out that molecular analysis of tumours from patients is increasingly possible and that there is growing acceptance of studying outlier patients. "Nevertheless," he says, "it requires that we stay focused on exploring the most significant outlier responses to ensure the greatest return for patients."

Yes selection helps but we must also use verifiable models of the disease or the putative curative process. If we have some immune response technique, then perhaps it is not a PD-1 problem, but some receptor we do not know yet. Find it, work into the shadows, and assume that it is there and then go looking.



Labels: [Cancer](#)

TUESDAY, APRIL 14, 2015

[FREE RANGE KIDS](#)

Tom Sawyer and Huck Finn were a prototype free range child. Whether down the Mississippi or convincing others to do their work, it was a process of learning and development. In the present day one gathers that even walking home from school becomes the business of the state. As [Cato](#) notes:

On Sunday afternoon Montgomery County, Maryland police and Child Protective Services seized the free-range ...v children, 10 year old ... and 6 year old ..., after their parents, .. and her husband .., had again let them play by themselves at a park in Silver Spring, just outside D.C

Now back some sixty plus years walking to school or anywhere in New York was de rigeur. In fact when I was I believe 9, I set out on my bike, across State Island, then across the Goethals Bridget, up Route 1 and 9 to Newark Airport. Doing that a few time got me to know the pilots. Then on board an Eastern shuttle, a Constellation, and well, today we would have dozens of folks under some legal mess.

Adventures are part of childhood. Understanding risks, and understanding the world come hand in hand. Government nanny states destroy the fundamentals of individualism and imprint stateism. Free Range children are individuals in search of adventure. We need more of them.



Labels: [Commentary](#)

[FOREIGN POLICY AND THE CHURCH](#)

Foreign Policy and treaty negotiations is really complex. In my experience back in the 1970s working on the Comprehensive Test Ban Treaty with the then Soviets I learned that nothing is necessarily as it appears to be. Later while having one of my companies in Russia I was able to add some dimensions to that complexity. Now add to that the Iranian situation, I also had some folks there as well before the revolution, I could see that nothing is really what it may appear to be.

The main interests should be the security of US interests and furthermore a stable world situation is good for all. But we now have many wild cards. Iran is one and unfortunately so is Russia. China has its own games to play and it is not clear that having an unstable Middle East is good or bad for them.

Now add to the mix the US Bishops who for reasons known only to them have written Congress asking approval of a phantom deal. Nothing is in writing, and in fact what was oral was denied by the other side. But the [Bishops write](#):

Despite the challenges, it is vital to continue to foster an environment in which all parties can build mutual confidence and trust in order to work towards a final accord that enhances peace. For this reason, our Committee continues to oppose Congressional efforts that seek to undermine the negotiation process or make a responsible multi-party agreement more difficult to

achieve and implement. The alternative to an agreement leads toward armed conflict, an outcome of profound concern to the Church. We welcome the most recent step the United States and its international partners have taken with Iran and encourage our nation to continue down this path. Now is the time for dialogue and building bridges which foster peace and greater understanding. We urge Congress to support these efforts.

Nice but I recall the days of Soviet nuclear threats and plans such as RISOP 9B, a total devastation of humanity by some insane nuclear power. As I had said in the late 1970s regarding the USSR and its positioning, one must be very careful who to trust, even more so, trust but verify is perhaps not enough.

The old MAD, mutual assured destruction, plan of Kahn and the others in the 1960s made sense only if the other side wanted to survive. If on the other hand the other side is seeking total destruction as some religious salvation, then one may face a true dilemma. From Xerxes onwards we have been in a push and shove with Persia. Now add a religious element and it makes it ever so more threatening. This is not the distribution of loaves to the poor. This is a matter of the survival of civilization.



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

[THE END OF SOCIAL SECURITY AND MEDICARE](#)

One of the [potential Presidential contenders](#) has proposed both an increase in the age of both Social Security and Medicare and an elimination of any Social Security inheritance you were somewhat successful in life, nowhere near the top 1%, well below that.

[NJBIZ](#) states:

On Social Security, the potential 2016 Republican presidential candidate proposed gradually raising the national retirement age to 69, hiking the early retirement age to 64 and imposing income caps on payments. Under ...s plan, future retirees making \$80,000 annually in income exclusive of Social Security will see benefits gradually phased out and those making in excess of \$200,000 annually will see them eliminated entirely. "I'm suggesting that Americans pay into this system throughout the course of their life knowing that it will be there if they need it to support them. So that seniors will not grow old in back-breaking poverty," ... said in prepared remarks distributed by his Leadership Matters for America PAC. "But if you are fortunate enough not to need it, you will have paid into a system that will continue to help Americans who need it most. That is what we have always done for each other through private charity and good government. This is fair and it is what we must continue to do by changing Social Security."

That's right, you pay into this plan and if you were successful you get nothing, zip, da nada, zero, zilch, whatever. Thus if one follows the rule the year you sell your home, the profit becomes income and as a result of the ACA you are taxed 3% for Medicare and this new plan then makes certain your SSI is terminated! Wow.

I would vote for Elizabeth Warren who seems to be well to the right of this erstwhile candidate!



Labels: [Politics](#)

[WHAT'S UP WATSON?](#)

I am always amazed when massive companies make monumental announcements about some new thing. I recall back when IBM tried to get into the satellite data business with SBS. Tons of money spent with a management who really did not understand the technology. Then they tries on line services with Trintex with almost the same cast of carriers, and the list goes on. Gerstner seemed to have a focus by bringing them to the world of professional services, giving their customers what they wanted. All too often telling customers what they should have has not been an IBM forte.

Now comes Watson and Medicine. I would like them to consider a recent NEJM case [D is for Delay](#). I like this one because it exemplifies the current practice of medicine. Simply a patient who has taken poor care of himself enters a hospital after many prior admissions with a list of complaints. Then off they go looking for the zebras only to find that he has a niacin deficiency. Not that the professionals did anything wrong, it was just a messy case. There were many shadows. How would a Watson handle this?

[Becker's](#) states:

- 1. IBM introduced a new healthcare unit, IBM Watson Health, which will use cognitive computing to advance innovation using the volume of personal data that is created everyday. The health unit will be headquartered in the Boston area.*
- 2. The company is also establishing the Watson Health Cloud, a secure and open platform for physicians, researchers, insurers and other healthcare companies to access individualized insights and a holistic image of what can affect people's health.*
- 3. To help support IBM Watson's foray into health IT, the company is collaborating with Apple, Johnson & Johnson and Medtronic to create new offerings that leverage information collected from health, medical and fitness devices.*
- 4. With Apple, IBM will provide the new Watson Health Clod as a secure platform and analytics offering for Apple's HealthKit and ResearchKit. IBM will de-identify and store health data in the cloud to foster an "open ecosystem environment" that also offers researchers and developers to utilize IBM's data mining and predictive analytics capabilities.*
- 5. Johnson & Johnson and IBM will collaborate to create intelligent coaching systems regarding preoperative and postoperative patient care for procedures including joint replacement and spinal surgery. The new solutions will utilize Waton's cognitive capabilities and access Watson Health Cloud's data. Additionally, J&J plans to launch health apps focused on chronic conditions.*
- 6. Leveraging insights from Watson Health Cloud, Medtronic and IBM plan to develop personalized care management solutions for people with diabetes. The solutions will gather and analyze patient information from Medtronic devices, such as glucose monitors and insulin pumps, and provide personalized management strategies to patients and their providers.*

Now that is a great deal of investment and involvement in a market rant with regulation. I am

reminded of many a physicians difficulties dealing with the "shadows", namely symptoms that may lead anywhere but with no clear path. A recent example was that of an individual with intermittent head pain, somewhat localized, and not controlled. The age was an issue and thus one looked after vasculitis, lesions, strokes, trigeminal neuralgia, and the list goes on. And yes even dental issues, with three different dentists. Lots of suggestions, down the trail of differential diagnosis but to no avail.

Then the patient just gave up, went to an oral surgeon and said to take out the damn wisdom tooth. Well, guess what, the root had wrapped around the trigeminal branch and could not be seen, and after surgery, problem solved. Try that one Watson, it was the patient who found the solution!



Labels: [Health Care](#)

SUNDAY, APRIL 12, 2015

[“YOU DIDN’T BUILD THAT”](#)



[Boudreaux](#) at George Mason has a bit of a sparkling post on the left wing's current stupidity on “you didn’t build that” stuff. It is akin to the "privilege" non-sense that they spout. What Boudreaux seems to miss is my personal example of building a company in 20 countries, outside of the US. Do I thank Vladimir Putin for my Russian operations? Frankly yes, in a strange way. Now in Czech Republic, who do I thank there, well frankly my Czech partners who believed in me and trusted what we did and worked their hearts out!

Did Senator Warren and the US help at all? Frankly the success was despite the US, because locals had seen the arrogance of the AT&T's and the US public companies, what I gave them was self ownership, not vassalage.

Thanks for nothing may be my mantra here. It was the FCC and many other US entities that stood in the way. It was Russian, Czech, Austrian, Polish, Slovak, Bulgarian, Hungarian, Thai, Korean, etc creativity that made it work. Thus Boudreaux should consider those of us who set out with a credit card and some local contacts and created something extra the US. Frankly there is only one country more complicated and Government controlled to work in, Greece.

No, I didn't build that, we built it! Yes it included the Russians, one of the best of partners.



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

FRIDAY, APRIL 10, 2015

[THERE ONCE WAS A TIME WHEN PEOPLE DID SOMETHING](#)

I read an [MIT press release](#) article which stated:

As director of the MIT Mediated Matters group, explores “material ecology” — the practice of integrating design principles inspired by nature into digital fabrication. In her TED presentation, ... debuted a wearable digestive system that could be worn by future inhabitants of Jupiter’s moons. Powered by photosynthesis, the system is designed to digest matter, absorb nutrients, and expel waste. “Think of it not as evolution by natural selection but evolution by natural design,” suggested

Just think of what your alumni donations are going for, "poop" on Jupiter! I spent my day trying to clarify melanoma pathways and means to attack them to see if there was a way to reduce the suffering to those inflicted. I guess being on Jupiter the UV rays will be lower and the risk likewise, so perhaps I was wasting my time.

One really cannot make this stuff up. It is generational, give them one of those mikes that looks like a skin lesion and put them on a stage, and they act...not create...who will be left to build real things I wonder.



Labels: [Academy](#)

THURSDAY, APRIL 9, 2015

[COMING UP SHORT?](#)

Frankly I could not resist this one. In [NEJM](#) of all places there is an article purportedly showing that short people have greater risk of heart attacks.

The conclusion is:

There is a primary association between a genetically determined shorter height and an increased risk of CAD, a link that is partly explained by the association between shorter height and an adverse lipid profile. Shared biologic processes that determine achieved height and the development of atherosclerosis may explain some of the association. (Funded by the British Heart Foundation and others.)

Now several observations:

1. The number of authors almost exceed the number of patient samples. Just kidding but there

appears to be several dozen authors. This is an ever evolving trend, at some point the list of authors may eventually exceed the length of the paper.

2. The result may be interesting but it is not prognostic or diagnostic. Also there is not much we can do about being short. Then again look at Napoleon.

3. This is a British funded project, wonder of NIH would do the same here.

4. Obesity is a much more significant risk factor for which we can really do something. Why even do this study and why in NEJM?

Every once in a while it is worth looking at the other side of the weighty research.



Labels: [Health Care](#)

WEDNESDAY, APRIL 8, 2015

[POST DOCS: A CAREER CHOICE?](#)

In the current issue of [Nature](#) there is a superb discussion of the post-doc phenomenon. Simply stated, there has been an explosion in post-docs, even in such applied fields as engineering. Frankly give the Silicon Valley world etc one wonders why there is even a post doc in an engineering school, they should be out earning a living doing engineering. Engineers with PhDs are trained to do engineering, that ultimately means doing something to make something, not research for the sake of research.

How did this come about? Simple, the Government and its funding mandates. Now we see the big name labs. Got to any campus and you will not see say the "Antibody Lab" or the "Electromagnetic Lab". You now see the "Joe Smith Lab" in the "Sally Jones Center" of the "Fred Brown School" of the XYZ University. Everything has a name of some person; researcher of funder. Strange, imaging the MIT Rad Lab being the "Harry Hopkins Lab" for example.

The Government now funds well funded labs which are few but they get bigger by getting more low cost researchers. The researchers in question are post-docs, paid less than most of the cleaning help, and working three times as hard. They somehow "believe" that they are doing productive research and as a result will eventually get their own chance. My comment is; read whose name is on the Lab Door, the Building Entry etc.

Secondly the Government now also wants both multidisciplinary and multi-institutional funded research. Thus we have papers with fifty authors. That means that tenure opportunities get muddled, one may ask what "you" really did.

As Nature states:

These highly skilled scientists are a major engine driving scientific research, yet they are often poorly rewarded and have no way to progress in academia. The number of postdocs in science has ballooned: in the United States alone, it jumped by 150% between 2000 and 2012. But the

number of tenured and other full-time faculty positions has plateaued and, in some places, it is even shrinking . Many postdocs move on to fulfilling careers elsewhere, but those who want to continue in research can find themselves thwarted. They end up trapped as 'permadoes': doing multiple postdoc terms, staying in these positions for many years and, in a small but significant proportion, never leaving them. Of the more than 40,000 US postdocs in 2013, almost 4,000 had been so for more than 6 years

Is there a solution to such a problem? I believe there is. One saw it after WW 2 with such Labs as Lincoln, Hopkins, JPL, and the like. They were non-departmental laboratories doing research and were off campus. One was an employee of the Lab and one could advance. One had the dignity of being employed, compensated on industry par and yet "affiliated" with a first class institution.

Perhaps getting the post-docs, who are professionals, into a professional environment is a reasonable alternative. The current system is unsustainable.

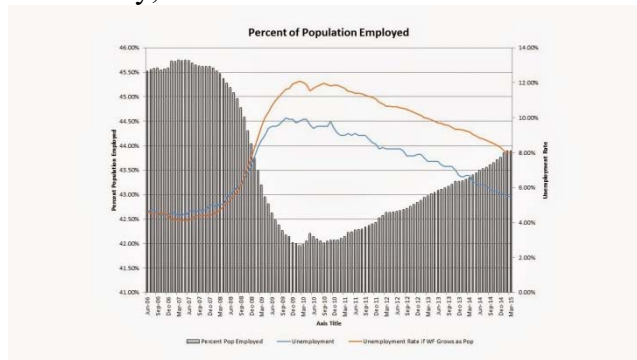


Labels: [Academy](#)

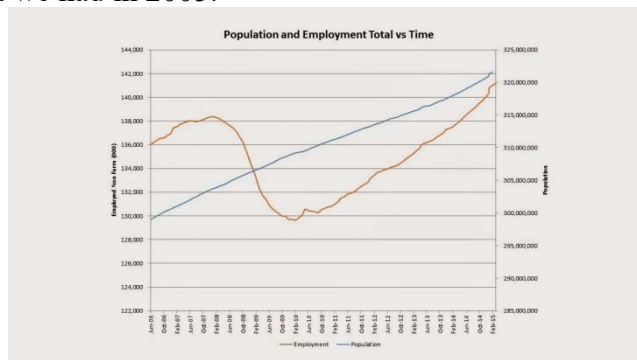
SUNDAY, APRIL 5, 2015

EMPLOYMENT NUMBERS APRIL 2015

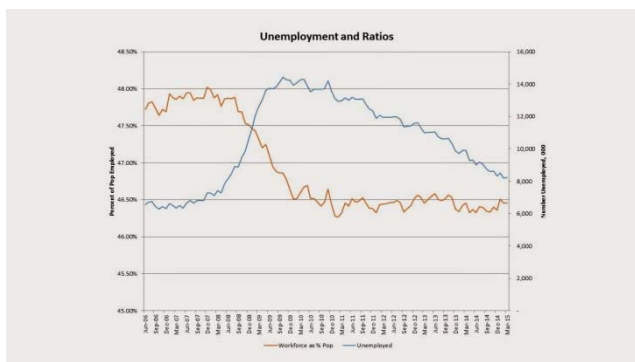
The employment numbers are always akin to reading tea leaves. We examine them again here are are always reminded of the Romer guesses of January 2009. Those prognostications seemed never to even come close to reality, but after all it was from an economist.



The above is the data we have from March 2015. A slow growth but still not return to full employment from what we had in 2005.



The above shows employment and population growth which somehow we never see discussed in the presentation of the numbers. Much of the population growth remain unemployed which is still a major concern.



This is the most worrisome. Namely the workforce participation rates. It has sunken and seems never even to try to return. Of all the numbers this is the long term concern. First because we do not get taxes from these people and second because they have a social cost.



Finally this is the articulation of that measure. The red line depicts the difference between jobs created and new people in the workforce. It has drop dramatically in this quarter. That does not bode well for the year.



Labels: [Economy](#)

[PROSTATE CANCER METASTASIS](#)

Cancer metastasis has generally considered that cancer is clonal, namely it starts with a single cell and that cell starts a process that laves its local environment and through a process of continual change manages to metastasize throughout the body. We examine a recent paper by Gundem et al which examines the metastatic behavior of prostate cancer and as a result of GWAS they show that it can be poly clonal and continually changing.

We the return to a paper we prepared well over a year ago regarding Cancer Dynamics and show that in that paper we had not only anticipated this but more. Although that paper does not yet treat epigenetic factors, nor does Gundem et al, it can be readily modified to do so.

The results have some significant consequences. Mostly is the treatment of such cancers. Namely if we have polyclonal metastatic propagation then pathway methods may have to be multifaceted, namely dealing with the multiplicity of differing pathway anomalies.

Recent Research

In a recent paper by Gundem et al the authors describe an analysis they have performed on metastatic prostate cancer cells in a group of patients. Their general conclusions seem to be two fold; (i) that there are certain metastases that are polyclonal, namely there are multiple cells initiating the process, (ii) that the progression of the metastases is complex with ever increasing changes in genetic expression.

Gundem et al state:

By plotting the cancer cell fractions of mutations from pairs of samples, we determined the clonal relationship between the constituent subclones and found evidence for polyclonal seeding of metastases,

This is a powerful observation. Their approach was in simple terms to do genome wide analysis and doing so over a set of metastatic locations. Then using a clustering method they could determine with reasonable accuracy the clonal and polyclonal results as well as the progression. Specifically:

Using whole-genome sequencing, we characterized multiple metastases arising from prostate tumours in ten patients. Integrated analyses of subclonal architecture revealed the patterns of metastatic spread in unprecedented detail. Metastasis-to-metastasis spread was found to be common, either through de novo monoclonal seeding of daughter metastases or, in five cases, through the transfer of multiple tumour clones between metastatic sites. Lesions affecting tumour suppressor genes usually occur as single events, whereas mutations in genes involved in androgen receptor signalling commonly involve multiple, convergent events in different metastases. Our results elucidate in detail the complex patterns of metastatic spread and further our understanding of the development of resistance to androgen-deprivation therapy in prostate cancer ... We identified a set of high-confidence substitutions, insertions/deletions, genomic rearrangements and copy number changes present in each tumour sample....

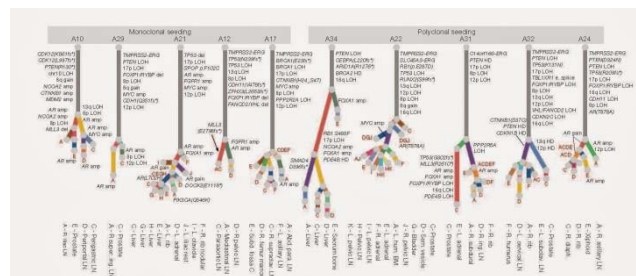
They conclude as follows:

Our analyses allow us to view with unprecedented clarity the genomic evolution of metastatic prostate cancer, from initial tumorigenesis through the acquisition of metastatic potential to the development of castration resistance. A picture emerges of a diaspora of tumour cells, sharing a common heritage, spreading from one site to another, while retaining the genetic imprint of their ancestors. After a long period of development before the most recent complete selective sweep, metastasis usually occurs in the form of spread between distant sites, rather than as separate waves of invasion directly from the primary tumour. This observation supports the 'seed and soil' hypothesis in which rare subclones develop metastatic potential within the primary tumour, rather than the theory that metastatic potential is a property of the primary tumour as a whole.

Transit of cells from one host site to another is relatively common, either as monoclonal metastasis-to-metastasis seeding or as polyclonal seeding. Clonal diversification occurs within the constraining necessity to bypass ADT, driving distinct subclones towards a convergent path of therapeutic resistance. However, the resulting resistant subclones are not constrained to a single host site. Rather, a picture emerges of multiple related tumour clones competing for dominance across the entirety of the host.

The challenge in the above analysis is to note as we had in Cancer Dynamics that as the genetic profile of the cancer cells change, there is a survival of the fittest occurring, namely a certain cell tries to dominate, and there is also the issue of stem cells and stem cell control and proliferation. The issue is one of understanding just what constitutes metastatic growth. Clearly the cells are in a steady state of genetic change, altering in a survival based manner to dominate.

Figures 3 and 4 of the paper are the most significant. In Figure 3 we see depicted the evolving changes in gene structure in clonal and polyclonal mets. In Figure 4 we see the same in a Nuclear Medicine scan showing the mets. We show that Figure from Gundem et al below since it is of such significance.



The above shows the mutations or gene expression alterations and as they progress. This is a complex but quite important description of the process. (NOTE: The above is Figure 3 as modified from Gundem et al, Nature, 2015).

As Shen states in a Nature commentary on the Gundem et al paper:

Next-generation DNA sequencing technologies have made it apparent that primary tumours are not clonal (consisting of a single population of genetically identical cells). Instead, they are composed of subclones, subpopulations of genetically identical cells that can be distinguished from other subclones by the mutations they harbour. Such subclones compete for dominance during cancer progression, and drug treatment can lead to formerly minor tumour subclones becoming dominant if they are resistant to treatment. Thus, clonal evolution shapes the properties of tumours and can explain their plasticity in response to therapy. Until now, however, clonal evolution has not been explored in detail in the context of metastasis.....Taken together, the current studies might explain why, given the prevalence of circulating tumour cells in patients with solid tumours, successful metastasis is relatively rare — metastasis may be facilitated by seeding by cell clusters containing cooperating clones with distinct properties. If so, it is attractive to speculate that disseminated single cells could remain dormant until reawakened by interaction with a cooperative metastatic cell arriving at the same secondary site. Such a model has the potential to revise our conception of the properties of tumour-initiating

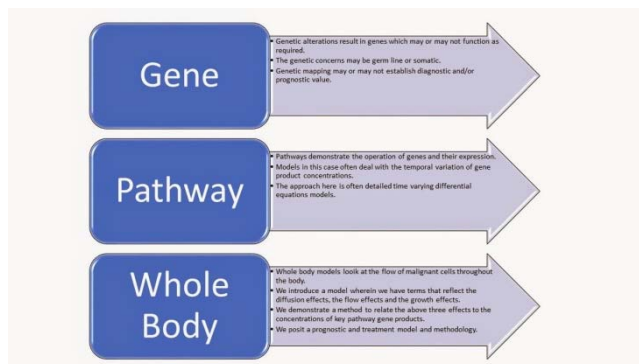
cells, as well the metastatic niche, and may have implications for therapeutic strategies. For example, understanding the signalling pathways that mediate such clonal cooperativity may lead to effective therapies using drugs that target these pathways.

The signally pathway issue is a complex one especially since we know that suppressing one pathway may excite another. The problem will be targeting all of the cells.

Previous Work

We have considered this before when we wrote a detailed paper in 2013 on Cancer Dynamics. In our analysis we examined a set of continually changing cancer cells, and we further assumed that any cell may have changed to a cancer cell. We then further assumed a diffusion/flow model for the propagation of those cells and at the same time assumed a continual process of genetic change. We also assumed that we could find an organ specific environment which may be most favorable to growth via ligand/receptor combinations. Finally we also assumed that cell to cell communications could facilitate the process. We did not consider at that time any epigenetic factors.

Namely when considering cancer propagation we must consider the genes, the pathways and the whole body. It is a complex process which we had developed in the referred to paper.



The equations for the propagation over space and time for a specific type of cell containing a specific genetic makeup has been shown below. Here $n(x,t)$ is the concentration or density of a specific cell type, let us assume a malignant prostate cancer cell, and with a specific genetic profile. If we examine the Gudem paper we see that this is what they are looking at from the perspective of a GWAS study of metastatic PCa. However we have already developed a model and further we had developed an identification process to provide the drivers in the model itself. Note below that the general equation is a diffusion plus flow model, diffusion due to evolving concentrations and flow due to movement within the body itself such a blood flow dissemination.

$$\frac{\partial \overline{n(x,t)}}{\partial t} = \tilde{L} \overline{n(x,t)} + \Lambda \overline{n(x,t)}$$

$$\tilde{L} = [\tilde{L}_1, \dots, \tilde{L}_N]$$

and

$$\Lambda = \begin{pmatrix} -\lambda_{11} & \lambda_{12} & \lambda_{13} \\ \lambda_{21} & -\lambda_{22} & \lambda_{23} \\ \lambda_{31} & \lambda_{32} & -\lambda_{33} \end{pmatrix}$$

The L value are operators and the others are constants determined in the paper. Our model then allows for polyclonal development and moreover a complex cell to cell growth stimulus as well

Observations

Now Cancer UK comments on this work as follows^{17[1]}:

The team has already revealed a huge amount of genetic diversity between cancer cells taken from different sites within each man's prostate...this new study shows that, despite the diversity, prostate cancer cells that break free from the tumour and spread share common genetic faults unique to the individual patient.

Study author ... said: "We gained a much broader view of prostate cancer by studying both the original cancer and the cells that had spread to other parts of the body in these men. And we found that all of the cells that had broken free shared a common ancestor cell in the prostate. The common faults we found in each man could potentially offer new targets for treatment. But we found that, once cancer cells have spread, they continue to evolve genetically, so choosing the most effective treatments will remain a key challenge."

"The diversity we've found suggests multiple biopsies might be needed to identify the 'trunk' of the cancer's tree of mutations – we need treatments that target these core weaknesses to destroy all cancer cells in a clean sweep, rather than trimming the branches. We must also study more patients to learn how to apply these findings to develop more personalised treatments for people with the disease."

"In the phylogenetic trees that our data have produced, we see that most of the oncogenic mutations are shared clonally by all the tumour sites in each patient. This common genetic heritage is a potential achilles heel of the metastases, however, many of these shared mutations

^{17[1]} <http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2015-04-01-scientists-drill-down-to-genetic-root-of-prostate-tumour-development> also see <http://www.sciencedaily.com/releases/2015/04/150401161514.htm> and <http://www.sciencedaily.com/releases/2015/04/150402114659.htm> and <http://scienceblog.cancerresearchuk.org/2015/04/04/news-digest-prostate-cancer-family-tree-pineapples-walnuts-and-more/>

are in tumour suppressor genes and our approach to therapeutically targeting these needs to be prioritised.

“It takes a while before a tumour develops the ability to metastasise but once it does the patient’s prognosis changes significantly. We have to zoom in on this crucial junction and gather more data on the impact different therapies have on prostate cancer’s evolution and spread.”

Moreover there are many more concerns. For example:

1. Epigenetic Factors: The analysis does not appear to deal with the epigenetic factor such as methylation, miRNAs, lncRNAs and the like. We clearly know that they also have significant impact.
2. Stem Cell Issues: There is also the issue of the stem cell. Is there such a factor included in or includable in this analysis?
3. Pathway Modifying Therapeutics: As discussed by one of the commentators the therapeutic implications are evident but in our opinion not at all clear.
4. Prognosis Analysis: Here we have a significant concern. Many prognostic tests have been developed. However if we examine for one gene profile are we missing many others due to poor sampling. Namely one type of polyclonal cells may be in the profile match but another may not. How, then does this observation impact the many PCa prognostic profiles out today?

References

1. Gudem et al, The evolutionary history of lethal metastatic prostate cancer, Nature 2015. doi:10.1038/nature14347
2. McGarty, T., Cancer Cell Dynamics, Telmarc, TWP January 2014, https://www.researchgate.net/publication/271907544_Cancer_Cellular_Dynamics
3. Shen, M., The complex seeds of metastasis, Nature, 2015, doi:10.1038/nature14377



Labels: [Cancer](#)

THURSDAY, APRIL 2, 2015

NEW CRISPR VEHICLES

In [Nature](#) we have an article demonstrating a variant on the now standard CRISPR cas9 vehicle. As they first note:

Type II CRISPR-Cas systems require only two main components for eukaryotic genome editing: a Cas9 enzyme, and a chimaeric sgRNA derived from the CRISPR RNA (crRNA) and the

noncoding trans-activating crRNA (tracrRNA). Analysis of over 600 Cas9 orthologues shows that these enzymes are clustered into two length groups with characteristic protein sizes of approximately 1,350 and 1,000 amino acid residues, respectively

Thus the classic source is *Streptococcus pyogenes* and as noted:

The RNA-guided endonuclease Cas9 has emerged as a versatile genome-editing platform. However, the size of the commonly used Cas9 from Streptococcus pyogenes (SpCas9) limits its utility for basic research and therapeutic applications that use the highly versatile adeno-associated virus (AAV) delivery vehicle.

But the same vehicle with a Cas9 is in many other bacteria and they note:

Here, we characterize six smaller Cas9 orthologues and show that Cas9 from Staphylococcus aureus (SaCas9) can edit the genome with efficiencies similar to those of SpCas9, while being more than 1 kilobase shorter. We packaged SaCas9 and its single guide RNA expression cassette into a single AAV vector and targeted the cholesterol regulatory gene Pcsk9 in the mouse liver.

Thus we have a variant but the same functionality. They conclude regarding in vivo changes:

Here, we develop a small and efficient Cas9 from S. aureus for in vivo genome editing. The results of these experiments highlight the power of using comparative genomic analysis in expanding the CRISPR-Cas9 toolbox. Identification of new Cas9 orthologues, in addition to structure-guided engineering, could yield a repertoire of Cas9 variants with expanded capabilities and minimized molecular weight, for nucleic acid manipulation to further advance genome and epigenome engineering. ...We examined these sites in liver tissue transduced by AAV-SaCas9 and did not observe any indel formation within the detection limits of in vitro BLESS and targeted deep sequencing. Importantly, the off-target sites identified in vitro might differ from those in vivo, which need to be further evaluated by the applications of BLESS or other unbiased techniques such as those published during the revision of this work. Finally, we did not observe any overt signs of acute toxicity in mice at one to four weeks after virus administration.these findings suggest that in vivo genome editing using SaCas9 has the potential to be highly efficient and specific.

This an an interesting next step.



Labels: [CRISPR](#)

[CALIFORNIA AND WATER](#)

In a recent post [Mankiw](#) has proposed using pricing as a control mechanism for water in California. Generally that is a sensible and correct way to manage the problem. However, from many trips to out of the way places in California I believe that there are many unintended consequences that drive the problem. Let me explain two:

1. Most of California is desert. San Diego has but a few inches or rain a year and people there

want lawns etc. The climate supports at best a few cacti and scorpions. Not much more. Then add humans and you get a mess.

2. Almonds. Now a few years back I spent time with almond growers. Almonds are those nuts that airlines used to serve in Business Class before dinner. I do not know anyone who really eats almonds. But USDA subsidizes almond growing in the I5 valley, thousands of acres and billions of gallons of water. These almonds must be stored somewhere, I do not know where. Yet USDA policies mandate what is grown and who gets paid. Thus in some perverse manner the USDA policy and payments mandate excess agriculture and thus massive amounts of water usage.

3. Lawns: People moved from the East to California and wanted it to look the same. New York gets 45" of rain a year and it has winters and dormant plants. LA gets less than half that and no winter. Thus trees and lawns are fed by water to do what they would not do normally. The result is the sucking of water from where it was naturally for eons.

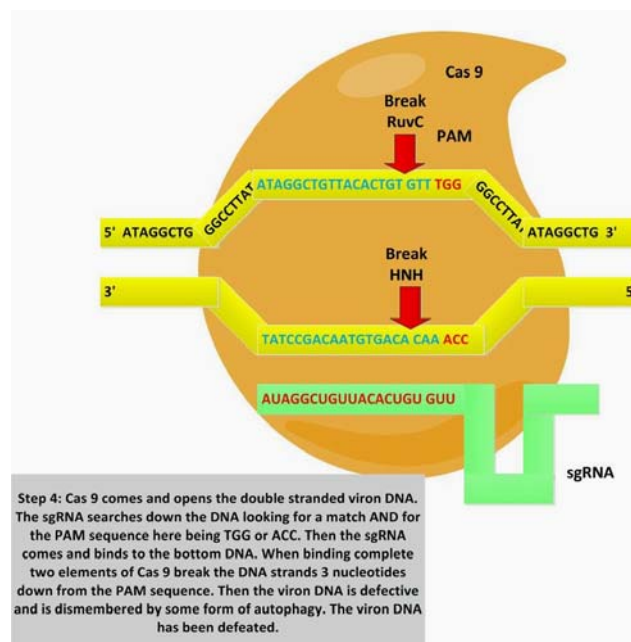
Thus charging more may help but perhaps examining the underlying Government rules and realigning them would help. Try peanuts and get rid of almonds!



Labels: [Economics](#)

WEDNESDAY, APRIL 1, 2015

[CRISPR CAS9 TOOLBOX](#)



We have [published a DRAFT paper in CRISPR Cas9](#) as a tool for genomic engineering. This is an attempt to outline the essential elements in its operations. This enzyme/RNA complex is quite powerful yet has concerns regarding its less than beneficial applications.



Labels: [CRISPR](#)

MOOC ASSESSMENTS

The assessments of MOOCs has been a spotty effort yet MIT has published some detail in 2014 and it has been announced by [MIT](#) that they will be publishing an up to date assessment. We highlight and comment on what is made available:

First, while many MOOC creators and providers have increased access to learning opportunities, those who are accessing MOOCs are disproportionately those who already have college and graduate degrees.

That is interesting in a way. First I have observed many via Discussion groups who have little or no experience. Further those who may have limited in the fields in which they are trying to gain knowledge. Perhaps a better sampling at more detailed levels is necessary. For example how many PhDs in what fields, and when it was obtained. I suspect that many spend some time getting some knowledge but often drop out because of time spent and also because of poor teaching techniques.

Second, if improving online and on-campus learning is a priority, then “the flow of pedagogical innovations needs to be formalized,” Chuang says. For example, many of the MOOCs in the study used innovations from their campus counterparts, like physics assessments from MIT and close-reading practices from Harvard’s classics courses....The real potential is in the fostering of feedback loops between the two realms,” Chuang says. “In particular, the high number of teacher participants signals great potential for impact beyond Harvard and MIT, especially if deliberate steps could be taken to share best practices...

Indeed feedback would be useful. For example, a classic presentation is Lander's. Others could learn from video style. Others could also learn from presentation style. An interesting analysis would be a critique of the instructors and then cross tabbing the instructor with the demographics of the ones doing the critique. There is a great deal of improvement and learning in style of presentation. The instructor who just "presents" as the always do and then assumes that a video of it is sufficient is truly making a mistake. The Lander presentation is wonderful because on the one hand he acknowledges and works with the students in class and also acknowledges the person online, albeit displaced in space and time. In many ways the MOOCs must learn the way early television did, there must be producers and directors, and style is as important as content.

Also the feedback is critical. Now, frankly, there is none. Discussion groups may be there but the TA or equivalent is monitoring at best. Focus Groups would be essential, online focus groups with the instructors would be a substantial benefit. This is especially true when one has such a diverse group of participants.

Third, advancing research through MOOCs may require a more nuanced definition of audience. Much of the research to date has done little to differentiate among the diverse participants in these free, self-paced learning environments.

Marketing was always a part of television. They needed advertisers and the advertisers really wanted to know what the audience watched and wanted. Perhaps that element is necessary.

Market segmentation has always been a part of the research and that segmentation should be part of what the MOOCs do. If all else fails listen to the customer!



Labels: [MOOCs](#)

TUESDAY, MARCH 31, 2015

INCIDENTAL FINDINGS

Medicine is oftentimes filled with surprises. Consider the issue of incidental findings. Suppose a patient had bad back pain. They had lifted something and as their physician you just want a simple plain X-ray to see if it is really L4-L5 as you suspect. You get a call from the Radiologist, not the usual response, in fact you hardly know them. But they tell you that there are multiple thoracic lesions, possibly a lymphoma. Now what?

That is an incidental finding. You were not looking for zebras but you found a herd.

Now consider dermatological mobile apps. [I saw](#) one today that may or may not apply, but it was a mobile dermatological app. Looking at acne, a common ailment especially with younger people.

The article notes:

Users who want to consult with a dermatologist can select a condition they want to get treated for in the app, which is currently only available for the iPhone. After they choose their condition, the app will provide users with an explanation of what to expect from the service. From there, they can choose a doctor. If users want to get the opinion of the first available doctor, they are guaranteed a 24 hour response, but they also have the option to choose a specific doctor. All doctors have a full profile that shows users where the doctor practices medicine, where they went to school...Then, they can upload pictures of their condition and after 24 hours, they will receive a response from the doctor with a treatment plan and a prescription, if needed.

Now assume a patient uploads a picture of their acne. Next to an acne lesion is a suspicious pigmented lesion. The patient did not ask about it, this after all is an iPhone picture, but you are concerned. The patient may have a melanoma. Incidental finding, lots of zebras.

Now what do you do? Contact the patient immediately? Who does the biopsy, where, how fast? You are now faced with a plethora of issues and possibly legal issues as well. What is your responsibility?

The problems may be significant. The problem with many mobile apps is that there may always be incidental findings. If one were in a physician's office perhaps a dermoscope would be available, a biopsy made, a record of the visit detailed, a discussion had. But arms length apps may present significant problems and massive legal issues.



Labels: [Internet](#)

[NEW DIMENSIONS IN PEER REVIEW](#)

I noticed that Peer Review is now a paid process if you want it expedited. [The Scientist](#) reports:

Private peer review is now a multimillion dollar industry, with many journals now offering a service through which authors can fast-track their manuscripts through the process—for a price. Last week (March 24), Scientific Reports announced that, for a cost of \$750, it had begun offering such expedited service, through the peer-review service Rubriq, which pays its editors \$100 each per review. (Rubriq also offers pre-review services for researchers looking for feedback before submitting to a journal.)

It is not clear that such a process is good or bad. The purpose of Peer Review was to filter out bad papers, bad because they may have been incorrect, duplicated, unreadable, or just outright wrong. However as one having done it for years, Peer Review was a process of sending out proposed publications to individuals who would without prejudice examine and critique a work so that it became better if published.

Over the years the Editorship became more club like and if the right senior author appeared on a paper then it was published. This often led to publications not properly reviewed by the senior author and then retractions having been made. Internal reviews were often left to the external reviewer and then external reviewer assumed the internal reviewer did the work. The result is an explosion of retractions.

How will paying someone help. Not at all clear. It appears that the readers have become the reviewers, namely the marketplace.



Labels: [Academy](#)

MONDAY, MARCH 30, 2015

[QUALITY AND VALUE](#)

Words sometimes mean something. But at other times they mean a lot of different things and oftentimes they mean nothing at all. Take Quality and Value. I am always drawn back to the Quality idea that drove the prime character in Zen and the Art of Motorcycle Maintenance to insanity. He spent a lifetime trying to define it. Perhaps like pornography it is in the eyes of the beholder. But what is quality to me may not be quality to you.

The value in Health Care is all too often measured in QALYs, the subjective measure of the use of some treatment or lack thereof. In fact the ACA was written to prohibit its use. Alas, with the current administration even their own laws don't count!

Now in [Healio](#) we have an interesting piece worth tracking. They state:

In response to concerns over Medicare's current fee-for-service payment system, the Obama administration announced in January that by 2018 Medicare instead will aim to associate half of

all payments to the quality and value of health care provided...Some of the changes that private insurers and the government are hoping to advance are the use of bundle payments, population-based payments and Accountable Care Organizations....under the Affordable Care Act, Medicare will be cut significantly.... “Relative to the rates that private insurers pay, the rates for Medicare and Medicaid are going to trend down over time. In fact, by the middle of the century, they are going to be about half of what private insurance pays hospitals,” he said. “We should be concerned that quality may suffer unless we do something about this.”...Research has shown that when Medicare payments to hospitals are cut, it leads to higher patient mortality and other negative outcomes,...

Yes, cut Medicare and people die. But ironically the Democrats blame the Republicans for that yet it is the ACA which mandates it.



Labels: [Health Care](#)

FRIDAY, MARCH 27, 2015

[NUMBERS DO NOT ADD UP](#)

Sometimes people should read what they write. I do, at times, and that is why I am wont to change what I said...it may not add up. But if you are in the NY Times it seems to me that you get away with almost anything. Just look at the number of corrections to the on line stories.

Today in the [Times](#) I read a piece which I think spoke of scientists, and most likely engineers too, as well as physicians and surgeons, can get insight by looking at something differently. Wow, that is big news! As if what we have been done for two and a half *millennium* has been something different. But this statement really rang a bell:

*In a recent experiment at the University of Virginia, researchers used a perceptual-learning module to train medical students about gallbladder removal. In the past, doctors removed gallbladders by making a long cut in the abdomen and performing open surgery. But since the 1980s many doctors have been doing the surgery by making tiny incisions and threading a slender tube called a laparoscope into the abdominal cavity. The scope is equipped with a tiny camera, and the surgeon must navigate through the cavity based on the images the scope transmits. All sorts of injuries can occur if the doctor misreads those images, and it usually takes hundreds of observed surgeries to master the skill. Half the students practiced on a computer module that showed short videos from real surgeries and had to decide quickly which stage of the surgery was pictured. The other half — the control group — studied the same videos as they pleased, rewinding if they wanted. The practice session lasted about 30 minutes. **On a final exam testing their knowledge of the procedure, the perceptual-learning group trounced their equally experienced peers, scoring four times higher. Their instincts were much sharper.***

Now slowly reread the last sentence. These are erstwhile surgeons removing a simple gallbladder via a scope procedure. Those that had this so-called perceptual technique score 4 time higher than the others. Now assume they all scored 100%. That means the regular docs got 25%! You want a surgeon who scored 25%, are you kidding me. Worse, there is zero chance the top group

got all 100% most likely 80% average. That means the characters in the regular learning mode got 20%. But wait! We have no idea how badly the top group did, only that the others got only 25% of what they got!

Can we really believe this, does it make logical sense, does the "pattern" make sense? Not really. Perhaps they should go back and check the numbers, or make certain than none of them ever practice surgery...at least on my gallbladder!



Labels: [Commentary](#)

[FIBER TELECOMMUNICATIONS AND THE MID EAST](#)

[Telegeography](#) has an interesting map on the many fibers going down the Red Sea through the Gulf of Aden and then to Asia. We all too often fail to recognize that this now Hot Spot is also a key strategic point for global telecommunications. A couple of years ago I was working on a proposed fiber across the Arctic above Russia and had indicated to various US Government types its strategic importance, the Russians notwithstanding. The current situation in the Gulf region further intensifies this issue. In a brief moment these lines could be severed and global finance and commerce could suffer. It will be interesting to watch this effort. The irony is that Russia could have established itself as a Global conduit for such efforts but alas it has soured the well over the last year.



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

THURSDAY, MARCH 26, 2015

[CLIMATE CHANGE AND THE ACADEMY](#)

There are small groups forming on many campus locations whose goal is to eliminate any investments in what they see as "dirty energy" companies, and to support a program of "sustainability". At one extreme it is the banning of bottled water, never really drink the stuff, to reverting to a zero carbon footprint existence. Now I can appreciate that as I sit amongst my 4,000+ seedlings sprouting up around my office ready for their outside potting once the winter ends, it is the longest in 30 years here in New Jersey.

Now Harvard has had a bit of a time on this issue and their President has decided to answer the call to have a Campus wide discussion. As the [Crimson](#) announces:

University President Drew G. Faust will convene a panel about climate change on April 13, following several requests on behalf of a faculty group calling for an open forum about Harvard's investment in fossil fuel companies. The panel will be moderated by talk show host and journalist Charlie Rose, who has interviewed Faust on television in the past. The roster of panelists is scheduled to include Harvard science and public policy professors as well as experts from outside the University.

The Harvard President has done a superb job on all she has handled and this is one way to address the campus debate. On additional consideration the choice of Rose is frankly quite wise.

He has an amazing manner to evoke what a guest, presenter, position taker, really has to say, more so than any others in today's market. Unlike many other PBS types who spend time telling listeners what they think, Rose get to people and get them to tell what they think, which is useful.

This is an interesting approach and worth following.

In contrast MIT has a [Sustainability Program](#). It allegedly purports to:

The Sustainability Initiative at MIT Sloan is built on the promise of a new future. We believe that environmental, societal, economic, business, and personal wellbeing are parts of an interconnected whole. The strains we face in each of these domains demand that we think differently and invent new ways of living and working. We are committed to creating a new vision for progress and prosperity and a world that will flourish and thrive for generations. We empower students, faculty, researchers, and business leaders to join together in this endeavor.

Somehow the above is reminiscent of my old days at MIT in the 60s with one small protest group after another. Now however they seem to set up Centers, appoint faculty, provide space and resources and put it on the students tab. Again, we see an ever growing cost of getting an education.



Labels: [Academy](#), [Climate Issues](#)

[CRISPR CAS 9 AGAIN](#)

The system used by bacteria to defend against a virus attacking is the CRISPR Cas 9 system. An interesting use of a protein, enzyme, and a DNA segment that can open DNA at desired locations and cut and insert new segments of DNA. We have been discussing this for well over a year now and have discussed its potential and its risks.

Now along come researchers who instead of doing this in somatic cells do it in germline cells, thus changing the potentially maturing entity. Thus each cell has this changed gene or genes.

In a recent [Nature](#) article the authors state:

There are grave concerns regarding the ethical and safety implications of this research. There is also fear of the negative impact it could have on important work involving the use of genome-editing techniques in somatic (non-reproductive) cells....In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications. We are concerned that a public outcry about such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited. At this early stage, scientists should agree not to modify the DNA of human reproductive cells. Should a truly compelling case ever arise for the therapeutic benefit of germline modification, we encourage an open discussion around the appropriate course of action.

Now this point is well made. Germline cell changes introduce all sorts of issues. Not only is

there the issue of what this new gene will do, we hardly have begun to understand gene interactions, but the issues of epigenetic factors such as methylation dramatically change the risks.

Frankly I miss Michael Crichton, in this case he would have clearly shown us the mistakes we could be making with an unruly unleashing of this technology. Jurassic Park would be a walk in the park as compared to what these could unleash. Imagine correcting those few genes in Apes and the other close to man mammals and see what we could get!

The again you do have the advocates in [Technology Review](#), that somewhat unidentifiable magazine sent to MIT alumni and others, that states:

When I visited the lab last June, ... proposed that I speak to a young postdoctoral scientist named ..., a Harvard recruit from Beijing who'd been a key player in developing a new, powerful technology for editing DNA, called CRISPR-Cas9. With ..., ...had founded a small company to engineer the genomes of pigs and cattle, sliding in beneficial genes and editing away bad ones. As I listened to ..., I waited for a chance to ask my real questions: Can any of this be done to human beings? Can we improve the human gene pool? The position of much of mainstream science has been that such meddling would be unsafe, irresponsible, and even impossible. But ... didn't hesitate. Yes, of course, she said. In fact, the Harvard laboratory had a project to determine how it could be achieved. She flipped open her laptop to a PowerPoint slide titled "Germline Editing Meeting." Here it was: a technical proposal to alter human heredity. "Germ line" is biologists' jargon for the egg and sperm, which combine to form an embryo. By editing the DNA of these cells or the embryo itself, it could be possible to correct disease genes and to pass those genetic fixes on to future generations. Such a technology could be used to rid families of scourges like cystic fibrosis. It might also be possible to install genes that offer lifelong protection against infection, Alzheimer's, and, ... told me, maybe the effects of aging. These would be history-making medical advances that could be as important to this century as vaccines were to the last.

The problem is as the writers in Nature and in Science, led by David Baltimore, have noted, the germ line modifications could be unwieldy.

Just because we have a new technology is no reason to let it loose. The problem with this technology is that it not only can be weaponized but that it can be done in a basement lab. This not building a nuclear weapon. This is potentially setting the world afire.

The again there is the issue of Government regulation. In an interesting piece in [Xconomy](#) the author remarks:

But researchers' and investors' fear that a patchwork of regulation would cripple biotechnology in the United States did not disappear right away. Biologist Thomas Maniatis of Harvard left his home lab to work on the techniques in tighter-security conditions at Cold Spring Harbor Laboratory in New York. Others went abroad. Biogen, founded in 1978, put its first major lab in Geneva, Switzerland. This was a time of intense concern about environmental dangers from the chemical industry in particular and science in general. It took some years for biologists to gain

respect among local state, and federal officials for their sense of responsibility in the recombinant DNA maelstrom of the mid-1970s. But politicians did accept that biotechnology was a significant new industry that other countries, like Japan, might seize if America dropped the ball.

A valid point, but in the 70s we worried about errant scientists. Now we are terrified about terrorist post docs! One wonders what would be worse; the Government Regulators or the Terrorist?



Labels: [CRISPR](#)

WEDNESDAY, MARCH 25, 2015

[AND WHY IS TUITION INCREASING?](#)

In the "You can't Make This Up" category we now have a Dean, yes most likely one of hundreds, at Cornell, advising a putative ISIS group to train on campus. All of this caught on video.

In the UK [Daily Mail](#) they state:

A dean at Cornell University has been filmed apparently endorsing the idea of an ISIS 'training camp' at the college. ..., assistant dean for students at the Ivy League college in Ithaca, New York, said such an initiative would be 'just like bringing in a sports coach'. Video has emerged of Mr ... speaking to an undercover reporter who was posing as a Moroccan student.

This rather rotund looking individual, whose Medicare I am may now be paying into, supports the training of what? If he were in a real business he would be applying for a job elsewhere...

This is a classic example of what is wrong with our Education systems. Positions like this should not exist at all, people like this should find out what life is really like!

On the otherhand the [President of Cornell](#) states:

Project Veritas, the organization behind this shoddy piece of "journalism" has been repeatedly vilified for dishonest, deceitful activity. It is shameful that any individual would pose as a student facing racial discrimination at another university, ask leading questions on hidden camera about Cornell's tolerance for differing viewpoints and backgrounds, and then conveniently splice together the resulting footage to smear our assistant dean and our University. After speaking with Assistant Dean ..., I am convinced that he was not aware of what he was being asked.

Thus what are we left to believe, what is on the video or what the President says. Perhaps if the University filed a defamation suit against the perpetrators and won in Court we could have some faith in the process. A rejection with what appears to be a limited examination is a bit of a weak stand to be in.

The problem is that the words seem to speak for themselves. Also anyone near American Universities is tempted to believe this, especially since we see all too much of this type of action.

Perhaps in lieu of a rapid defense one should have take a deep breath and set out to examine this in detail. It appears that this has not been the case.



Labels: [Academy](#)

SUNDAY, MARCH 22, 2015

[THE FEDS EVALUATE HIGHER ED](#)

In the [Crimson](#) is an interesting piece on the proposed Administrations proposal to rank our higher education establishments.

They state:

The U.S. Department of Education is considering revising its controversial draft college rating system to create two systems instead of the one system initially proposed, according to a report by the Chronicle of Higher Education. The dual rating system would have two parts, tailored to different audiences, that would use different metrics of evaluation, according to the Chronicle. The first, using raw outcome data, would be directed towards a consumer audience, while the second, using data adjusted for individual institutions, would be aimed to help policymakers and researchers measure accountability. First proposed by President ... in 2013, the college rating system intends to evaluate institutions of higher education along a number of proposed criteria, such as graduation rates, average net price, student loan debt, and post-college earnings, according to the draft report. The drafted version would classify colleges and universities as high-, middle-, or low-performing based on these and other metrics, but would not rate institutions numerically.

Well now consider this. Some group of GED GS9s grading Harvard, Princeton, MIT. The chicken comes home to roost! What a nightmare this will be. Our last vestige of competence, now being invaded by politicians. The final step in destroying any future competence in this country.

Higher education is already rated by the market place. By other nations. Perhaps we need to take the advice of our Government employees to make things more like Washington. Shudder the thought! We get a mass crowd of uneducated GS9s wandering around with massive forms and reviews and reports. It will make the Health Care EHR Meaningful Use fiasco along with ICD 10 look like Kindergarten.

This is truly a monumental mess!



Labels: [Academy](#)

FRIDAY, MARCH 20, 2015

[EHRS, MEANINGFUL USE AND THE DEATH OF MEDICINE AS WE KNOW IT](#)

The [HHS](#) is issuing a new set of regulations on the EHR use for Medicare and Medicaid. The rule is massive over 300 pages. It mandates will surely place a tremendous load on any physician driving up costs and reducing any level of care.

They state:

This Stage 3 proposed rule would specify the meaningful use criteria that eligible professionals (EPs), eligible hospitals, and critical access hospitals (CAHs) must meet in order to qualify for Medicare and Medicaid electronic health record (EHR) incentive payments and avoid downward payment adjustments under Medicare for Stage 3 of the EHR Incentive Programs. It would continue to encourage electronic submission of clinical quality measure (CQM) data for all providers where feasible in 2017, propose to require the electronic submission of CQMs where feasible in 2018, and establish requirements to transition the program to a single stage for meaningful use. Finally, this Stage 3 proposed rule would also change the EHR reporting period so that all providers would report under a full calendar year timeline with a limited exception under the Medicaid EHR Incentive Program for providers demonstrating meaningful use for the first time. These changes together support our broader efforts to increase simplicity ...

Yet one just read thrus say the first 50 or so pages and ask; when is any physician going to get through this. The demands are truly counterproductive and pure Government overhead.....



Labels: [Health Care](#)

[CRISPR CAS 9](#)

CRISPR Cas 9 is a new technique to cut and splice genes. [We had written about](#) it about a year ago regarding its use in cancer treatment and also regarding the patent so quickly issues. Now David Baltimore, a highly respected scientist, and colleagues have in [Science](#) suggested a prudent set of steps as to its use in humans. It is reminiscent of the concerns some 49 years ago regarding recombinant DNA.

Baltimore et al recommend:

In the near term, we recommend that steps be taken to:

1) Strongly discourage, even in those countries with lax jurisdictions where it might be permitted, any attempts at germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations. (In countries with a highly developed bioscience capacity, germline genome modification in humans is currently illegal or tightly regulated.) This will enable pathways to responsible uses of this technology, if any, to be identified.

2) Create forums in which experts from the scientific and bioethics communities can provide information and education about this new era of human biology, the issues accompanying the risks and rewards of using such powerful technology for a wide variety of applications including the potential to treat or cure human genetic disease, and the attendant ethical, social, and legal implications of genome modification.

3) Encourage and support transparent research to evaluate the efficacy and specificity of CRISPR-Cas9 genome engineering technology in human and nonhuman model systems relevant to its potential applications for germline gene therapy. Such research is essential to inform deliberations about what clinical applications, if any, might in the future be deemed permissible.

4) Convene a globally representative group of developers and users of genome engineering technology and experts in genetics, law, and bioethics, as well as members of the scientific community, the public, and relevant government agencies and interest groups—to further consider these important issues, and where appropriate, recommend policies.

Baltimore et al have a point. Not only can this be significant on a person by person basis but it also has the potential to be weaponized. The technology is out there, thousands are now proficient in it, the cost is low and the means for distribution is high.

Clearly a sensible effort in collaboration with others is essential. The problem is that with much of science, the genie is out of the box.



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

TUESDAY, MARCH 17, 2015

[HAPPY SAINT PATRICK'S DAY](#)



Oh then, tell me Sean O'Farrell, why you hurry so
hush—a buach-aill hush and listen and his cheeks were all a glow.
I bear orders from the captain get you ready quick and soon
for the pikes must be together at the risin' 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](#)

SUNDAY, MARCH 15, 2015

FINDING ASTEROIDS

[NASA](#) has announced an asteroid hunting program for the masses. As they state:

Astronomers find asteroids by taking images of the same place in the sky and looking for star-like objects that move between frames, an approach that has been used since before Pluto was discovered in 1930. With more telescopes scanning the sky, the ever-increasing volume of data makes it impossible for astronomers to verify each detection by hand. This new algorithm gives astronomers the ability to use computers to autonomously and rapidly check the images and determine which objects are suitable for follow up, which leads to finding more asteroids than previously possible.

Apparently using this program every one of us can set up our small Mount Polamar scopes and watch for small segments of the universe and its pending asteroids.

They continue:

Through NASA's asteroid initiative, the agency seeks to enhance its ongoing work in the identification and characterization of near-Earth objects for further scientific investigation. This work includes locating potentially hazardous asteroids and identifying those viable for redirection to a stable lunar orbit for future exploration by astronauts using NASA's Space Launch System rocket and Orion spacecraft. The Asteroid Grand Challenge, one part of the asteroid initiative, expands the agency's efforts beyond traditional boundaries and encourages partnerships and collaboration with a variety of organizations.

Now I would be very cautious in downloading any program sent to me by the Government. Who knows what agency has deposited what little things to watch inside our computers.

But NASA needs our help. So spend you nights looking skywards.



Labels: [NASA](#)

LEARNING TO PROGRAM

Is learning to program computers an essential skill for each student? Now let me lay out my experience. In 1963 I got the opportunity to work on an IBM 7090 tape based computer using FAP, Fortran Assembly Programming language, an assembly language that was a base to Fortran. I stumbled over its use in some technical areas and got piles of paper which I eventually had to plot by hand.

By 1966 I had picked up Fortran and Cobol, why Cobol I will never know, and slowly saw other languages. Then over the years Basic, ADA, Pascal, C, C+, etc, then Python, Java, and the list continues. I remember using my Atari 800 with a Basic Interpreter and was overjoyed to play around with it.

Now did I really benefit from this? Kind of, but my thought process was not in any way enhanced by it. I found programming like Chess, addictive and time consuming, you can get hooked. You want to get better at it.

So must all students learn to program?

The first question is; what is programming? Is it Basic, simple equations. Is it Python, with a bit more complex abilities to manipulate strings. I used it to make a DNA to protein encoder. Yet I find I can do a great deal with Excel, yes manipulating it to get answers. And it makes nice graphs.

Now there are entities like [Codecademy](#) and [Code to Learn](#) who think we should all be taught this skill. Now I never had shop, yet I did electrical work on houses for my father. And yes I can still do it now, just in case the demand for EEs drops by the wayside. But demand for programmes is different, it can be done in China and India, whereas my electrician skills cannot be outsourced. I have to enter the customers location and apply my skills. Not that way with programming.

As Code to Learn states:

We view coding as a new form of literacy, another way for people to express themselves and share ideas. Just as learning to write is valuable for everyone (not just professional writers), we believe that learning to code can be valuable for everyone (not just professional programmers). We promote approaches to coding that engage young people in thinking creatively, reasoning systematically, and working collaboratively—essential skills for everyone in today's society. The ultimate goal is not just learning to code, but coding to learn.

Learning Spanish may be more helpful, it teaches grammar as well. Learning to code may be a distraction unless there is a clear objective. I learned to code to accomplish a task; calculate an equation or plot a trajectory or analyze data. Yet each was a specific task. Coding works in my opinion if task driven, accomplishing something.

Code Academy states:

Hear how Tommy went from knowing nothing about code to building one of Time's '50 Best Websites' after learning with Codecademy.

But one could argue that "Tommy" may have better spent his time elsewhere, learning better social skills, interacting in a social environment, reading about political science. Why do a web site. What is the reward? What is the benefit? Most importantly why everyone?

This in many ways sounds like the rebirth of the New Math post Sputnik. Coding is a skill, useful for some, addictive for some, but highly fungible. It does not assure any future skill. Software techniques change in a real time manner and today's Python will be tomorrows ADA. Also India and China, Vietnam and Thailand are much cheaper.



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

SUNDAY, MARCH 15, 2015

[QALYS ARE BACK](#)

Despite the ACA not allowing the use of QALY as measures in the delivery of Health Care the academics are flooding the airwaves. In a recent [Health Affairs](#) paper by some Dartmouth folks they state:

Compared to Western Europe, for three of the four costliest US cancers—breast, colorectal, and prostate—there were approximately 67,000, 265,000, and 60,000 averted US deaths, respectively, and for lung cancer there were roughly 1,120,000 excess deaths in the study period. The ratio of incremental cost to quality-adjusted life-years saved equaled \$402,000 for breast cancer, \$110,000 for colorectal cancer, and \$1,979,000 for prostate cancer—amounts that exceed most accepted thresholds for cost-effective medical care. The United States lost quality-adjusted life-years despite additional spending for lung cancer: -\$19,000 per quality-adjusted life-year saved. Our results suggest that cancer care in the United States may provide less value than corresponding cancer care in Western Europe for many leading cancers.

I suspect that this is a move to again eliminate PSA testing and allowing those with prostate cancer just to wait until it mets.

In a recent [OncLive](#) piece Dr Benson at Columbia is quoted as follows:

Active surveillance is increasingly employed in men diagnosed with low-risk prostate cancer despite a lack of high-level clinical trial evidence supporting this approach, and physicians should engage in careful patient selection before recommending the strategy, according to Mitchell C. Benson, MD. That note of caution was among the key points that Benson stressed during a presentation on localized prostate cancer that he delivered at the 8th Annual Interdisciplinary Prostate Cancer Congress in New York City.

The piece further states:

Benson said genetic analysis of the “true biologic behavior” of prostate cancer would eventually help clarify which patients should appropriately be recommended for active surveillance. Gene signature tests that assess risk can be used to help support decisions, he added. As it stands now, Benson said clinicians could improve patient selection by augmenting the standard evaluation through more extensive biopsies. He said a single transrectal ultrasonography should not be used to select patients for active surveillance. “Saturation biopsy improves risk stratification,” he said, adding that he performs an immediate confirmatory biopsy at presentation. Benson and colleagues conducted a study of confirmatory biopsies in 60 patients with low-grade prostate cancer and found that 31.7% (19 patients) would not be candidates for active surveillance based on the results

In [MedPage](#) the authors note about the Dartmouth study:

"We are experiencing declines in mortality from cancer in the U.S.," Soneji says. "But those declines are coming at the same pace as in Europe, which is spending a lot less money. Screening, prevention, and treatment have extended life, but that's coming at a much higher cost [in the U.S.] than in Europe." Soneji's paper is at odds with findings in the 2013 Economic Report of the President, which says that the U.S. has realized greater gains in breast and prostate cancer survival compared with Europe, and generated \$600 billion in value. That study, Soneji says, does not account for stage of cancer at diagnosis, making conclusions vulnerable to "well-known biases with diagnosis and screening that inflate survival time." That's because in more recent years, cancers are being diagnosed earlier, without corresponding changes in actual dates of death. In other words, he says, it just means people are finding out they have cancer earlier.

One must be very cautious regarding the QALY approach. We have written extensively about this in the past and demonstrated its dangers. Further, we must also pay attention to clinical data, especially from the likes of Benson and others since it deals with facts, not just figures.



Labels: [Health Care](#)

[MORE ON MOOCS](#)

As I do from time to time I examine new MOOCs as they come out. A recent one was of great interest but I was sorely disappointed. Here are the reasons:

1. The Video was Chaos. The Instructor had the habit of walking from left to right and then back again, while writing on a blackboard. The video tracked him and his one was seeing a constant flash of the marks on the board while watching the movement and attempting to understand what he said.
2. There is no text and there are no notes. A student asked why and in a slightly surly manner a TA responded that they felt you learned better by taking notes. Perhaps but also perhaps someone would tell the video person that the note should be visible and not just to follow the Brownian motion of the Instructor. I believe that having some form of content on line would help. Especially for international students. But there seems to be a bit of arrogance that is less than helpful.
3. Chaotic Content: This has to deal with DNA analysis using various tool kits available to the bench biologist. Now the result is akin to using a CSHL Lab book, following the protocol, and hopefully filling in the gaps.
4. Quizzical Class: The Instructor would ask a question of the MIT students and apparently there were few if any that even tried to answer. This feedback should have an affect on the Instructor. It did not.
5. Why? Here is where the engineer separates from the scientist. We engineers ask why, bench people ask what and how. Why does a certain protocol work, and why one is better than another.

Such a discussion is missing.

6. Lander and his exposition is still a sine qua non. Lander is like listening to a symphony, like listening to Shakespeare, and this was like listening to some reality TV program. Why? The Instructor is quite well known, he has even written the book that the on campus folks use. Why the disconnect? Good question. Perhaps there should be some feedback.

Remember, if all else fails, listen to the customer.



Labels: [MOOCs](#)

BEWARE THE IDES OF MARCH



Soothsayer Caesar!

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.

NOTE: Image from [Wikipedia. "Bust of Gaius Iulius Caesar in Naples" by Andreas Wahra - Photo by Andreas Wahra, first uploaded to de.wikipedia GiulioCesare.jpg. Modifications by Wolpertinger und Phrood.. Licensed under Public Domain via Wikimedia Commons - https://commons.wikimedia.org/wiki/File:Bust_of_Gaius_Iulius_Caesar_in_Naples.jpg#/media/File:Bust_of_Gaius_Iulius_Caesar_in_Naples.jpg](#)



TED AND SHARK TANK

I had the opportunity to attend an MIT Sloan Conference this past week and in the process they had students "pitch" their businesses to the audience. I sat through three of them and they were 5 minutes apiece. Now in each case they had the Shark Tank approach. Telling us of how big the market was and how unique they were. However I generally ask three questions:

1. How do you make money, namely cash flow.
2. Who is the team I am betting on.
3. What will kill the business.

In all three cases I had no clue as to how these questions would be answered. However they would show well on a Shark Tank episode.

Now for TED. Today in the [NY Times](#) is a fantastic piece comparing TED to a revival meeting. Now I have never attended a TED event, and frankly would never really desire to go, too West Coast "love in" in what I have seen. But the writer noted:

I grew up among Christian evangelicals and I recognize the cadences of missionary zeal when I hear them. TED, with its airy promises, sounds a lot like a secular religion. And while it's not exactly fair to say that the conference series and web video function like an organized church, understanding the parallel structures is useful for conversations about faith — and how susceptible we humans remain. The TED style, with its promise of progress, is as manipulative as the orthodoxies it is intended to upset. A great TED talk is reminiscent of a tent revival sermon. There's the gathering of the curious and the hungry. Then a persistent human problem is introduced, one that, as the speaker gently explains, has deeper roots and wider implications than most listeners are prepared to admit. Once everyone has been confronted with this evidence of entropy, contemplated life's fragility and the elusiveness of inner peace, a decision is called for: Will you remain complacent, or change? Jesus said to the crowds, "Whoever has ears, let him hear." A skilled tent revivalist can twist those words to suggest that simply showing up to listen makes you part of the solution.

Indeed they are. They are the antithesis of a technical presentation at some professional society, all dry and focused. They shout out new world views that the speaker has just recently been the sole discovered of. They are like so many 1960-1970 West Coast feel good sessions on new life realities, gurus who have discovered meanings of life.

In my limited exposure, I am told by some that I should watch some topic, I have found them to be truly evangelical. The speaker has found a truth and has converted it to a Shark Tank like exposition and is now enlightening us.

Is this of value? I am far from one to opine on this, never having attended. But those who have seem to have an EST like response. Frankly I would rather share a glass of good red wine on the Left Bank in September in Paris and speak of great ideas, at least the wine and food are great, as is the view. TV seems to have penetrated everything, and reality TV, at least some ersatz reality, is the most pervasive.



Labels: [Commentary](#)

SATURDAY, MARCH 14, 2015

[WISHFUL THINKING](#)

Medical Trials have gone through decades of improved sophistication and are also extremely expensive to conduct. I would argue that the main reason is patient compliance. Trials often spend time on recruiting and then monitoring patients.

Patients are the most difficult part. They lie. "I do not smoke", "I really did not eat that much", "I take the medications as you told me", "I am dieting every day", "I check my blood sugar", and "I don't drink that much" So consider this article describing Apple's view of patient self reported data.

In [MedCity News](#) they report:

Apple executives envision ResearchKit serving as an aggregator of medical and health data from hundreds of millions of iPhone users worldwide, helping researchers identify and track subjects for their work. That's a great idea, and would be an even greater idea if Apple follows the open-source model and builds or allows a third party to create an Android version. The company described ResearchKit as a framework to help medical researchers design apps for clinical studies, speeding up data collection on an exponential scale.

The problem is that we do not know whether the information is correct or not. Patients lie to their Physicians, patients lie to themselves. So what are they going to tell their iPhones? Is there some truth meter here?

The article continues:

Medicine is also going toward personalization as genomics grows in popularity and falls in price. Hopefully, someone will develop apps on the ResearchKit platform that helps make sense of the massive amounts of genomic data that sequencing is just starting to generate. According to Williams, ResearchKit will provide academicians and practitioners alike with nearly continuous data flows, not just occasional "snapshots" of information, so they will be able to track patient symptoms more accurately. "But perhaps the most significant challenge is the communication flow," Williams said. "When you participate in a study, you often don't hear back until the very

end of the study, if at all.”

It is not at all clear how an iPhone and genomics play out, are we placing a sequencer on the iPhone? Doubt it. But as to the continuous flow of information, if it relies on the patient then it is highly suspect. The purpose of many clinical trials is to take the patient out of the loop specifically because of this fact. Reliance is upon objective measures. Also patient compliance even in a Trial is a challenge.

Thus claims that these technologies are a panacea are at best specious.



Labels: [Health Care](#)

[PI DAY](#)

Every once in a while it is worth some useless comment. Today, 3-14-15 is Pi day, yes the pi related to the circle. Like $2\pi r$, etc.

The [Guardian](#) has a great historical piece:

The symbol π was popularised in 1737 by the Swiss mathematician Leonhard Euler (1707–83), but it wasn't until as late as 1934 that the symbol was adopted universally. By now, π is instantly recognised by school pupils worldwide, but few know that its history can be traced back to a small village in the heart of Anglesey. William Jones was born in 1674 on a small holding close to the village of Capel Coch in the parish of Llanfihangel Tre'r Beirdd, north of the county town of Llangefni in the middle of the island.

So we can thank these fellows for choosing pi rather than some other symbol for the ratio of the circumference and radius of a circle.

We I guess can thank them for pi day!

Oh yes,

$\pi = 3.1415\dots$

That is why today is pi day, unless you are in Europe and they switch day and month so today is 14-3-15.....so much for pi day.



Labels: [Commentary](#)

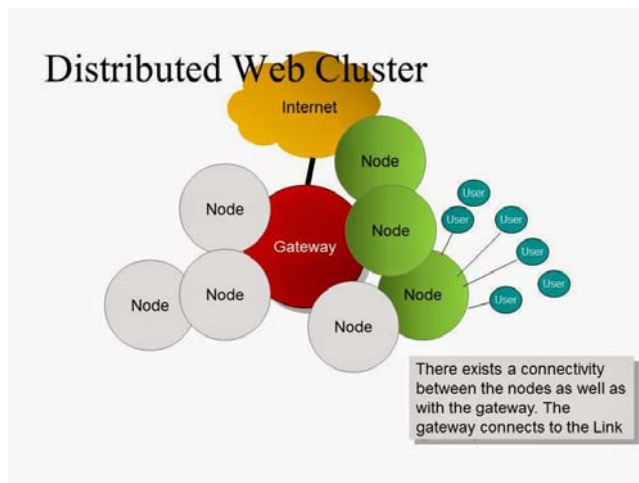
WEDNESDAY, FEBRUARY 25, 2015

[CABLEVISION SEEMS QUITE SMART](#)

As a Cablevision customer there were times I had my doubts. I even had doubts that a CATV company could execute a WiFi system. But Cablevision has exceeded all doubts. They are quite

smart in deploying WiFi.

About 10 years ago we tried a mesh WiFi system we called Linear A. It used a modified Roof Net software developed by MIT grad students who went on to found a Google funded start up called Meraki. It was sold to Cisco. But the bottom line was that mesh WiFi works. Make each customers cable modem a Meshed Wifi and you suddenly get a powerful system. I use Cablevision's WiFi as I come home from the City, one train stop after the other. Cheaper than any Verizon service.



In all, this meshed distributed approach has great potential. If Cablevision can execute this as well as it had its fiber backbone and WiFi network, then I believe it could be a real threat to major urban users.



In 2006-2009 we deployed many of these mesh units but the problem was that there were few dual mode sets, only cellular air interfaces. Now WiFi air interfaces are exploding.

As they state in [Fierce Wireless](#):

Just weeks after launching its low-cost Freewheel Wi-Fi calling and data service, Cablevision.... told investors during the company's fourth quarter earnings call that he believes Freewheel will

disrupt the cellular industry and his company is going to put more emphasis on its Wi-Fi initiatives. Specifically, ... said that his company is going to prioritize Wi-Fi over the company's traditional video business, which is facing rising programming costs. He noted that margins for data products such as Wi-Fi are increasing. Although ... admitted that it was too early to assess demand for Freewheel, he said that the company is seeing usage outside its footprint primarily by non-U.S. citizens who want a low-cost phone available for when they conduct American business.

Frankly, this is just a great idea, whose time has come. Cablevision has shown both interest and competence and it will be interesting to see how they execute on this. Unlike a Google approach, spend billions and make lots of noise, Cablevision just moves ahead elegantly and with great promise.



Labels: [CATV](#)

[NOW IT'S OATMEAL!](#)

There is a report in [Eureka](#) linking a mold on oats to renal cancer. They state:

some oat-based breakfast cereals in the U.S. contain a mold-related toxin called ochratoxin A (OTA) that's been linked to kidney cancer in animal studies. The findings could have implications for consumer health.

The [article](#) states:

Ochratoxin A (OTA) has been found in all major cereal grains including oat, wheat, and barley worldwide and considered as a potential concern in food safety. A total of 489 samples of corn-, rice-, wheat-, and oat-based breakfast cereal were collected from U.S. retail marketplaces over a two-year period, and OTA was determined by high-performance liquid chromatography. Overall, 205 samples (42%) were contaminated with OTA in the range from 0.10 to 9.30 ng/g. The levels OTA were mostly below of the European Commission Regulation (3 ng/g) except in 16 samples of oat-based cereals. The incidence of OTA was highest in oat-based breakfast cereals (70%, 142/203), followed by wheat-based (32%, 38/117), corn-based (15%, 15/103), and rice-based breakfast cereals (15%, 10/66). On the basis of the incidence and concentration of OTA, oats and oat-based products may need greater attention in further surveillance programs and development of intervention strategies to reduce health risks in consumers.

Molds are well known toxins and causes of a variety of cancers. The presence of this molecule in uncooked oats may or may not be significant but in processed oat cereals which are eaten uncooked is a concern. Especially since there is a strong push to eat oats to manage cholesterol.

Eureka continues:

Animals exposed to OTA in experiments developed kidney tumors. Although the U.S. doesn't currently regulate the contaminant, the European Union has set maximum limits for OTA in

food.

This may become a major FDA issue especially since the EU regulators have chimed in.



Labels: [Cancer](#)

MONDAY, FEBRUARY 23, 2015

[OOPS! GUESS I WAS RIGHT](#)

Looks like after the USPTF issued their "brilliant" dictum of not doing PSA tests that the result is more aggressive PCa and more dead men! Told Ya! Never trust a Government Panel, been there and saw what they do.

Now [Healio](#) describes the increase in PCa. As the piece states:

The US Preventive Services Task Force recommends against routine-based PSA prostate cancer screening for healthy men regardless of age. In 2009, the USPSTF issued that recommendation for men aged 75 years or older. In 2011, the task force issued draft guidance expanding that recommendation to include all men, and it finalized that recommendation in May 2012. A study by ...and colleagues was the first to measure changes in prostate cancer presentation since the USPSTF made these recommendations. "If you don't screen the people, then when they do show up with prostate cancer, the horse is out of the barn," ...said during a press conference. "They're more likely to be at intermediate risk because, by missing early disease, then you are going to catch it when it's palpable or causing symptoms. That, of course, makes it much more difficult to treat."

We stated this at the time of the USPTF report. We provided detailed evidence of the contrary of the re[port]. We demonstrated that the two NEJM studies were flawed. But think of all the PSA tests it saved. Then think of all the bone mets and DICs resulting. But then again we have our beloved GS9s and subsidized Government cafeterias... Welcome to the ACA, and we have not yet gotten to those "death panels". or have we?



Labels: [Cancer](#)

[MEDICARE AND OBESITY](#)

The ACA has allowed Primary Care physicians to get fully reimbursed for counselling Medicare Patients who are obese. [Kaiser](#) has a piece discussing its lack of success. They state:

For older adults, being mildly overweight causes little harm, physicians say. But too much weight is especially hazardous for an aging body: Obesity increases inflammation, exacerbates bone and muscle loss and significantly raises the risk of heart disease, stroke, and diabetes....o help the 13 million obese seniors in the U.S., the Affordable Care Act included a new Medicare benefit offering face-to-face weight-loss counseling in primary care doctors' offices. Doctors are paid to provide the service, which is free to obese patients, with no co-pay. But only 50,000 seniors participated in 2013, the latest year for which data is available....who is obese herself,

says she doesn't expect her older patients to lose a lot of weight. "I think you'll see weight loss of 10 to 20 pounds, but whether you're going to see people lose 50 to 100 pounds as they're older, I doubt it." Still, ... says, even with small amounts of weight loss in her older patients, she expects to see a decrease in the complications of chronic medical diseases, including diabetes-related leg amputations.

The facts are:

1. Obesity is an inflammatory enhancing state. Inflammation enhances the potential for and the exacerbation of various cancers.
2. Ongoing obesity has multiple sequella including costly kidney and cardiovascular problems.
3. Yes, Primary Care physicians have problems communicating with patients and worse patients just do not listen. Look at the number, 13 million obese Medicare patients and only 50,000 were dealt with, not necessarily successfully.

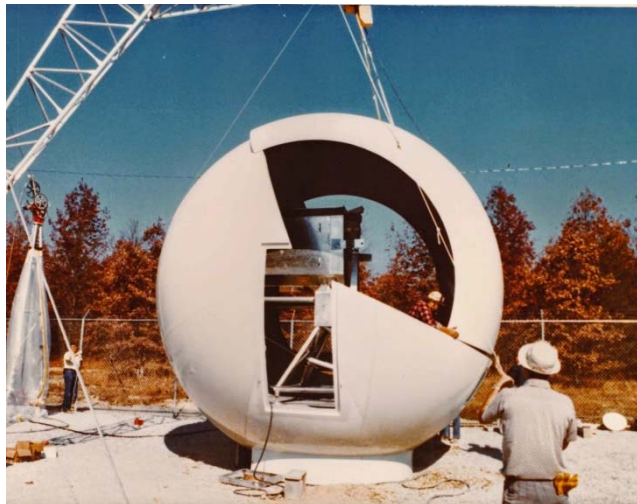
The problem of obesity starts young and then continues. Why not stop it in the teenage years? Why not before 40? Why wait until 65 and later. The costs of obesity on future generations will be explosive. The ACA may have had good intentions but adherence demands perhaps a heavy hand.



Labels: [Health Care](#)

SUNDAY, FEBRUARY 22, 2015

[THE END OF AN ERA](#)



I got a note today from COMSAT alumni that they are finally removing the 32 m antenna AND-03 at the old Andover Earth Station. I used that antenna to connect to European stations using the above antenna in the 70s to monitor Soviet Nuclear Weapons tests.

This is the end of an era. The old 4/6 GHz bands no longer serve the original purpose. COMSAT

was an interesting company, an evolution from a Government vision for satellite communications, managed by a collection of DoD types which lost sight of the commercial world and was slowly disassembled into nothing.

It was a great training ground to understand Washington...pure ruthless politics...played just for the sake of the game. Amazing what a monopoly can do...then it dies.



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

FRIDAY, FEBRUARY 20, 2015

[TELLING US THE OBVIOUS](#)

From the [Office of Disease Prevention and Health Promotion](#) comes this years guidelines. First off the name of this institution is right out of 1984 or the like. We have a group of folks sitting around on an annual basis telling us what to eat. The answer is simple, less. We are in generally too fat, too lazy, and costing the health care system too much. End of report. But no, it is our Government at work and they cannot say in a few words what they can spend tens of thousands on. You have to read this report.

For example they state:

The 2015 DGAC's work was guided by two fundamental realities. First, about half of all American adults—117 million individuals—have one or more preventable, chronic diseases, and about two-thirds of U.S. adults—nearly 155 million individuals—are overweight or obese. These conditions have been highly prevalent for more than two decades. Poor dietary patterns, overconsumption of calories, and physical inactivity directly contribute to these disorders. Second, individual nutrition and physical activity behaviors and other health-related lifestyle behaviors are strongly influenced by personal, social, organizational, and environmental contexts and systems. Positive changes in individual diet and physical activity behaviors, and in the environmental contexts and systems that affect them, could substantially improve health outcomes.

So what is new with any of this? Nothing. Yet the problem is solved by individual choice. Yes, if we burn 2000 kcal per day we better not eat 2100 kcal per day. 3500 kcal is one added pound. Been that way for a few centuries at least.

They continue:

The DGAC found that several nutrients are underconsumed relative to the Estimated Average Requirement or Adequate Intake levels set by the Institute of Medicine (IOM) and the Committee characterized these as shortfall nutrients: vitamin A, vitamin D, vitamin E, vitamin C, folate, calcium, magnesium, fiber, and potassium. For adolescent and premenopausal females, iron also is a shortfall nutrient. Of the shortfall nutrients, calcium, vitamin D, fiber, and potassium also are classified as nutrients of public health concern because their underconsumption has been linked in the scientific literature to adverse health outcomes. Iron is included as a shortfall nutrient of public health concern for adolescent females and adult females who are

premenopausal due to the increased risk of iron-deficiency in these groups. The DGAC also found that two nutrients—sodium and saturated fat—are overconsumed by the U.S. population relative to the Tolerable Upper Intake Level set by the IOM or other maximal standard and that the overconsumption poses health risks.

Any reasonable diet would overcome this. Eating fast foods will not. Again nothing new here.

The report then bemoans:

Obesity and many other health conditions with a nutritional origin are highly prevalent. The Nation must accelerate progress toward reducing the incidence and prevalence of overweight and obesity and chronic disease risk across the U.S. population throughout the lifespan and reduce the disparities in obesity and chronic disease rates that exist in the United States for certain ethnic and racial groups and for those with lower incomes.

Again, and for centuries, one knows that input less output is net accumulation. Added weight, above BMI 25 means increase inflammation, increased inflammation increases the risks of cancer, such as breast and prostate. We know that. So how does one regulate this? Simple, tax weight. Too simple, we become anti obese, yes, because it is to societies benefit. If one wants to be that way then one must carry the costs of being so. At least in a fair market.

They conclude:

It will take concerted, bold actions on the part of individuals, families, communities, industry, and government to achieve and maintain the healthy diet patterns and the levels of physical activity needed to promote the health of the U.S. population. These actions will require a paradigm shift to an environment in which population health is a national priority and where individuals and organizations, private business, and communities work together to achieve a population-wide “culture of health” in which healthy lifestyle choices are easy, accessible, affordable, and normative—both at home and away from home. In such a culture, health care and public health professionals also would embrace a new leadership role in prevention, convey the importance of lifestyle behavior change to their patients/clients, set standards for prevention in their own facilities, and help patients/clients in accessing evidence-based and effective nutrition and comprehensive lifestyle services and programs.

Nonsense! It does not take bold actions. Just put the fork down! The Government has de minimis role, since Government education programs are poor in influencing the public. The only factor is charging for obesity. Frankly there is no other way. It worked on tobacco!



Labels: [Health Care](#)

FRIDAY, FEBRUARY 20, 2015

[THE GOVERNMENT AND ITS OWN LAWS](#)

In the [NY Times](#) today is a piece about CMS sending out erroneous tax filing data. Surprise? Not really. Take Ginnie Mae in HUD. Despite the law requiring sending 1099s by February 14th, do not count on HUD sending anything on time! It is the Government, most likely one of the worst organizations known to man. One should read de Tocqueville's work on The French Revolution. He alleges the cause was the incompetent centralization of the governance of France by the administration in Paris. Centralized and overpowering.

The Times notes:

About 800,000 taxpayers who enrolled in insurance policies through HealthCare.gov received erroneous tax information from the government, and were urged on Friday to hold off on filing tax returns until the error could be corrected. The ... administration, under heavy pressure from congressional Democrats, also announced that it would give several million people more time to buy health insurance so they could comply with federal law and avoid tax penalties. The incorrect insurance information is used in computing taxes. Consumers can expect to receive corrected data in the first week of March. With the new data, officials warned, some taxpayers will owe more and some will owe less. Officials said they did not know why the error had occurred.

Is this a surprise, No. But after all, Officials did not know how it happened. Would one ever think to check.

For those seeking Government controlled Health Care, please just think about it. Remember its the same GS9 who did this one who will mandate your cancer coverage. Hope they don't make the decision on their way to a doughnut break!



Labels: [Commentary](#)

[A GREEK MARXIST](#)



Yanis Varoufakis has written a piece that appeared in the Guardian recounting his Marxist views and their relevance in today's economic climate^{18[1]}. I will try to recount some of his observations as they also lend a light upon the current Greek crisis. Greece is a challenging country. I had a company there once and unlike any of my other companies could never seem to get it started. There was one bureaucratic roadblock after another, one reason for delay, one need for another person, added space, and more time. Greece was and is fundamentally dysfunctional. This is quite strange because the Greeks outside of Greece are very entrepreneurial, very productive, and very successful. Thus one may ask; what does the Greek peninsula do to falter basic Greek capabilities?

Let us examine Varoufakis and his journey with Marx. He states:

My view on this dilemma has always been that the powers that be are never perturbed by theories that embark from assumptions different to their own. The only thing that can destabilize and genuinely challenge mainstream, neoclassical economists is the demonstration of the internal inconsistency of their own models. It was for this reason that, from the very beginning, I chose to delve into the guts of neoclassical theory and to spend next to no energy trying to develop alternative, Marxist models of capitalism. My reasons, I submit, were quite Marxist.

His argument is that capitalism is flawed and to demonstrate this fundamental flaw and to demonstrate it is necessary not to examine and defend Marx but to examine and explain the flaws of capitalism itself, many which he claims are self-evident from the current crisis.

He sees the Marxist world as did Marx, and he recounts it as follows:

Marx created a narrative populated by workers, capitalists, officials and scientists who were history's dramatis personae. They struggled to harness reason and science in the context of empowering humanity while, contrary to their intentions, unleashing demonic forces that usurped and subverted their own freedom and humanity.

The Marxist view of the existence of disparate but well defined "groups" rather than individuals was a means to explain the basis for the ultimate clash via his dialectic process. He continues with his dialectic understanding by stating:

This dialectical perspective, where everything is pregnant with its opposite, and the eager eye with which Marx discerned the potential for change in what seemed to be the most unchanging of social structures, helped me to grasp the great contradictions of the capitalist era. It dissolved the paradox of an age that generated the most remarkable wealth and, in the same breath, the most conspicuous poverty. Today, turning to the European crisis, the crisis in the United States and the long-term stagnation of Japanese capitalism, most commentators fail to appreciate the dialectical process under their nose. They recognize the mountain of debts and banking losses but neglect the opposite side of the same coin: the mountain of idle savings that are "frozen" by

^{18[1]} <http://www.theguardian.com/news/2015/feb/18/yanis-varoufakis-how-i-became-an-erratic-marxist>

fear and thus fail to convert into productive investments. A Marxist alertness to binary oppositions might have opened their eyes.

Here he posits some Marxist opposition yet he is near impossible to follow as to just what that binary opposition is. The US economic problems are fundamentally political and secondarily structural. The core to the collapse in 2008 was a result of political changes in the late 1990s as well as accomplices in Government who facilitated and then protected those whose actions led to the collapse. One must recall that it was the Government housing agencies which led the way with overextending in real estate and that were Government action and not a rational market response.

The Marxist view of anti-individualism, the existence and commonality of labor, may have had validity in the 19th Century but the core changes in the economy today are fundamentally driven by the destruction of that commonality. Production line workers are replaced by robots, the ultimate Marxist proletariat. Technology is fundamentally individual but it requires effort, more effort than just “showing up” at the assembly line. He continues:

Both electricity and labour can be thought of as commodities. Indeed, both employers and workers struggle to commodify labour. Employers use all their ingenuity, and that of their HR management minions, to quantify measure and homogenize labour. Meanwhile, prospective employees go through the wringer in an anxious attempt to commodify their labour power, to write and rewrite their CVs in order to portray themselves as purveyors of quantifiable labour units. And there's the rub. If workers and employers ever succeed in commodifying labour fully, capitalism will perish. This is an insight without which capitalism's tendency to generate crises can never be fully grasped and, also, an insight that no one has access to without some exposure to Marx's thought.

His observation above is of merit. Indeed one sees new workers trying to seek employment by commoditizing themselves as what they perceive are interchangeable units of production. In reality business needs flexible and creative workers. I have often said and have often acted upon the selection of a good High School grad versus a University post grad. It is essential in today's world to have an employee who can adapt rather than conform. That being so, the concept flies in the face of Marx.

The author continues:

If capital ever succeeds in quantifying, and subsequently fully commodifying, labour, as it is constantly trying to, it will also squeeze that indeterminate, recalcitrant human freedom from within labour that allows for the generation of value. Marx's brilliant insight into the essence of capitalist crises was precisely this: the greater capitalism's success in turning labour into a commodity the less the value of each unit of output it generates, the lower the profit rate and, ultimately, the nearer the next recession of the economy as a system. The portrayal of human freedom as an economic category is unique in Marx, making possible a distinctively dramatic and analytically astute interpretation of capitalism's propensity to snatch recession, even depression, from the jaws of growth.

Somehow he sees this power of “capital” and its control over “labor” as the ultimate Marxist dialectic. That view is in sharp contrast to the changing reality of the evolving entrepreneurial world. Greeks leave Greece and prosper by adapting, by being individuals, not by being cogs. In Greece, so many line-up at the dole of Government jobs, lack creativity, and become the Marxist pool of labor.

He then discusses the issue of markets. Namely “markets” as a mechanism to deal with everything in our daily lives from health care to pollution control. He states:

In his recent book Never Let a Serious Crisis Go to Waste, the historian of economic thought, Philip Mirowski, has highlighted the neoliberals’ success in convincing a large array of people that markets are not just a useful means to an end but also an end in themselves. According to this view, while collective action and public institutions are never able to “get it right”, the unfettered operations of decentralized private interest are guaranteed to produce not only the right outcomes but also the right desires, character, ethos even. The best example of this form of neoliberal crassness is, of course, the debate on how to deal with climate change. Neoliberals have rushed in to argue that, if anything is to be done, it must take the form of creating a quasi-market for “bads” (eg an emissions trading scheme), since only markets “know” how to price goods and bads appropriately. To understand why such a quasi-market solution is bound to fail and, more importantly, where the motivation comes from for such “solutions”, one can do much worse than to become acquainted with the logic of capital accumulation that Marx outlined and the Polish economist Michal Kalecki adapted to a world ruled by networked oligopolies. Neoliberals have rushed in with quasi-market responses to climate change, such as emissions trading schemes.

Indeed markets have limits, and sometimes economists tend to value them where they really do not belong. Take the market mechanism to control pollution or carbon emissions. Frankly, if it is a problem, then the solution is technical, not political, that is a “market” solution. All too often these “market” solutions are euphemisms for political beliefs. A prime example is the Pigou tax. Some neo-liberal economists are enamored with them. They see them as a fancy and efficient way to control a perceived problem. In fact if it is a technical problem, carbon gas, then the solution must be a technical one, not a political one.

Finally he makes some interesting remarks as to the mathematical characterization of economics.

Why did Marx not recognize that no truth about capitalism can ever spring out of any mathematical model? If I am right, Marx knew what he was doing. He understood, or had the capacity to know, that a comprehensive theory of value cannot be accommodated within a mathematical model of a dynamic capitalist economy. He was, I have no doubt, aware that a proper economic theory must respect the idea that the rules of the undetermined are themselves undetermined. In economic terms this meant a recognition that the market power, and thus the profitability, of capitalists was not necessarily reducible to their capacity to extract labour from employees; that some capitalists can extract more from a given pool of labour or from a given community of consumers for reasons that are external to Marx’s own theory.

Indeed, mathematical models in economics work if they are ex post facto accounting models, dealing with tautological facts, but all too often stretch the slightest truth when they prognosticate.

As a closing statement he appeals to the perceived loss of human equality. He bases that view on the following observation:

My personal nadir came at an airport. Some moneyed outfit had invited me to give a keynote speech on the European crisis and had forked out the ludicrous sum necessary to buy me a first-class ticket. On my way back home, tired and with several flights under my belt, I was making my way past the long queue of economy passengers, to get to my gate. Suddenly I noticed, with horror, how easy it was for my mind to be infected with the sense that I was entitled to bypass the hoi polloi. I realized how readily I could forget that which my leftwing mind had always known: that nothing succeeds in reproducing itself better than a false sense of entitlement. Forging alliances with reactionary forces, as I think we should do to stabilize Europe today, brings us up against the risk of becoming co-opted, of shedding our radicalism through the warm glow of having "arrived" in the corridors of power.

Instead of bemoaning his failure to be with the masses, he should be happy that the masses have the ability to travel. The economic messes we have, albeit shabby at times, have actually enabled the masses to live better lives and enjoy a modicum of equality amongst the power elite.



Labels: [Economics](#), [Economy](#)

[GENETIC TESTING](#)

The [FDA](#) has given approval to 23andMe for its genetic tests under a 510K ruling. They state:

The U.S. Food and Drug Administration today authorized for marketing 23andMe's Bloom Syndrome carrier test, a direct-to-consumer (DTC) genetic test to determine whether a healthy person has a variant in a gene that could lead to their offspring inheriting the serious disorder. Along with this authorization, the FDA is also classifying carrier screening tests as class II. In addition, the FDA intends to exempt these devices from FDA premarket review. The agency plans to issue a notice that announces the intent to exempt these tests and that provides a 30-day period for public comment. This action creates the least burdensome regulatory path for autosomal recessive carrier screening tests with similar uses to enter the market.

In addition they also specifically stated:

"The FDA believes that in many circumstances it is not necessary for consumers to go through a licensed practitioner to have direct access to their personal genetic information. Today's authorization and accompanying classification, along with FDA's intent to exempt these devices from FDA premarket review, supports innovation and will ultimately benefit consumers," said

Alberto Gutierrez, Ph.D., director of the Office of In Vitro Diagnostics and Radiological Health in the FDA's Center for Devices and Radiological Health. "These tests have the potential to provide people with information about possible mutations in their genes that could be passed on to their children."

The problem is that consumers would generally have no clue as how to interpret the results and even more so most physicians would be equally at a loss.

Certain genetic markers are definitive and others are suggestive. How is a consumer to understand that? This may present a substantial challenge to the health care system.



Labels: [Health Care](#)

THURSDAY, FEBRUARY 19, 2015

[SHOVELING SNOW](#)



In the [NY Times](#) there is a piece on how our towns have managed to clamp down on any individual spirit. When I was a young man I sold Christmas Cards in July, had a paper rout of 112 customers spread over some 8 miles, mowed lawns, shoveled snow, and other similar tasks. I learned a great deal from the process and never once did a NYC Police Officer approach me for what I was doing, other than my father just to make sure I got an opportunity to do more!

But alas, in our new Mommy State, yes in New Jersey, you need a permit to ask to shovel snow. Yes folks, a permit, at the cost of \$200! You cannot make this up. Frankly this shows we have too much Government, if they have time to spend on this issue. But wait, it gets worse. They even dispatched the Police to send the young snow shovelers a packing! This is New Jersey, not Berkeley, not Burlington VT. It is the Soprano's State! People have just too much spare time.

As the Times records;

Armed with about 100 fliers,, both 18 and seniors atHigh School, went door to door in ..., N.J., and then headed to ..., a neighboring town of about 10,000, to offer snow-shoveling services for a reasonable price the following day. The ensuing combination of neighborhood vigilance,

community policing, social media, local and national news coverage, libertarian ideology and the New Jersey Legislature swirled into an unexpected narrative about small-town living, or media fishbowls, or perhaps snowstorms. After handing out about 40 fliers with their names and cellphone numbers, around 5:45 p.m. on Jan. 27, the two teenagers were stopped by police officers responding to a call that some suspicious characters were traipsing through yards, going door to door. ... met the description and were told that soliciting without a permit was "technically illegal" according to a town ordinance, said. They were also violating the town's travel ban, which had gone into effect at 5 p.m., six hours before the state's.

Yep, the town sent a car with Police to scatter the wandering snow shovelers. Now how much did that dispatch cost the town? I have seen bullet holes, smashed mail boxes, vandalism, and the like that at best gets a Police report but in my experience never an investigation. But go outside to make a few dollars and the hounds of Hell descend.



Labels: [Economy](#)

[METFORMIN AND STATINS](#)

Prostate cancer has frequently been seen related to inflammatory processes. The exact connection is yet to be determined. However recent results have indicated that metformin has shown some effect on PCa and a recent paper by Danzig et al shows significant effects with metformin and statins. Both drugs have a certain antiinflammatory role, one in glucose metabolism management and the other through lipid pathways. In this paper we examine both the Danzig et al results as well and the details regarding the specific pathways involved. Specifically the drugs deal with metabolic related pathways, which is no surprise given the nature of Type 2 Diabetes. However the statin usage is not directly metabolic but may very well be so. In a recent [White Paper](#) we expand upon the results, summarized herein.

Shao et al state^{19[1]}:

The widely used anti-diabetic drug metformin has been shown to exert strong antineoplastic actions in numerous tumor types, including prostate cancer (PCa). In this study, we show that BI2536, a specific Plk1 inhibitor, acted synergistically with metformin in inhibiting PCa cell proliferation. Furthermore, we also provide evidence that Plk1 inhibition makes PCa cells carrying WT p53 much more sensitive to low-dose metformin treatment. Mechanistically, we found that co-treatment with BI2536 and metformin induced p53-dependent apoptosis and further activated the p53/Redd-1 pathway.

Moreover, we also show that BI2536 treatment inhibited metformin-induced glycolysis and glutamine anaplerosis, both of which are survival responses of cells against mitochondrial poisons. Finally, we confirmed the cell-based observations using both cultured cell-derived and patient-derived xenograft studies. Collectively, our findings support another promising

^{19[1]} <http://www.jbc.org/content/290/4/2024.abstract>

therapeutic strategy by combining two well tolerated drugs against PCa proliferation and the progression of androgen-dependent PCa to the castration-resistant stage.

For example in the work of Margel et al they note:

By using fractional polynomials, we verified that the association between cumulative metformin use after PC diagnosis and PC specific mortality is linear. On multivariable analysis, for each additional 6 months of metformin use after PC diagnosis, there was a 24% reduction in PC-specific mortality (adjusted HR [aHR], 0.76; 95% CI, 0.64 to 0.89). Increasing durations of cumulative use of all other antidiabetic medications was not associated with PC-specific mortality.

In a similar manner in a study with statins Allott et al noted^{20[2]}:

In this retrospective cohort of men undergoing RP, post-RP statin use was significantly associated with reduced risk of BCR. Whether the association between post-RP statin use and BCR differs by race requires further study. Given these findings, coupled with other studies suggesting that statins may reduce risk of advanced prostate cancer, randomized controlled trials are warranted to formally test the hypothesis that statins slow prostate cancer progression.

Thus it would be reasonable to try an analysis with metformin and a statin combined. It is this study that we have focused upon as a vehicle to explore the effects on prostate cells using drugs that have effects on processes which are fundamentally inflammatory; excess blood glucose and excess blood lipids. To do this we use the most recent paper of Danzig et al where they state:

The combination of statins and metformin in men undergoing RP for prostate cancer (PCa) may be associated with a lower BCR risk than would be predicted based on the independent effects of both medications. A synergism between these two agents is biologically plausible based on our current understanding of their diverse molecular pathways of action. The results of future clinical trials involving the use of either medication in men with PCa should be carefully assessed for confirmatory evidence of such a relationship.

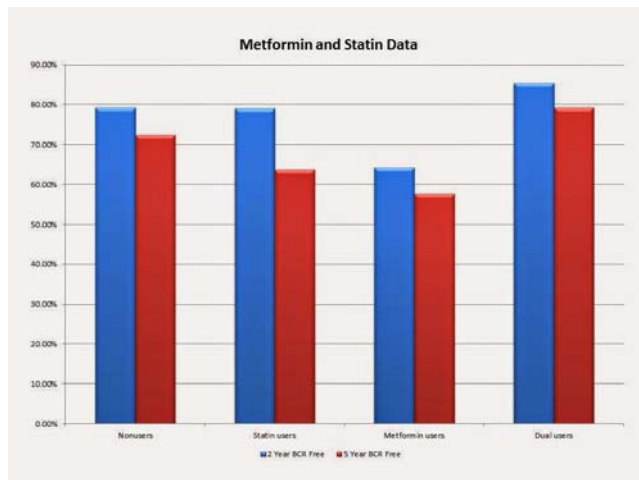
Thus there may very well be a beneficial result of such an approach. We briefly examine this and the details beneath in terms of the cellular pathway dynamics. In this analysis we utilize the Danzig et al paper and examine in some details the functions of the specific drugs and their pathway characteristics. We specifically focus on metabolic pathway elements such as mTOR, AMPK, and how these are influencing a pathogenic characteristic leading to PCa.

Our focus is on the results from the Danzig et al paper. It demonstrates a synergism between metformin and statins in reducing mortality from both HGPIN and PCa. The issue of concern is; just how do these two medications function and what if anything can be generalized from this observation? It is well known that statins have an ameliorative effect on certain cancers and it is also well known that cancers can be initiated and exacerbated by inflammatory processes such as

^{20[2]} <http://onlinelibrary.wiley.com/doi/10.1111/bju.12720/abstract>

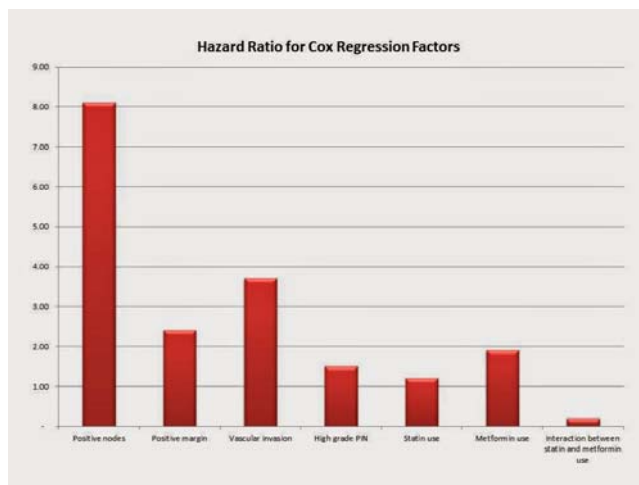
Type 2 Diabetes. We examine some of the basic observations presented in the paper and then proceed to examine the details of the pathway controls.

From the Dantzig paper we have the following survival across the four groups:

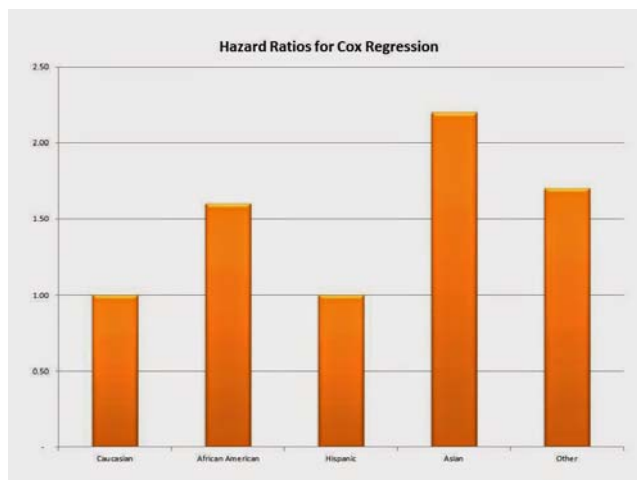


Note the alleged improvement. Also presented in the paper are Hazard Ratios. We summarize three key ones below.

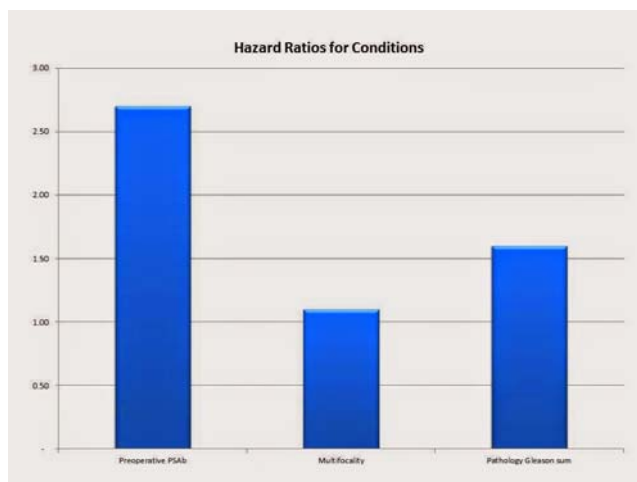
First, we summarize the results of Hazard Ratios on several key factors in the initial stages of presentation. These are all related to biochemical recurrence, BCR.



Second the Hazard Ratios for race are presented. Surprisingly Asia is higher than African American.



Third, below is the Hazard Ratio summary for conditions of the lesion. What is interesting is the importance of pre-operative PSA levels. Perhaps this is a marker for reflecting on the importance of continuing to measure PSAs since the higher it is pre-operatively the greater the chance of post-operative recurrence.



As Danzig et al conclude:

In conclusion, we found that the combination of statins and metformin in men undergoing RP for PCa may be associated with a lower BCR risk than would be predicted based on the independent effects of both medications. A synergism between these two agents is biologically plausible based on our current understanding of their diverse molecular pathways of action. The results of future clinical trials involving the use of either medication in men with PCa should be carefully assessed for confirmatory evidence of such a relationship. Finally, continued research into the molecular mechanisms by which these drugs affect cancer behavior will be highly instructive.

Thus the study presents some significant additional insight into pathways via the use of these medications. We thus start with pathways and then consider the effects of the medications.

Now metabolic factors in a cells environment place stress upon a cell that can result in loss of control as shown above. One metabolic or environmental factor is inflammation, others such as excess glucose or loss of glucose control is another. We examine the latter here.

For example, regulating p53 expression is known to be a major goal. Loss of that regulation is a major concern. One of the major players in that role is AMPK, AMP kinase. AMPK is a metabolic regulatory gene product that on the one hand manages cell energy control and on the other hand can control p53. Thus controlling this element is essential.

This then leads us to other gene products such as mTOR and essential metabolic gene product as well as LKB1.

[AMPK Pathway](#)

Cell metabolism is the process whereby a cell uses energy that is made available to it to maintain normal processes and to grow and reproduce as may be required. Normal metabolic processes in a cell allow for the control of all of the elements in a balanced manner. Excess glucose as seen in Type 2 Diabetes can result in quasi-inflammatory states and loss of homeostasis.

Let us focus briefly upon AMPK, AMP kinase, as an initial point to understand the intra-cellular metabolic processes. AMPK is a key control element in many intracellular pathways^{21[3]}.

From the paper by Mihaylova and Shaw we have^{22[4]}:

One of the central regulators of cellular and organismal metabolism in eukaryotes is AMP-activated protein kinase (AMPK), which is activated when intracellular ATP production decreases.

AMPK has critical roles in regulating growth and reprogramming metabolism, and has recently been connected to cellular processes such as autophagy and cell polarity. Here we review a number of recent breakthroughs in the mechanistic understanding of AMPK function, focusing on a number of newly identified downstream effectors of AMPK.

From the work of Shackelford and Shaw we have^{23[5]}:

^{21[3]} <http://www.cellsignal.com/contents/science-pathway-research-cellular-metabolism/ampk-signaling-pathway/pathways-ampk> This is a useful pathway description worth examining in detail.

^{22[4]} <http://www.nature.com/ncb/journal/v13/n9/full/ncb2329.html>

^{23[5]} <http://www.nature.com/nrc/journal/v9/n8/full/nrc2676.html>

In the past decade, studies of the human tumour suppressor LKB1 have uncovered a novel signalling pathway that links cell metabolism to growth control and cell polarity.

LKB1 encodes a serine–threonine kinase that directly phosphorylates and activates AMPK, a central metabolic sensor. AMPK regulates lipid, cholesterol and glucose metabolism in specialized metabolic tissues, such as liver, muscle and adipose tissue. This function has made AMPK a key therapeutic target in patients with diabetes.

The connection of AMPK with several tumour suppressors suggests that therapeutic manipulation of this pathway using established diabetes drugs warrants further investigation in patients with cancer.

In particular Shackelford and Shaw demonstrate the impact of Metformin on this pathway.

As Mendelsohn et al state:

While growth factor–stimulated signaling cascades promote cell growth under favorable conditions, cells have sophisticated nutrient sensing systems that serve to block growth when the internal energy supply is limiting. These regulators ensure that, during periods of intracellular nutrient depletion, metabolites are redirected from anabolic pathways and instead used to fuel catabolic pathways that will provide the energy required to survive the period of nutrient limitation. The AMP-activated protein kinase (AMPK) plays a major role coordinating cellular energy status with appropriate metabolic responses.

AMPK directly senses cellular energy levels in the form of the AMP/ATP ratio. Falling energy levels increase the cellular AMP/ATP ratio, priming AMPK for activation by the liver kinase B1 (LKB1). AMPK phosphorylates multiple targets with the cumulative effect of blocking anabolic reactions and stimulating energy-generating catabolic pathways.

For example, AMPK phosphorylates and inhibits acetyl-CoA carboxylase (ACC), with the dual effect of blocking fatty acid synthesis and activating fatty acid oxidation. AMPK also directly inhibits cell growth, both by inducing a p53-dependent cell cycle arrest and by blocking mTOR activity at multiple levels. Through these diverse activities, AMPK functions as a metabolic checkpoint, ensuring that cell growth is halted until bioenergetic conditions are favorable for growth.

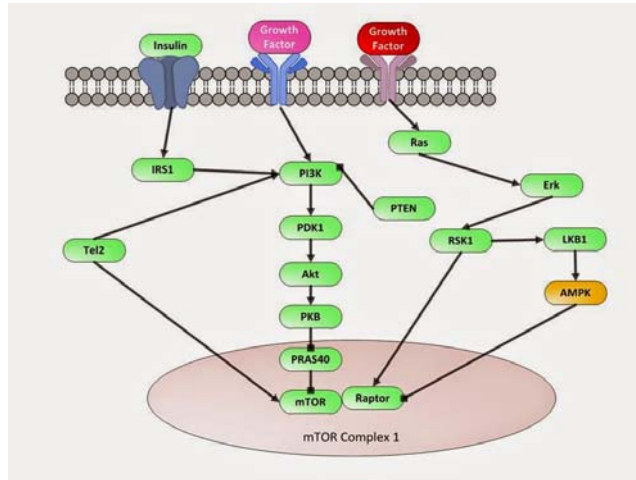
AMPK is a powerful regulator of cell dynamics. It senses and manages energy via the ATP control cycle. Its impact on p53 which we have discussed earlier is also a major factor which may lead to cell oncogenesis. Thus examining how AMPK reacts to excess glucose and how it can be reset is a key observation.

[mTOR Elements](#)

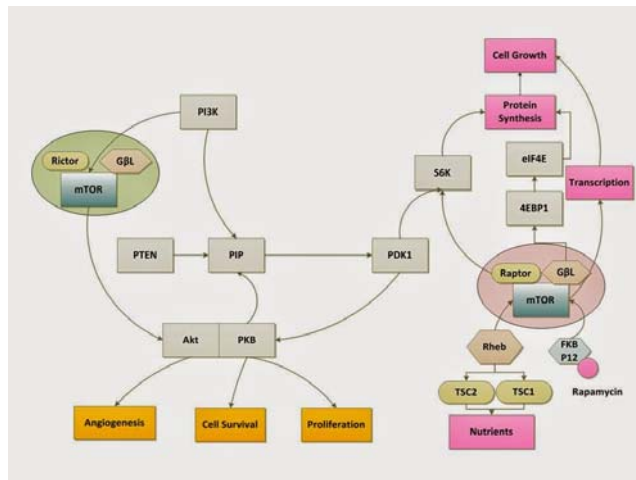
mTOR is a control protein that is involved in metabolic related pathways. mTOR, the mammalian target of rapamycin, is a gene product (1p36.2) is a protein which acts in a critical manner in interconnecting the genetic circuits in mammals, and especially man. It fundamentally

controls glucose transport and protein synthesis. The pathway depicted below is a modification of the graphic from Weinberg (p 785) which shows mTOR in its two modes, one with Raptor assisting and one with Rictor. The Rictor/mTOR mode activates the Akt pathway via the placement of a phosphate and this manages the protein synthesis portion. The inclusion of rapamycin will block the Raptor/mTOR path and reduce the protein synthesis and cell growth portion. The inhibitory effect on Akt/PKB by rapamycin is assumed to be the main factor in its anti-cancer effects.

We depict the mTOR C1 pathway below:



The following chart presents a more complex version of the mTOR C1 pathway (Raptor). This allows us to best understand the complex interactions. The mTOR C1 and C2 pathways are depicted in the combined chart below:



Looking at the complexity of the mTOR pathway it presents an interesting one for addressing PCa. Kinkaide et al (2008) indicate:

Among the major signaling networks that have been implicated in advanced prostate cancer are the AKT/mammalian target of rapamycin (AKT/mTOR) and MAPK pathways. Indeed, deregulated expression and/or mutations of the phosphate and tensin homolog tumor suppressor gene (PTEN) occur with high frequency in prostate cancer, leading to aberrant activation of AKT kinase activity as well as its downstream effectors, including the mTOR signaling pathway. In addition, many prostate tumors display deregulated growth factor signaling, which may result in activation of MAPK kinase 1 (MEK) kinase and ultimately ERK MAP.

Notably, previous studies have demonstrated that the AKT/mTOR and MAPK signaling pathways are alternatively and/ or coordinately expressed in advanced prostate cancer and function cooperatively to promote tumor growth and the emergence of hormone- refractory disease. These observations formed the basis for our hypothesis that targeting these signaling pathways combinatorially may be effective for inhibiting tumorigenicity and androgen independence in prostate cancer.

Kinkaide et al also demonstrate the creation of HGPIN via their work. This represents another pathway of HGPIN to PCa.

LoPiccolo et al state:

The PI3K/Akt/mTOR pathway is a prototypic survival pathway that is constitutively activated in many types of cancer. Mechanisms for pathway activation include loss of tumor suppressor PTEN function, amplification or mutation of PI3K, amplification or mutation of Akt, activation of growth factor receptors, and exposure to carcinogens. Once activated, signaling through Akt can be propagated to a diverse array of substrates, including mTOR, a key regulator of protein translation. This pathway is an attractive therapeutic target in cancer because it serves as a convergence point for many growth stimuli, and through its downstream substrates, controls cellular processes that contribute to the initiation and maintenance of cancer. Moreover, activation of the Akt/mTOR pathway confers resistance to many types of cancer therapy, and is a poor prognostic factor for many types of cancers.

As we have shown with the more complex Weinberg model, here mTOR and PTEN play a strong role in the overall control. The authors show the points of possible control. The complexity of the pathways will be a challenge. It is less an issue of size complexity than a feedback and instability complexity. Nelson et al (2007) have demonstrated similar results as well.

Other researchers have also posited other simple models. We demonstrated the one by Hay as has been stated:

The downstream effector of PI3K, Akt, is frequently hyperactivated in human cancers. A critical downstream effector of Akt, which contributes to tumorigenesis, is mTOR. In the PI3K/Akt/mTOR pathway, Akt is flanked by two tumor suppressors: PTEN, acting as a brake upstream of Akt, and TSC1/TSC2 heterodimer, acting as a brake downstream of Akt and upstream of mTOR.

The Baldo et al model is quite similar to the Weinberg model shown initially. It clearly demonstrates the overall controlling influence of mTOR. As Baldo et al state:

There is a great body of evidence supporting consideration of the mTOR signaling system as an important network in cell regulation, differentiation and survival. mTOR is a sensor of mitogen, energy and nutritional levels, acting as a “switch” for cell-cycle progression from phase G1 to phase S.

The antibiotic Rapamycin, a potent mTOR inhibitor, has been known to the National Cancer Institute and recognized for its potential anticancer properties since the 1970s. The observation that cell lines from different cancer types exposed to low doses of Rapamycin underwent cell-cycle arrest in phase G1, provided the basis for considering mTOR as a target for cancer therapy.

Development of mTOR inhibitor compounds has proceeded empirically due to the lack of understanding of the precise molecular targets and the required dose of the new compounds . The development of Rapamycin analogs (“Rapalogs”), but also of other, structurally different, mTOR inhibitors, was directed at the selection of specific cancer type sensitivity and an optimization of pharmaceutical forms.

The mTOR pathway controls cell size and cellular proliferation....nutrient metabolism, mRNA translation and cell survival control. Disruption of TOR leads to early embryonic death in flies and mammalian cells, indicating mTOR plays an important role in regulating cell survival. ... deregulation of several mTOR components leads to modified cell proliferation patterns and, on the other, that many mTOR components are deregulated in several human cancers.

... Therefore, inhibition of mTOR leads to slowing or arrest of cells in the G1 phase. Translational control may have an important role in the balance of cell survival and death, and hence for apoptosis. Importantly, components of mTOR are deregulated in some human cancers, for example, breast and colon. Alteration of PI3-K/Akt is frequently observed in head and neck cancer .

As Easton and Houghton state:

Proteins regulating the mammalian target of rapamycin (mTOR), as well as some of the targets of the mTOR kinase, are overexpressed or mutated in cancer. Rapamycin, the naturally occurring inhibitor of mTOR, along with a number of recently developed rapamycin analogs (rapalogs) consisting of synthetically derived compounds containing minor chemical modifications to the parent structure, inhibit the growth of cell lines derived from multiple tumor types in vitro, and tumor models in vivo.

Results from clinical trials indicate that the rapalogs may be useful for the treatment of subsets of certain types of cancer. The sporadic responses from the initial clinical trials, based on the hypothesis of general translation inhibition of cancer cells are now beginning to be understood owing to a more complete understanding of the dynamics of mTOR regulation and the function

of mTOR in the tumor microenvironment. This review will summarize the preclinical and clinical data and recent discoveries of the function of mTOR in cancer and growth regulation.

The other observation here is that we often find multiple characterizations of the pathways. Namely there is no canonical form, and often a pathway is depicted to demonstrate a specific protein function. Thus we may see an emphasis on one set of proteins while others are neglected. As much as we currently attempt to unify this process we are left somewhat adrift in model development at this stage. This can be exemplified by now looking at the next section on LKB1. There we show its control over PTEN whereas in an earlier model we have it controlling AMPK. In reality there are multiple links as we have discussed. The literature can be even more confusing on this issue as well.

As Mendelsohn et al state:

It is now widely accepted that mTORC1 positively controls an array of cellular processes critical for growth, including protein synthesis, ribosome biogenesis, and metabolism, and negatively influences catabolic processes such as autophagy—all of which have roles in cancer pathogenesis. Elucidating the key downstream targets of mTORC1 driving these events is an intense area of research.

Originally, much of the study of mTOR relied on experiments in which rapamycin was used acutely to inhibit mTOR (which we now know was mTORC1) in cultured cells. This led to extensive characterization of the best known mTORC1 substrates eIF-4E-binding protein 1 (4E-BP1) and S6 kinase 1 (S6K1), both of which regulate protein synthesis.³ In the unphosphorylated state, 4E-BP1 binds and inhibits the cap-binding protein and translational regulator eIF4E. When phosphorylated by mTOR, 4E-BP1 is relieved of its inhibitory duty, promoting eIF4E interaction with the eIF4F complex and the translation of capped nuclear transcribed mRNA.

Following co-regulatory phosphorylation by mTORC1 and another kinase called phosphatidylinositol 3-dependent kinase 1 (PDK1), S6K1 positively affects mRNA synthesis at multiple steps including initiation and elongation by phosphorylating several translational regulators. Although the preponderance of evidence indicates that S6K1 and 4E-BP1 are directly phosphorylated by mTOR, an unidentified phosphatase activity may also be involved in their regulation. For example, the rapamycin-sensitive phosphorylation site on S6K1 is rapidly dephosphorylated (i.e., within minutes) of exposure to the drug.

They continue:

Conditions that inhibit growth, such as decreased energy, low oxygen, and insufficient nutrients, are associated with the harsh microenvironment of poorly vascularized tumor. The ability of cancer cells to overcome these adverse conditions would promote tumor growth, putting the desensitization of mTORC1 signaling in the spotlight as a potential mechanism cancer cells could exploit to enhance their viability. Whether mutations in the amino acid- and glucose-sensing pathway that activates mTORC1 exist in cancer is not known. Mutations in the growth factor inputs to mTORC1 are prominent in cancer...

Therefore, understanding the contribution and relevance of mTORC1 signaling in the progression of cancers with aberrant PI3K-AKT signaling is an important area of research.

LKB1

LKB1 has been demonstrated to be the underlying control element in Peutz-Jeghers syndrome, a proliferative melanocytic genetically dominant disorder. It controls certain pathways and as a result can be considered as a candidate in the development and progression of melanoma. Generally LKB1 is a gene whose protein stabilizes the growth and location of melanocytes. Understanding its impact in Peutz-Jeghers allows one to examine what happens when its function is suppressed in melanoma. Albeit not an initiator in the process, its aberration in a melanocyte argues for movement and loss of control.

In a recent paper by Liu et al the authors examine this premise and conclude that loss of LKB1 is significant especially in metastatic evolution. As Liu et al state:

*Germline mutations in LKB1 (STK11) are associated with the Peutz-Jeghers syndrome (PJS), which includes aberrant mucocutaneous pigmentation, and somatic LKB1 mutations occur in 10% of cutaneous melanoma. By somatically inactivating Lkb1 with K-Ras activation ($\pm p53$ loss) in murine melanocytes, we observed variably pigmented and highly metastatic melanoma with 100% penetrance. LKB1 deficiency resulted in increased phosphorylation of the SRC family kinase (SFK) YES, increased expression of WNT target genes, and expansion of a CD24⁺ cell population, which showed increased metastatic behavior in vitro and in vivo relative to isogenic CD24⁻ cells. **These results suggest that LKB1 inactivation in the context of RAS activation facilitates metastasis by inducing an SFK-dependent expansion of a prometastatic, CD24⁺ tumor subpopulation.***

Earlier work by Zheng et al noted:

The LKB1-AMPK signaling pathway serves as a critical cellular sensor coupling energy homeostasis to cell growth, proliferation, and survival. However, how tumor cells suppress this signaling pathway to gain growth advantage under conditions of energy stress is largely unknown. Here, we show that AMPK activation is suppressed in melanoma cells with the B-RAF V600E mutation and that downregulation of B-RAF signaling activates AMPK. We find that in these cells LKB1 is phosphorylated by ERK and Rsk, two kinases downstream of B-RAF, and that this phosphorylation compromises the ability of LKB1 to bind and activate AMPK. Furthermore, expression of a phosphorylation-deficient mutant of LKB1 allows activation of AMPK and inhibits melanoma cell proliferation and anchorage-independent cell growth.

Thus Zheng et al putatively identified these two pathways as sources for melanoma development. Liu et al appear to have extended this to metastasis.

The LKB1 gene, also called STK11, which encodes a member of the serine/threonine kinase, regulates cell polarity and functions as a tumour suppressor. This is clearly demonstrated in the

above. Now recall that mTOR is a protein kinase and is a key regulator of cell growth^{24[6]}. mTOR stimulates mRNA translation thus facilitating the conversion into proteins. mTOR also facilitates the formation of ribosomes which as an important condition of cell growth under specific physiological conditions. Through the effects of mTOR on the ribosome machinery it becomes a significant factor in increasing translational activity in a cell.

As Marks et al state regarding the above flow we have (p 337):

Activation and effects of the mTOR protein kinase By inactivating the GAP TSC2 of the small G-protein Rheb, extracellular signals stimulating the PI3K-PKB signaling cascade prompt Rheb to activate mTOR. mTOR enhances the activity of the protein kinase S6K and represses 4E-BP1 and eEF2 activities, resulting in an increased rate of translation (whether 4E-BP1 and eEF2 kinase are phosphorylated directly by mTOR, as shown here, or by S6K or by both kinases is not entirely clear). mTOR may also be directly phosphorylated and activated by PKB.

Now Liu et al state regarding this pathway model:

Two independent pathways appear to be critically important in regulating cell growth in response to nutrient supply and mitogenic stimulation:

- (i) the PKA/PRKARIA-LKB1 tumour suppressor protein pathway, acting via AMPK, and*
- (ii) the PI3K/AKT pathway.*

Recent evidence suggests that the tumour suppressor gene complex, TSC1/TSC2, orchestrates the signal from both pathways to the downstream target, mTOR, which in turn regulates the ribosomal protein S6 and 4EBP-1, a repressor of the translational initiation factor eIF4E. In this model, at times of nutrient stress LKB1/AMPK activation of the TSC1/TSC2 complex results in inhibition of mTOR and a decrease in protein synthesis.

Under stimulation of mitogenic pathways, PI3K phosphorylates PIP2 to PIP3 resulting in recruitment of AKT to the membrane where it is activated by PDK1. Activated AKT inhibits the TSC1/TSC2 tumour suppressor complex leading to increased mTOR activity. In the later pathway, PTEN antagonises PIP3 action through dephosphorylation, and thus provides an “off” switch for regulating mitogenic pathway induced cellular growth and proliferation.

Cross talk of several other pathways appears to play important regulatory roles in the lentiginoses syndromes to include the Ras/MAPK pathway in the regulation of translation, the LKB1 pathway in cellular polarity, the AKT pathway (as well as the TSC1/TSC2 complex) in the regulation of the Wnt/GSK3b/b-Cat pathway, and the BMP pathway in the regulation of PTEN (see text for further discussion). Lastly, both PTEN and mTOR appear to have negative

^{24[6]} See Marks et al pp 335-345.

regulatory effects on VEGF through loss of stabilisation of the hypoxia inducible transcription factor 1 (HIF1).

When LKB1 is inactivated we have the following changes observed in a melanocyte. Note the deactivation of normal LKB1 proteins as well as a PTEN loss of function. We then have the models of Bauer and Stratakis, which we graphically depicted before and they are compelling and establish a paradigm which the work of Liu et al can be considered.

Let us go back to LKB1 and its function. From NLM database we have^{25[7]}:

LKB1 is a primary upstream kinase of adenine monophosphate-activated protein kinase (AMPK), a necessary element in cell [metabolism](#) that is required for maintaining energy [homeostasis](#). It is now clear that LKB1 exerts its growth suppressing effects by activating a group of other ~14 kinases, comprising [AMPK](#) and [AMPK-related kinases](#).

Activation of [AMPK](#) by LKB1 suppresses growth and proliferation when energy and nutrient levels are scarce. Activation of AMPK-related kinases by LKB1 plays vital roles maintaining cell polarity thereby inhibiting inappropriate expansion of tumour cells. A picture from current research is emerging that loss of LKB1 leads to disorganization of cell polarity and facilitates tumour growth under energetically unfavorable conditions. Also it is known as PJS; LKB1; hLKB1.

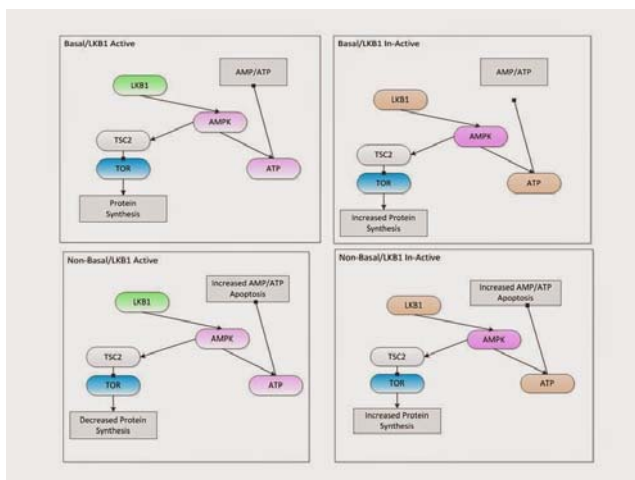
From the results of Shaw et al we have^{26[8]}:

AMP-activated protein kinase (AMPK) is a highly conserved sensor of cellular energy status found in all eukaryotic cells. AMPK is activated by stimuli that increase the cellular AMP/ATP ratio. Essential to activation of AMPK is its phosphorylation at Thr-172 by an upstream kinase, AMPKK, whose identity in mammalian cells has remained elusive. LKB1-deficient murine embryonic fibroblasts show nearly complete loss of Thr-172 phosphorylation and downstream AMPK signaling in response to a variety of stimuli that activate AMPK. Reintroduction of WT, but not kinase-dead, LKB1 into these cells restores AMPK activity. Furthermore, we show that LKB1 plays a biologically significant role in this pathway, because LKB1-deficient cells are hypersensitive to apoptosis induced by energy stress.

Also Shaw et al demonstrate several ways in which LKB1 can function when activated in vivo from either a basal or non-basal state. The description can be shown in the following Figure taken from Shaw et (Fig 6 in Shaw et al as modified):

^{25[7]} http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=retrieve&dopt=default&rn=1&list_uids=6794

^{26[8]} <http://www.ncbi.nlm.nih.gov/pubmed/14985505>



Shaw et al describe the above as follows:

Model for LKB1 as a sensor of low energy and negative regulator of tumorigenesis and apoptosis. Under basal conditions, LKB1 serves as a sensor of low energy, keeping ATP-consuming processes including protein synthesis in check via AMPK phosphorylation of TSC2. In response to stresses such as low glucose, hypoxia, nutrient deprivation, or mitochondrial poisons, LKB1 phosphorylates AMPK, which shuts off ATP-consuming processes and up-regulates ATP production to offset the elevated AMP/ATP ratio. This activity prevents the cells from going into apoptosis in response to elevated AMP. In LKB1-deficient cells, under some basal conditions, there may be increases in TOR signaling due to the lack of TSC2 phosphorylation by AMPK, resulting in increased growth or tumorigenic potential. In response to further increases in intracellular AMP, these cells have no mechanism to offset the elevated AMP and go straight into apoptosis.

We now want to examine some of the details of each of the two medications and specifically their cellular pathway elements and how putatively the two medications may function. We begin by returning to Danzig et al and seeing what they state about the specifics.

For metformin Danzig et al remark:

Metformin has been shown to inhibit mitochondrial respiration, to induce apoptosis through activation of the AMPK/p53 pathway,

and to trigger a G2-M cell cycle arrest independent of its effect on p53.

Its AMPK activation results in diminished mTOR and S6K1 activity, impeding translation.

Independent of AMPK, metformin also induces G0/G1 cell cycle arrest via reduction of cyclin D1 levels and pRb phosphorylation.

Finally, metformin inhibits nuclear factor κ B (NF κ B) and Erk 1/2 and reduces levels of c-MYC.

For statins the author's remark:

Statins, through HMG-CoA reductase inhibition, limit mevalonate production, which is used in protein prenylation.

This has been shown to induce apoptosis through Ras inhibition and to reduce invasiveness by preventing intracellular Rho relocalization.

Another cholesterol-dependent effect is statins' interference with lipid raft signaling, which reduces activation of the PI3k/Akt proliferation pathway.

Independent of HMG-CoA reduction, statins can also induce apoptosis through the MEK/ERK pathway, inhibit cell proliferation through blockade of the G1-S and G2-M cell cycle transitions, induce apoptosis by caspase activation and reduce angiogenesis through diminished endothelial nitric oxide production.

Finally, statins inhibit leukocyte migration and the resultant inflammation, which has been linked to PCa progression.

The statin effects are significant in overall pathway modulation.

[Metformin](#)

Metformin is a classic Type 2 Diabetic control medication and has been used extensively with many patients for several decades. We demonstrate below the areas in which Metformin exercises its influence.

It reduces, inhibits, and activates a variety of pathway elements all of which control cell cycles and apoptosis. It controls the metabolic cycles that relate to the pathway elements we have shown in the previous sections.

The impact of AMPK and in turn p53 is a significant pathway. AMPK is as we have seen a significant metabolic player and metformin modulates its behavior. It manages the Cyclin D1 which controls cell cycle growth. One may wonder why so effectively in the prostate, however. The mTOR management is via AMPK as well and then through mTOR C1.

As Mendelsohn et al state:

Metformin belongs to the biguanide class of antidiabetic drugs and activates the LKB1/AMPK axis (mediating glucose and energy homeostasis) and inhibits cancer cell viability through the inhibition of mTOR. Metformin can also downregulate mTOR and subsequent cell growth through AMPK-independent mechanisms. A recent study using mouse models of lung cancer to assess the protective effect of metformin suggested two possible mechanisms: decreased levels of circulating insulin and lowered energy stress leading to inhibition of mTOR.

Owing to the fact that studies show metformin is associated with a decreased risk of cancer incidence compared with other treatments (such as insulin) among diabetic patients, metformin

is rightfully garnering interest for its role in cancer prevention and therapy and supports further testing in the clinical setting.

The Mendelsohn comment has been demonstrated in Danzig somewhat.

[Statins](#)

Statins are used to reduce VDL levels. The typical mechanism is shown below. The statin blocks the production of intracellular cholesterol which in turns sets off a cascade that sends out LDL receptors to collect LDL from the blood thus lowering serum LDL.

Overall this is a simple and straightforward mechanism. However, just how this affects the PCa process has been postulated in the paper we have focused on but may be likely to a topic of discussion. Chan et al have discussed several general mechanisms.

As Chan et al note:

HMG-CoA reductase inhibitors have been shown to synchronize tumor cells by blocking the transition of G1-S in the cell cycle, thereby exerting its antiproliferative effect. This effect is reversed with the addition of mevalonate. In primary cultures of human glioblastoma cells, inhibition of Ras farnesylation by lovastatin is associated with reduction of proliferation and migration. However, the inhibition of cell growth by lovastatin may be independent of Ras function .

These findings suggest that geranyl-geranylated proteins (but to a much lesser degree, farnesylated proteins such as Ras) are essential for progression of C6 glioma cells into the S phase of the cell cycle. In addition, N-Ras mutated, primary AML cells were no more sensitive to simvastatin than AML cells without the mutation, suggesting that the inhibition of AML cell proliferation by HMB-CoA reductase inhibitors may be independent of the Ras signaling pathway.

The results by Danzig et al present an interesting window to possible control of PCa expansion by using metabolic pathway elements which may also have been causative factors in its initiation. We examine here several observations which may expand the work provided therein.

Let us examine a few additional issues:

What impact will methylation have and is it also driven by similar modalities? We know that methylation is also a factor especially in inflammation like states. Thus what effect does methylation have in this specific case?

Does the process activated by metformin and statins affect all altered prostate cells including stem cells or does it deal solely with the proliferating cells? Here is the issue regarding changes not only to prostate cells but to all cells. There is no specificity of these two therapeutics to prostate cells. The affect cells across the body. Are these effects stabilizing as they may be to the prostate or are they potentially unstabilizing?

How does this combo deal with other cells? This is a corollary to the above observation. Namely here we would examine the impacts, beneficial and harmful, to other cells. These medications are modulating metabolic processes. These metabolic processes are common across many cell areas. It would be useful to see what the balanced effect is.

This must be a common combination. If so that a study may reveal a significant different in end-stage mortality in such a large population. Namely we know that this combination is quite common. If so, then a retrospective study may be beneficial. However, as we have noted before, we do not have either compliance or detailed measurements regarding lipids or blood sugar (eg HbA1c) information.

What is the cause of the synergy between the two? As noted by Danzig et al:

Several potential mechanisms of synergism between the two medications have been explored in preclinical studies. In one study of fatty liver pathogenesis, type 2 diabetic mice fed with a high-fat diet developed increased levels of markers of inflammation and oxidative stress, including C-reactive protein, interleukin-6 and tumor necrosis factor- α . The combinatorial use of atorvastatin and metformin attenuated these effects to a significantly greater degree than either drug alone.

Another study found that the proapoptotic and anti-survival effects of an AMPK activator similar to metformin on malignant melanoma cell lines were enhanced by combination with simvastatin or fluvastatin. As discussed earlier, these two drugs are thought to have a wide range of effects on both metabolic and pleiotropic pathways.

Therefore, the possible means by which they may interact intracellularly to impact cancer behavior are plentiful and diverse.

The cause of the synergy is not really understood. Frankly, even single drug cause is at best generically understood. The range of impact of statins is not fully grasped and thus it may be the statin which has the greater effect. At this stage we need added information regarding the nature of effects.

References

1. Allott, et al, Postoperative statin use and risk of biochemical recurrence following radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database, BJU International, Volume 114, Issue 5, pages 661–666, November 2014
2. Baldo, P., et al, mTOR Pathway and mTOR inhibitors as Agents for Cancer Therapy, 2008, Curr Can Drug Targets, pp 647-668.
3. Bass, A., et al, Complete Polarization of Single Intestinal Epithelial Cells upon Activation of LKB1 by STRAD, Cell, Vol. 116, 457–466, February 6, 2004
4. Bauer, A., C. Stratakis, The lentiginoses: cutaneous markers of systemic disease and a window to new aspects of tumorigenesis, J Med Genet 2005;42:801–810. doi: 10.1136
5. Chan K, et al. The statins as anticancer agents. Clin Cancer Res 2003; 9: 10–19.

6. Danzig, et al, Synergism between metformin and statins in modifying the risk of biochemical recurrence following radical prostatectomy in men with diabetes, *Prostate Cancer and Prostatic Disease* (2015) 18, 63–68
7. Easton, J., P. Houghton, mTOR and Cancer Therapy, *Oncogene*, 2006, pp 6436-6446.
8. Kinkaide, C., et al, Targeting Akt/mTOR and ERK MAPK Signalling Inhibits Hormone Refractory Prostate Cancer in Preclinical Mouse Model, *Jrl Clin Inv* 2008, 99 3051-3064.
9. Liu, A., et al, Correlated Alterations in Prostate Basal Cell Lauer and Basement Membrane, *Int Jrl Bio Sci*, V 5, 2009, pp 276-285.
10. LoPiccolo, J., et al, Targeting the PI3K/Akt/mTOR Pathway, *Drug Res Up*, 2008, pp 32-50.
11. Margel, D., et al, Metformin Use and All-Cause and Prostate Cancer Specific Mortality Among Men With Diabetes, *JCO* Sep 1, 2013:3069-3075; DOI:10.1200/JCO.2012.46.7043.
12. Marks, F., et al, *Cellular Signal Processing*, Garland (New York), 2009
13. McGarty, T. P., Obesity and Type 2 Diabetes: Cause and Effect, DOI: 10.13140/2.1.2118.5929
https://www.researchgate.net/publication/265206539_Obesity_and_Type_2_Diabetes_Cause_and_Effect
14. McGarty, T. P., Prostate Cancer: A Systems Approach, DOI: 10.13140/2.1.2475.2007
https://www.researchgate.net/publication/264960277_Prostate_Cancer_A_Systems_Approach
15. Mendelsohn, et al, *The Molecular Basis of Cancer*, Elsevier (New York) 2014.
16. Mihaylova, Maria, Reuben J. Shaw, The AMPK signalling pathway coordinates cell growth, autophagy and metabolism, *Nature Cell Biology* 13, 1016–1023 (2011)
doi:10.1038/ncb2329
17. Shackelford, D., Reuben J. Shaw, The LKB1–AMPK pathway: metabolism and growth control in tumour suppression, *Nature Reviews Cancer* 9, 563-575 (August 2009) |
doi:10.1038/nrc2676
18. Shao, et al, Inhibition of Polo-like Kinase 1 (Plk1) Enhances the Antineoplastic Activity of Metformin in Prostate Cancer, *J. Biol. Chem.* 2015 290: 2024-2033.
19. Shaw, R., The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress, *PNAS* March 9, 2004 vol. 101 no. 10 3329–3335
20. Weinberg, R., *Cancer*, Garland (New York), 2008.
21. Weinberg, R., *The Biology of Cancer*, Garland (New York) 2007.
22. Zheng, L. et al, NF-κB Regulates Androgen Receptor Expression and Prostate Cancer Growth, *Am Soc Invest Path*, V 175, 2009, pp 489-499.



Labels: [Cancer](#)

THURSDAY, FEBRUARY 19, 2015

HAPPY NEW YEAR



Happy Chinese New Year! Goat and sheep!



Black sheep and white sheep!



Labels: [Commentary](#)

MONDAY, FEBRUARY 16, 2015

[THE LANGUAGE OF DIPLOMACY?](#)

Decades ago when learning French one of the reasons given was it was the language of diplomacy, just in case. English was for trade and French was too fine a language to be abused with the trivialities of commerce.

Now comes the Australians, and its Foreign Minister. The [BBC](#) reports:

Australia's Foreign Minister Julie Bishop says relations with the US are :-) in an interview with Buzzfeed conducted almost entirely in emojis. In what the website says is a world first, Ms Bishop also uses the icons to indicate she is a cat not dog person. She also touched on serious issues, using a frowning face to describe Russian leader Vladimir Putin and a :-| for her view of ties with Indonesia. Ms Bishop is widely seen as a potential future Australian prime minister.

You really can't make this up, or can you? After all we have a current president prancing around taking personal photos and displaying it on multiple media outlets. We have a bare chested Russian leader on a horse, and so forth. I wonder what the Chinese really think of the West? Possibly just wait a bit and it will fall of its own self selfies!

Gone is the elegance of Diplomatic French, I really liked those old days. No emojis.



Labels: [Commentary](#)

[WHAT IS AN APPLIANCE?](#)

A few decades ago a fellow who was brilliant in design worked for me and taught me a simple lesson. Don't build an integrated toaster and blender, no matter how much counter space it may save. Something along the line of form and function. As an engineer I could envision building a toaster, how large, how much power, what type of controls, and the like. I could not envision its form. I also had the common sense of knowing that if one integrated it with a blender then some user would pour something into the toasting side, and well...

Thus the form and function of appliances developed. Kitchen counters are a marvel of this type of display. All sorts of appliances. Waffle makers, blenders, choppers, toaster ovens, big toasters and the like.

Now take a look at the evolution of the mobile phone. For some of us we look at it as an appliance. I have a phone and I have a pad. One is for talking and one is for reading and writing. I like a big pad, not one of those small Apple things which always seem to have cracked screens. Half the people I know have had a cracked screen.

But I was interested in reading about the Japanese, often trend setters, going back to a phone qua

phone. In [Reuters](#) they state:

Japanese shipments of traditional flip-phones rose in 2014 for the first time in seven years while smartphone shipments fell, highlighting Japanese consumers' tenacious attachment to the familiar and typically less expensive older models. Dubbed "Galapagos" phones because they have evolved to meet unique Japanese standards and tastes, flip-phone shipments rose 5.7 percent to 10.58 million in 2014, data from market researcher MM Research Institute Ltd shows. Smartphone shipments fell 5.3 percent to 27.70 million, down for a second year.

Is this a cost issue or is it a trend in appliance theory?



Labels: [Commentary](#)

SUNDAY, FEBRUARY 15, 2015

[HAS THE WEB CREATED CHAOS IN COMMUNICATING?](#)

In the old days, as an MIT alum one got a magazine, [Technology Review](#), that told you what was going on back at Tech and also some updates on former classmates and colleagues. I still get the magazine from Columbia and even Columbia P&S albeit not even a student there, just passing through. But not Technology Review, taken over a decade or more by some West Coast "dot com" types is now a totally incomprehensible jumble of rumors, opinions, half ideas, and ads. There is no structure to it and re-connecting with MIT is the farthest thing in mind.

One often wonders about Development Offices. Harvard is great, Columbia P&S not bad, but MIT in my experience seems to be run by amateurs. First if the Technology Review was the flagship communications method to alumni, would one not think it should be clear? It appears as a want to be Scientific American, the new one, not the good old one.

On the other hand the MIT now has many on line news feeds, from the [student newspaper](#) to the news releases from the [Institute's News Office](#). There is also a self proclaimed "quirky" thing called [The Slice](#) which frankly is not bad. It is sort of reminiscent of the old days, somewhat techy and seeing humor in strange places.

This even makes the efforts of Technology Review seem ever so much more strange. Why, one wonders, have the alumni magazine appear as a sci-tech National Inquirer? Filled with prognostications more opinion than reasoned fact and in addition scattered about a minefield of pop up ads? One may ask, who is this targeted to?

Frankly I have no clue, but alas, no one really asked me anyhow. It is just well below freezing and wind blowing in excess 50 mph so I thought it good to let this out.

But simply the question should be: what does one want the reader/viewer to do with what is presented on the screen? Today we have pop ups, moving images, foot note images, blinking ads, things that make noise and so forth. They all seem to be demanding my attention. It is akin to a carnival sideshow. A typical abuser recently is Science, the flagship of the AAAS. When

one enters the site the first thing one sees is one of those moving dioramas telling one tale or another using images to attract our attention. Then the flashing and blinking ads for some now form of instrumentation. How does one find the articles in the current addition?

In contrast the Brits equivalent, Nature, seems not to have been hit by the extreme distaste of the New York youth driven techno media types. In New York there appears to be a desire to show how many new tricks they can do with html. I now find myself going to Nature rather than Science because Science and the media kids just annoy me! Vendors should take notice. As an example, Google is still understated, like an old Brooks Brothers store, they just get generations returning.

Thus the question for many of the media types is; who is your target reader and why? If you run an alumni magazine then perhaps you should focus on that. If you run a scientific publication, try to respect your subscribers.

In a sense the multimedia types have a set of tools in their tool box and they want to show how they can use each and every one, all the time. It is akin to a 6 year old getting their first big box of Crayolas, some 72 different colors, and using everyone in the drawings just to make the point. I liked Burnt Umber but would use as many as possible. It did not look like a multicolord quilt, it was chaos.



Labels: [Commentary](#)

MONDAY, FEBRUARY 9, 2015

[ECONOMICS IS NOT A SCIENCE, AT BEST IT IS A RELIGION](#)

In a [NY Times](#) piece several supporters discuss the alleged value of Economics, as a science. One quote is:

Economic science is the foundation of sound policies and techniques in business and government.

First economics is NOT a science. It cannot predict and it cannot be used by any practitioner in the way an engineer uses physics to design and build a bridge which will not collapse. Yes it is used to establish policies but policies based upon a belief set.

The next statement is:

Economics succeeds when used as a forensic tool, employing history and data, not creating unrealistic expectations.

Just what does even mean? Forensic so as to establish a cause? If it is not a science then how can it determine cause. If a science then it should reliably predict. It does not predict, its practitioners hardly even agree amongst themselves.

Then there is a quote:

Much of economic science is esoteric and preoccupied with internal struggles. Ideological divisions, exploited by politicians, defy clarity.

Indeed, many economists have adopted the techniques of the theoretical researchers and although they may work in an engineering environment where science is verifiable in a Popperian manner it does not even come close with economists.

Bottom line, economists are mouths for political belief sets, they are religious tent preachers issuing threats of eternal damnation and seeking converts.



Labels: [Economics](#)

SUNDAY, FEBRUARY 8, 2015

[WHY I LIKE NEW JERSEY](#)



In the wake of the deadly accident last week in Westchester i read a piece in the [New Yorker](#) somewhat bemoaning the bucolic life in Westchester.



The problem in both New York and especially Connecticut is a road system not upgraded since the Revolution. Above are two examples of Connecticut. First the Merritt and its winding cow paths where the drivers easily exceed 80mph on wet dark nights. The second is I 95 where the construction closes the highway stranding thousands of trucks and resulting in one collision after another if not a massive economic cost.

Then add the cow paths. I know the section where the accident occurred and visual disorientation can be instantaneous. The Taconic is a well known road with multiple mortalities.

Yet as the author comments on rail transport:

Well, nothing new there: the car as symbol of America's rise and fall. But the Harlem-line disaster was, most disturbingly, a car-meets-train disaster: the engineer trying to brake as the S.U.V. loomed squarely in his sights. To many of our fellow-citizens, the idea of commuting by rail seems archaic, or even un-American. (Never mind the marvels of high-speed rail in Europe and Asia.) To get somewhere, the thinking goes, you should be in the driver's seat, with your own hands on the wheel. But, in fact, the American romance of rapid transit—of speed and freedom, of the beckoning open thoroughfare—began with trains. And, back in the day, we approached this novelty in our novel American fashion. "American railroads were constructed in the quickest way, and with little regard to safety, comfort, or durability," Daniel Boorstin writes in "The National Experience," the second volume of his trilogy "The Americans." Charles Dickens, on his famous stateside visit, in 1842, "found his first ride in an American train of the Boston & Lowell line a terrifying experience. Generally foreigners touring the United States by rail were appalled by the frequency of accidents and still more amazed that Americans should accept them as routine."

Rail transport in the US is stuck somewhere in the late 1930! While living in Europe it was clear that no respectable European country would tolerate such conditions. Imagine a third rail exposed in a highly populated area! Why not an open natural gas line. Why bury them, just hang them on telephone poles! Back roads in New York are adventures, but adventures are exposed to massive risks.

Now in New Jersey, a state of equal historical heritage, one sees roads much more carefully controlled. Wider roads, more well lit roads. In New Hampshire the same is true. There is break down space, even in the White Mountains with its typical ground cover of 4' of snow or more, one can move. Not so in New York and almost never in Connecticut. If there were a way to avoid Connecticut roads I would do so, no matter, except the only way to do so is to use the Taconic, drinking arsenic is safer!

This tragic event is just a recent sign of what must be done. In West Virginia one comes across RR crossings where we see 2 mile long trains loaded with coal, one is certain to stop, wait, then proceed cautiously. But on a random detour, most likely set up because of the authorities closing a road, leads to that form of dissonance that confuses, delays, and leads to tragedy.

Is this a new phenomenon? Hardly.

Certain technologies seem never to change, especially those owned or controlled or monopolized by the Government. Cable converters have a life time of fifteen years, rail crossing have not been updated technology in over a hundred, power distribution systems are just a few years beyond Edison's first implementation.

Somehow, and this is the duty of the Government, new winds must blow to make certain we use what we have learned so this never happens again.

Ironically both Connecticut and New York have some of the highest gasoline taxes. One wonders what they do with those funds. From my fifty-five years of experience, it seems very little!



Labels: [Commentary](#)

SUNDAY, FEBRUARY 8, 2015

[WHAT'S IN A CLASSROOM?](#)

One of the major reasons college is costing more is the intrusion by those who "think" they know better. Take the recent UNH classes in Manchester. In a [NHPR piece](#) they laud the introduction of the best ideas in classroom designs.



Take the above classroom, at MIT. Yes they are my two grandsons, and it was a while ago, but the chairs were sitable and there was no room for laptops, iPads, cellphones etc.

The NHPR pieces states:

“And then it’s learning by doing. So the instructor would walk through the classroom or the lab and listen to what’s happening, providing advice or when asked to, solve certain problems.” Sabin uses round tables she calls “pods” that seat a handful of students who huddle in front of their laptops and easily talk with peers. It’s an idea she got from other STEM studios in places like MIT. And other teachers are taking note.

Not clear where they walked through MIT other than a meeting room or cafeteria but learning by

doing is called problem sets and homework. Lectures are learning by listening and asking. It is an iterative process. You learn a little, do a little, learn a little, etc.

The piece continues:

So for example, we have some faculty members who as soon as they get in to the class want to put the students in circles. We have other faculty who may start lecturing so the idea of that five rows works, but then want to get students into groups.” But to accomplish this, they need something as simple as better chairs. As part of a faculty-led design team, Gamtso organized a “sit test” in the library where students could try out dozens of chairs and provide comments. The crowd favorite? A chair with a larger table which can pivot for right or left-handed users and has storage space for bags. It even has a cupholder...

How about a taxpayer favorite, a chair and table. I am always amazed that when a state owned institution hires an expert that all too often the expert recommends something "new" and all too often expensive.

Take the MIT Stata Center, the architectural monster which leaks and appears near impossible to maintain. Someone had the great idea that this would be a landmark, well it is, it is an eyesore! Perhaps these chairs will have an equal effect.



Labels: [Academy](#)

MONDAY, FEBRUARY 2, 2015

[PERSONALIZED VS PRECISION](#)

The [NIH web site](#) defines Precision as follows:

Precision medicine refers to the use of information about the genes, proteins, and other features of a person's cancer to diagnose or treat their particular disease.

Not at all clear how that differs from personalized. The [IOM](#) also has a report on Precision Medicine.

Over the past few years we have been examining and commenting on various approaches and schemes directed at diagnosis and prognosis based upon individual genes. Some cancers are simple, such as CML and the Philadelphia Chromosome. A simple translocation and a kinase inhibitor works, for a while.

Yet when we examine say melanoma and BRAF V600 mutations, the therapeutics work, sometimes, and just for a while. No real home runs.

Now I suspect the intent is to amass a massive data base on 1 million people and examine how they perform. Nice idea but at what cost? For example even in a simple trial the costs could easily be \$10,000 per person over a simple tracking lifetime. That is \$10 Billion, not the \$300M suggested. That is how we get into trouble. Then the question is; track what? We can get the

somatic DNA from several organs but what if they have a malignancy, say MDS. Just what are we trying to detect, we do not know now. Moreover, we know that even a simple cancer, say prostate, have multiple genetic changes, just look at the putative prognostic markers using dozens of gene expressions.

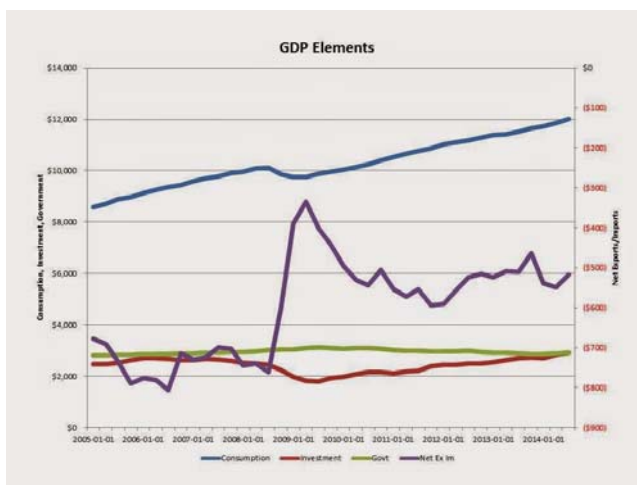
Thus the problem is that such a program has merit if it is socialized and agreed to and built up to, not jumped on full force with so many loose ends. To some degree in my opinion it is a shame that NIH and its centers are fronting such an effort while so many other opportunities need examination.



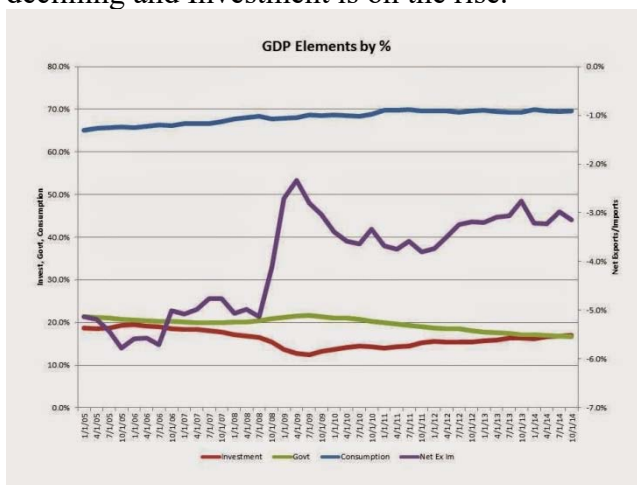
Labels: [Cancer](#), [Government](#), [Health Care](#)

SUNDAY, FEBRUARY 1, 2015

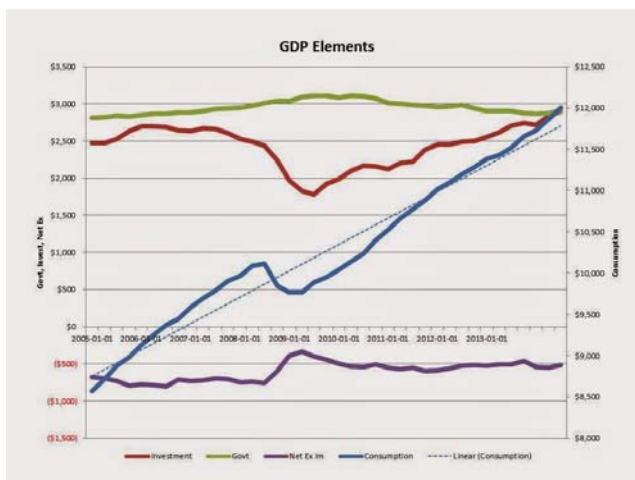
[MORE ON THE GDP Q4 2014](#)



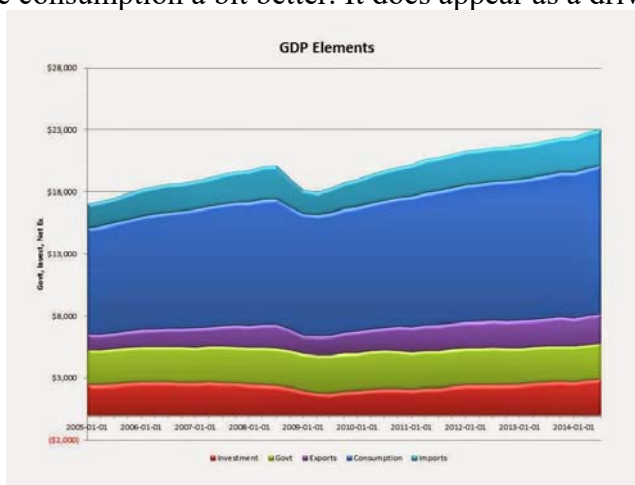
Thought it would be helpful to add a bit to the GDP discussion. Here we have the totals of the key elements from Jan 2005 through the present. Consumption is again on the rise. Net Ex-Im are flat. Government is declining and Investment is on the rise.



The above is the percent numbers.



Here we try to delineate consumption a bit better. It does appear as a driver.



The above is total GDP by breakouts. Just some data for discussion.



Labels: [Economy](#)

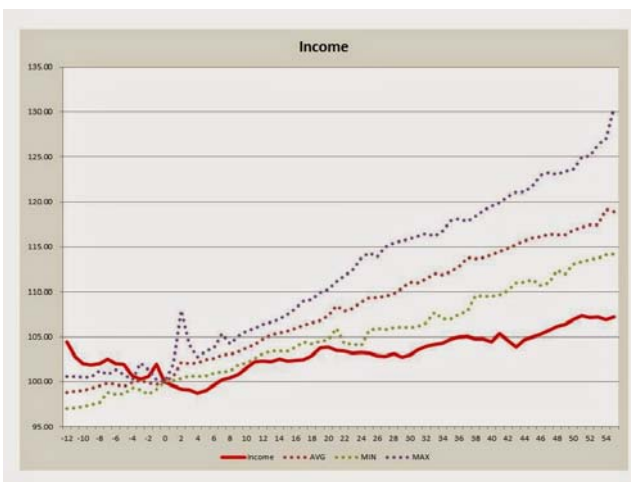
SATURDAY, JANUARY 31, 2015

[RECESSION STATS THRU Q4 2014](#)

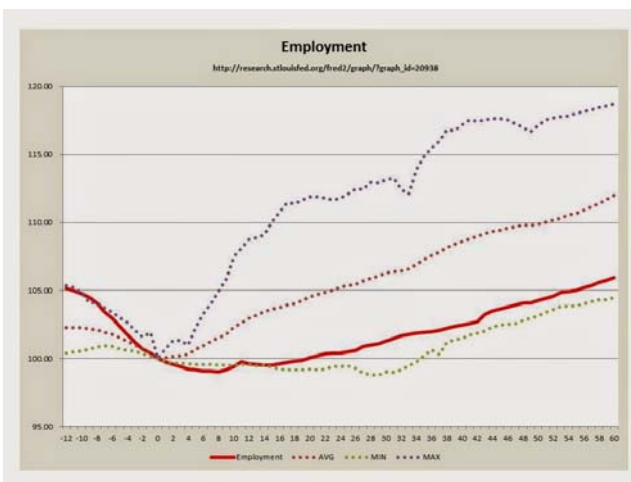
These are the most recent St Louis FED Recession Comps. They tell a powerful tale that we are still mired in a long term mess. Recall that employment looks good only because we lowered the denominator, namely the workforce. That means we have permanently removed 6 million people from doing anything productive. Why? Lots of answers but like terrorism if we fail to identify it and call it what it is then it will never go away. But the current Administration eschews such acts.



First Production is not bad. It follows the average growth from a Recession and looking at this things may seem fine.



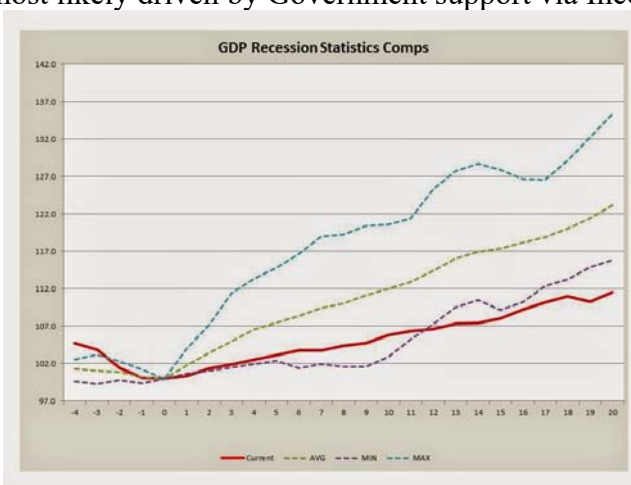
Now the above is Income growth. It is horrible, there is NONE. We have given a new bottom to Income.



Employment is rock bottom as well, and this only looks slightly better because of the elimination of people from the work force.

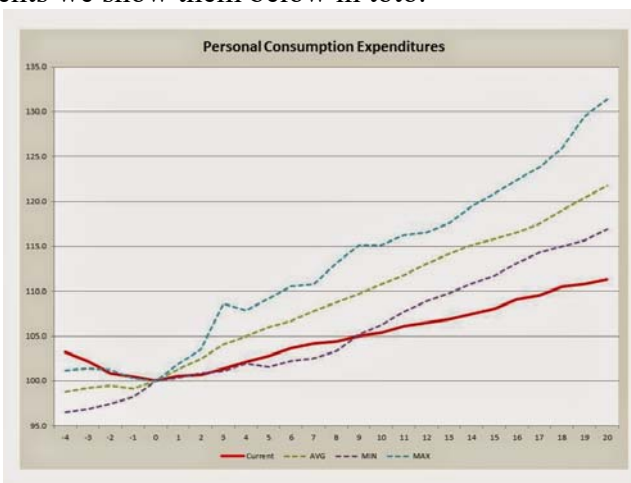


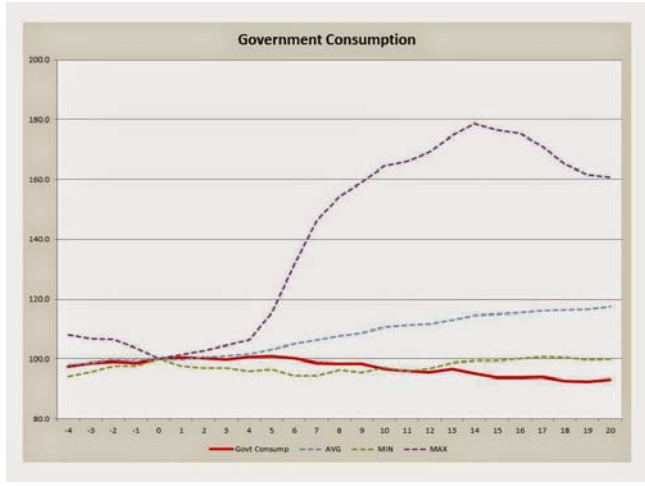
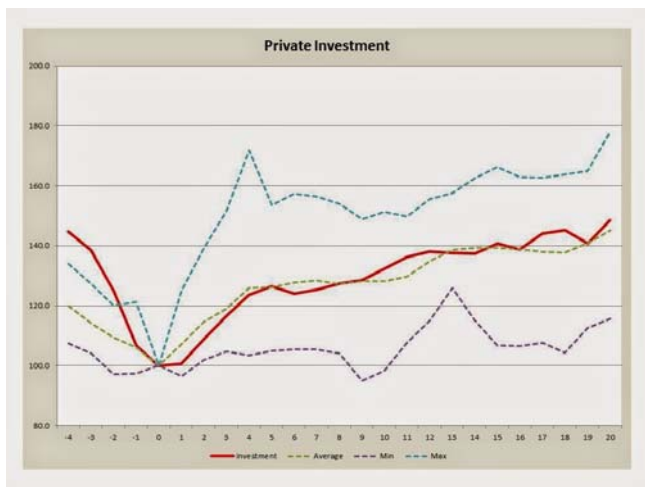
Retail Sales is on par, most likely driven by Government support via Income Transfers.

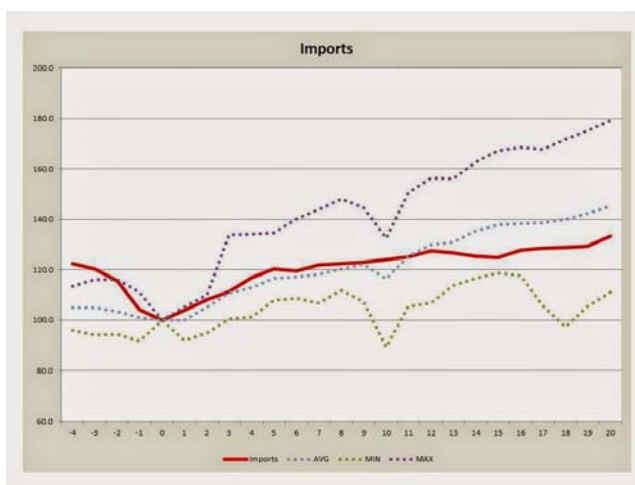
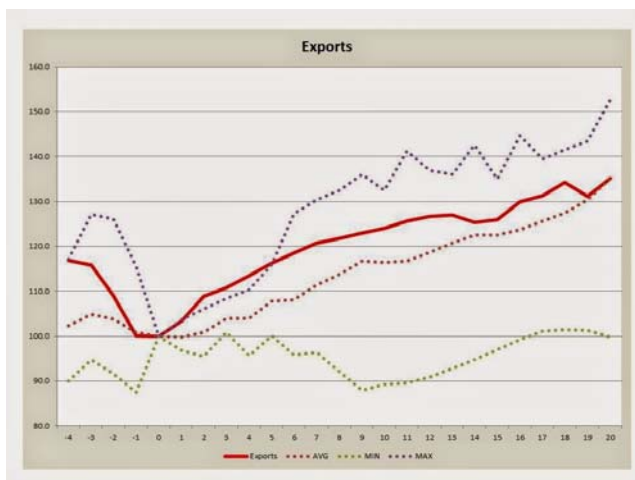


The GDP growth is also rock bottom. We may have some growth but relative to all other Recessions we are below them for the past 10 Quarters!

Now for the GDP elements we show them below in toto.







Personal Consumption is low. Government Consumption is also low. They are the two laggards. The others seem fine. Overall we still appear to have a concerned private sector and Washington seems to neglect it.



Labels: [Economy](#), [Recession Statistics](#)

FRIDAY, JANUARY 30, 2015

WHOSE MONEY?

There are times that I truly wonder what has happened to some reporters. [Medscape](#) reports on the proposed genetic tracking proposal of the Administration, yes that is what it really is, and they state:

Putting his money where his mouth is, President Obama will seek \$215 million to finance the

Precision Medicine Initiative he first mentioned in his State of the Union speech on January 20.

Putting whose money! It is NOT his \$215 million, it is ours you nimwhit! This is the problem many folks have. The fail to understand the very fundamentals of our economy. They continue:

Putting his money where his mouth is, President Obama will seek \$215 million to finance the Precision Medicine Initiative he first mentioned in his State of the Union speech on January 20.

They continue:

The NIH has been in contact with 200 studies that have at least 10,000 enrollees each, which it hopes to integrate into the overall cohort, Dr Collins said. Volunteers will be needed to round it out.

The data will be accessible to qualified researchers and likely also will be used by pharmaceutical, device, and diagnostic companies, he said. An early outcome "will be to take this field of pharmacogenomics — the right drug at the right dose for the right person — and really put it to the test," Dr Collins said. The FDA has approved more than 100 drugs with labeling urging DNA testing before use. "And yet it's not being done because the logistics are all wrong." But with a database that offers results on a million people, "it's a click of the mouse for the doctor to figure out whether it's a different drug or a different dose," he said.

The proposal was in [NEJM](#). It stated:

The concept of precision medicine — prevention and treatment strategies that take individual variability into account — is not new¹; blood typing, for instance, has been used to guide blood transfusions for more than a century. But the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. What is needed now is a broad research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice. The proposed initiative has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are now within our reach because of advances in basic research, including molecular biology, genomics, and bioinformatics. Furthermore, the initiative taps into converging trends of increased connectivity, through social media and mobile devices, and Americans' growing desire to be active partners in medical research.

It simply is taking all of our personal genetic data and handing it over to the FEDs so they can figure out what is the "best" way they can deal with us.

One should beware. This is a massive intrusion into our lives and the results could be catastrophic. Precision medicine is not personal medicine. It is the development of least cost delivery and the tails be damned. Namely they will deal with the +/- one sigma and the rest may

just go by the wayside. Where is Nancy Pelosi when we really need her, she could have made this real clear!



Labels: [Health Care](#)

[JUST WHAT IS NEW HERE?](#)

In a [NY Times](#) article today there is a big announcement of a program to use genetic analysis on disease. They state:

White House officials said the “precision medicine initiative,” also known as personalized or individualized medicine, would begin with a down payment of \$215 million in the president’s budget request for the fiscal year that starts on Oct. 1.

Well have we not been doing this for a few decades. We have BRCA for breast cancer, BRAF for melanoma, we have translocations for CML and we have tones of putative diagnostic and prognostic tests for almost every cancer. So just what is new?

The we have in the same piece:

“Cancer,” he said, “is a disease of faulty genes. The goal of personalized medicine is to understand the unique characteristics of individual patients so therapies can be tailored to genetic mutations that underlie their disease.”

Well, kind of. If you assume that epigenetic factors such a miRNAs and methylation are genes in some broad sense.

The proposal is:

Federal officials described the project as a research consortium that would collect information from large numbers of people. The data could include medical records, laboratory test results, profiles of patients’ genes, and information about their diet, tobacco use, lifestyle and environment. The president’s budget request, to be unveiled on Monday, includes \$130 million for the consortium, White House officials said. In addition, they said, will request \$70 million for the National Cancer Institute, the largest of the National Institutes of Health units, to investigate genes that may contribute to the risk of developing certain types of cancer, and then to use that knowledge in developing more effective treatments.

So we will start to collect all of this info. I am a bit confused. Did we not hand out a few billion to docs to get EHR systems and that under meaningful use they were supposed to be doing this now. So what is the added millions for again?



Labels: [Health Care](#)

TUESDAY, JANUARY 27, 2015

WHERE'S THE FRANCHISE?

Google announced a massive expansion of fiber to the home. As the [Washington Post](#) announces:

After months of speculation, Google confirmed Tuesday that its ultra-fast Internet service will soon be coming to four more cities — Atlanta; Charlotte, N.C.; Nashville, Tenn.; and Raleigh-Durham, N.C. Those regions, along with more than a dozen cities in their immediate vicinity, will be the latest to benefit from high-speed Internet provided by the search giant. Google Fiber already sells Internet service with download speeds of up to 1 gigabit per second — roughly 100 times faster than the national average — for \$70 a month in other cities such as Provo, Utah. Google had been considering expanding to as many as nine metropolitan areas. In a blog post Tuesday, Google said it was still in talks with five of those cities — Phoenix, Portland, Salt Lake City, San Antonio and San Jose — and would decide whether to expand into those regions later this year. Construction in the four cities the company named Tuesday will begin in a few months, according to Google.

The questions are:

1. Does Google have to get Franchises and pole attachment agreements in all of these places or is there some "deal" that goes around that and if so why? This is a total of 12 major cities. In my almost 40 years of experience getting a Franchise especially with an incumbent is a long and costly process. Avoiding one is a miracle, namely very few miracles really happen, if any.
2. At the same time Google is buying in to wireless. As we have argued wireless is much less expensive, requires no franchise, is already enabled by customers and has near equal capacity. So why waste billions on fiber? Do the shareholders care?
3. What is the Google strategy and what are its goals? It appears that they can afford to play many games. But to what end? They can control the distribution channel but then what?



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

MONDAY, JANUARY 26, 2015

THE INSANITY OF QUALITY

[HHS](#) is mandating payment for quality for Medicare reimbursement. Specifically they state:

In a meeting with nearly two dozen leaders representing consumers, insurers, providers, and business leaders, Health and Human Services Secretary Sylvia M. Burwell today announced measurable goals and a timeline to move the Medicare program, and the health care system at large, toward paying providers based on the quality, rather than the quantity of care they give patients.

I would remind folks that in Zen and the Art of Motorcycle Maintenance that it was the attempt to define quality that drove the prime character insane. Quality is complex and near impossible to define no less measure.

They continue:

HHS has set a goal of tying 30 percent of traditional, or fee-for-service, Medicare payments to quality or value through alternative payment models, such as Accountable Care Organizations (ACOs) or bundled payment arrangements by the end of 2016, and tying 50 percent of payments to these models by the end of 2018. HHS also set a goal of tying 85 percent of all traditional Medicare payments to quality or value by 2016 and 90 percent by 2018 through programs such as the Hospital Value Based Purchasing and the Hospital Readmissions Reduction Programs. This is the first time in the history of the Medicare program that HHS has set explicit goals for alternative payment models and value-based payments.

Note that the goal is 85% to quality. [We have written](#) extensively on this topic and its complexity. The ability to deliver anything like a quality measure is not only problematic but we believe impossible. It is merely a Government plan to cut costs and ration service.



Labels: [Health Care](#)

WEDNESDAY, JANUARY 21, 2015

[WHY ARE ECONOMISTS SO, WELL JUST IGNORANT...?](#)

I read a piece by a [Stanford Economist](#) who is alleging that one should not allow Common Carriage over the Internet Transport companies, such as CATV companies. He alleges:

Under net neutrality, Owen said, Internet service providers are unlikely to offer costly service improvements to anyone if they cannot recover the costs. "At least on the surface, it seems that net neutrality would condemn all users to the same not-terrific and slow-to-improve service," he said. By the end of the 20th century, Owen said, a broad consensus developed among economists that price regulation of industries was unlikely to improve consumer welfare. "Maintaining efficient prices and providing incentives for progressive management of regulated firms rarely works," he wrote.

Now admittedly he is at Stanford, and down the street a way are all those app companies etc but he is an economist after all, so we cannot expect much regarding technical reality.

You see the Internet was designed and is looked at as an hourglass, thin in the middle, limited capabilities, just allowing say TCP/IP. The smarts were at the edge, then end, with the users. That has worked for a real long while. The problem is that we have allowed the CATV folks to get between the TCP/IP path and the end users. That is against the prime directive, that is what the argument concerning Internet Neutrality is all about. Imagine a world with only MSNBC, and you have Comcast's view of life.

By making the carrier a Common Carrier they do what they are supposed to. Common Carriage

does not mean rate regulation, never did, only in the minds of those who fail to understand it. It means openness and level playing fields, etc, those catch phrases so common in DC.

The Internet is meant to be minimalist and not really pay attention to what is being sent across it. Each packet is equal. Each packet gets charged the same. Competition helps, but frankly until the wireless companies get their acts together we are left with 1970 technology from CATV companies. Remember that we change out our mobile devices at least every other year while the average age of a cable modem is 10+ years. They have NO motivation to innovate. So why should they be motivated to do anything other than take actions to further disable their customers. The only answer is Common Carriage, as Elizabeth I set up in 1603!

But also from an economics perspective, why should we tolerate bundling. CATV companies are notorious for that. We all understand that, we should pay for what we get from them, transport to a meet point. Tell me what it is and don't get in the way! Simple economics, simple antitrust. But not simple for some folks.



Labels: [Internet Neutrality](#)

TUESDAY, JANUARY 20, 2015

[TRUST FUND KIDS VS COMMUNITY COLLEGE](#)



Fortunately I managed to go through college by means of scholarships, jobs, and no loans. Also I ate a lot of rutabagas and drank a lot of powdered milk. No car, no phone, one pair of shoes, never thought I needed two, and books were still cheap.

Nowadays college is a fortune and kids cannot get scholarships as a result of academic performance, they must conform to some politically correct formula to fit the scholarship route. So no matter how well you did, welcome to paying full freight. And most likely bearing that load for years.

Now at the other extreme is Community College. I actually went there for a year recently. I was denied entry initially because I was over 65, until I informed the EVP of Equal Opportunity that the law applied to us old folks as well. Amazing what sending them a copy of the law will do.

Then of course they demanded all my school records, High School, College, Grad School, Post Grad, Professional School, and then I was admitted. If I had a GED it would have been easier but I guess they just did not want some old educate guy there. Then the instructor asked whether I was qualified and his response was I was one of those over achievers. I guess it was not an actionable response.

Lesson learned from Community College was that 90% of the students failed to complete the course. Yet they all paid the tuition, most via Pell Grants. Namely we taxpayers footed the bill. Why did the drop out? Jobs, poor preparation, no support infrastructure, etc. Furthermore at Community College the instructors are marginal at best. Better than those I had at Manhattan College, there I was asked to teach Freshman Calculus and Sophomore Systems Theory. In the first case the instructor was terrified of the students and in the second the instructor admitted he had no idea what the subject was, he was a structural engineer. But at Community College the Instructors may have a modicum of understanding but their approach is akin to a low tier High School. For example Biology gives 100 question multiple choice questions. Pure memorization, no understanding.

Now to the increase in inheritance tax. If I were to generation skip and leave the money to my grandchildren then the tax increases. The proposal is if they work hard and get great grades but because of who they are cannot get a scholarship but I would like to help them, then the Government will take 60% of my funds and give it to the 90% in Community College who never graduate! Smart, it is not!

I continue to wonder what is in the minds of those who come up with this scheme. Destroy those who perform well and create mediocrity. Well it looks that way to me.



Labels: [Politics](#)

SATURDAY, JANUARY 17, 2015

[ECONOMISTS: WHAT VALUE ARE THEY?](#)

Over the years we have been quite critical of economists. They hold themselves out as practitioners of some scientific discipline yet their recommendations are often in conflict with one another and their ability to forecast is dismal. As [some economist](#) has recently noted in the defense of his practice of the art:

Since the global financial crisis and recession of 2007-2009, criticism of the economics profession has intensified. The failure of all but a few professional economists to forecast the episode – the aftereffects of which still linger – has led many to question whether the economics profession contributes anything significant to society. If they were unable to foresee something so important to people’s wellbeing, what good are they? Indeed, economists failed to forecast most of the major crises in the last century, including the severe 1920-21 slump, the 1980-82 back-to-back recessions, and the worst of them all, the Great Depression after the 1929 stock-market crash. In searching news archives for the year before the start of these recessions, I found virtually no warning from economists of a severe crisis ahead. Instead, newspapers emphasized the views of business executives or politicians, who tended to be very optimistic.

It was not a failure of a few but a failure of a community of them. Does the art of economics lend anything useful to society? The defense of that question is in the following quote:

But this criticism is unfair. We do not blame physicians for failing to predict all of our illnesses. Our maladies are largely random, and even if our doctors cannot tell us which ones we will have in the next year, or eliminate all of our suffering when we have them, we are happy for the help that they can provide. Likewise, most economists devote their efforts to issues far removed from establishing a consensus outlook for the stock market or the unemployment rate. And we should be grateful that they do.

This statement is unfair to physicians. Physicians do recognize the problems their patients will face and often cannot do anything. Just look at obesity. It leads to a plethora of disorders but try and get someone to diet. Just like Congress.

In reality Economics should be compared to Civil Engineering. Now observe:

1. Civil Engineers have building codes based upon facts.
2. Civil Engineers have a science they all agree to. Try and get two Economists to agree on anything. They are the nastiest bunch I have ever seen. And each one has at least two opinions on everything and there is no concurrence.
3. Civil Engineers get sued if the bridge they designed falls. Ever hear of an Economist getting sued for anything? Physicians get sued, even lawyers get sued. But Economists, no jury could ever understand them anyhow.
4. Civil Engineers design and build bridges. The bridges work, they do what they were supposed to, unless of course politicians get in the middle. Economists cannot predict anything with the same sense of accuracy. Economists have lots of equations and theories. Civil Engineers have a few thousands of years of experience.

Imagine what would have happened to an Economist in Imperial Rome!

So please, until economists can agree on their "laws" and take responsibility for their failures they are at best witch doctors who somehow make a lot of money.



Labels: [Economics](#)

FRIDAY, JANUARY 16, 2015

[CANCER STEM CELLS AGAIN](#)

There is an interesting update on cancer stem cells in [Science](#). They write:

THE CANCER STEM CELL model emerged in the mid-1990s, when stem cell biologist John Dick of the University of Toronto reported that his team had isolated rare cells in the blood of

people with leukemia that seemed to play a key role in the cancer. Although such patients' blood teems with aberrant white blood cells, only a few of them were capable of growing into a new leukemia when injected into mice. Those cells appeared to be misguided versions of the normal adult blood stem cells that differentiate into mature blood cells. Like normal stem cells, the cancer stem cells carried distinctive surface proteins and were self-renewing: They could divide to produce both a regular cancer cell and a new stem cell.

Now many researchers have examine the stem cell model and there are reasons for its validity. We have argued for Prostate Cancer and one suspects for hematologic cancers such as MDS. The article focuses on Weinberg at MIT and his new company where the authors state:

Verastem's strategy is to screen approved drugs and other chemicals for their ability to block focal adhesion kinase (FAK), an enzyme that helps tumor cells stick to each other and also helps cancer stem cells survive. In the body, Weinberg believes, blocking FAK kills cancer stem cells directly and also makes it harder for these rare cells within a primary tumor to travel through the bloodstream and seed metastases.

It should be interesting to see how this develops. Perhaps our understanding of the stem cell is not mature enough. It has also been argued that the stem cell uses exosomes to cause growth in other cells. There is still a great deal to understand.



Labels: [Cancer](#)

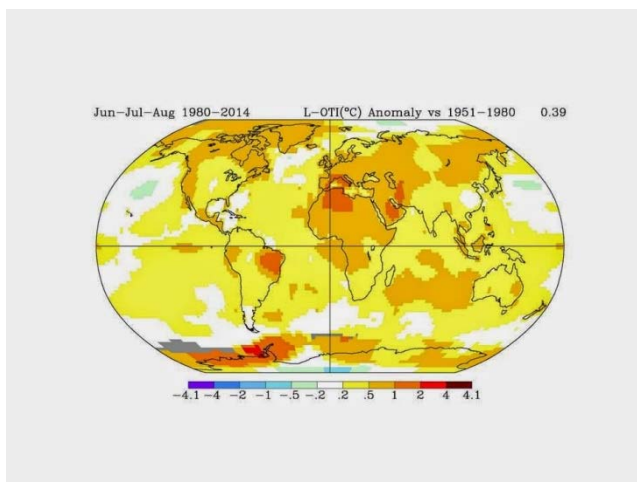
FRIDAY, JANUARY 16, 2015

[CLIMATE AND HOT SUMMERS](#)

[NASA](#) has announced that last summer was the hottest on record. Well I would beg to differ, at least my plants tell me so. NASA states:

The year 2014 ranks as Earth's warmest since 1880, according to two separate analyses by NASA and National Oceanic and Atmospheric Administration (NOAA) scientists. The 10 warmest years in the instrumental record, with the exception of 1998, have now occurred since 2000. This trend continues a long-term warming of the planet, according to an analysis of surface temperature measurements by scientists at NASA's Goddard Institute of Space Studies (GISS) in New York. In an independent analysis of the raw data, also released Friday, NOAA scientists also found 2014 to be the warmest on record.

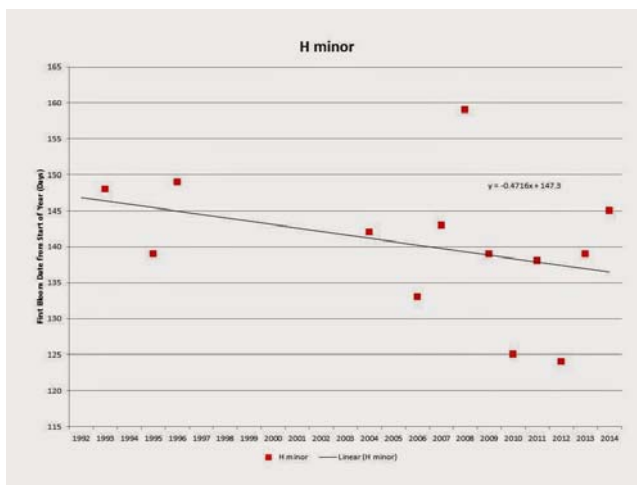
I ran their [map program](#) and obtained the following:

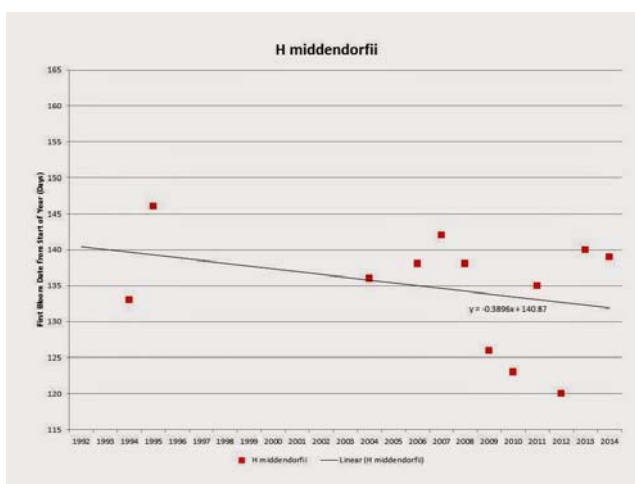
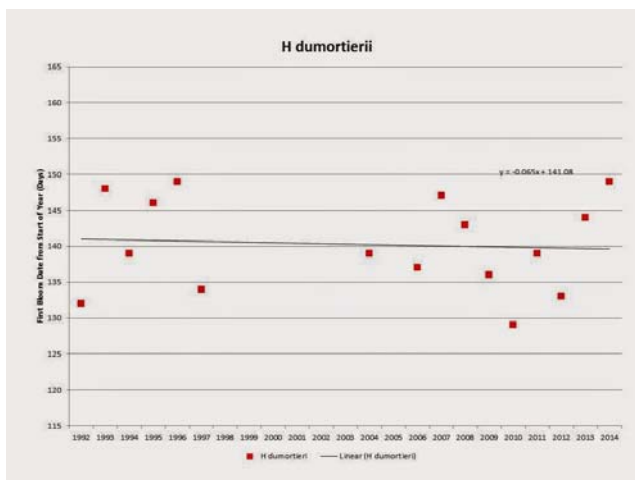


Now if one looks closely one sees that my area was not really that hot. It was Europe, East Russia and Canada that were hot and parts of Brazil.

Let us examine my backyard. Yes my very nice backyard, and my sentinel plants the *Hemerocallis* genus.

First we look at the date of first bloom on the three early species:

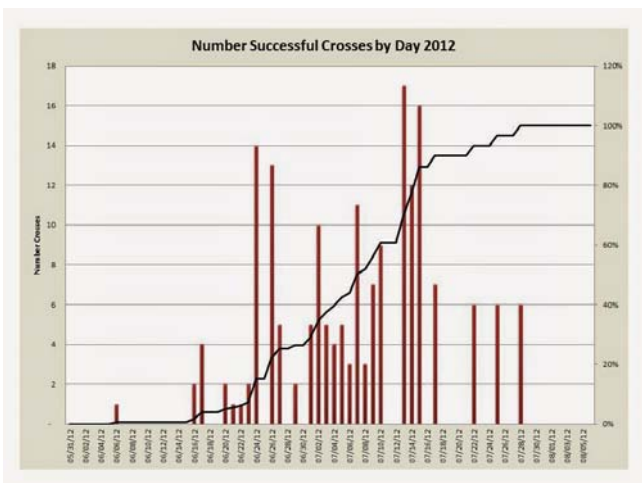
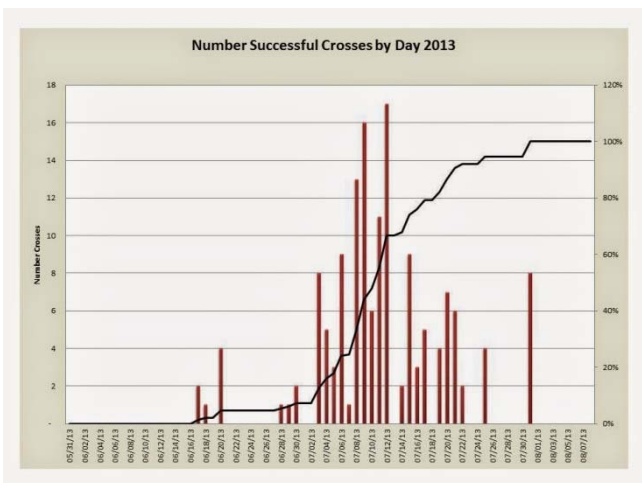
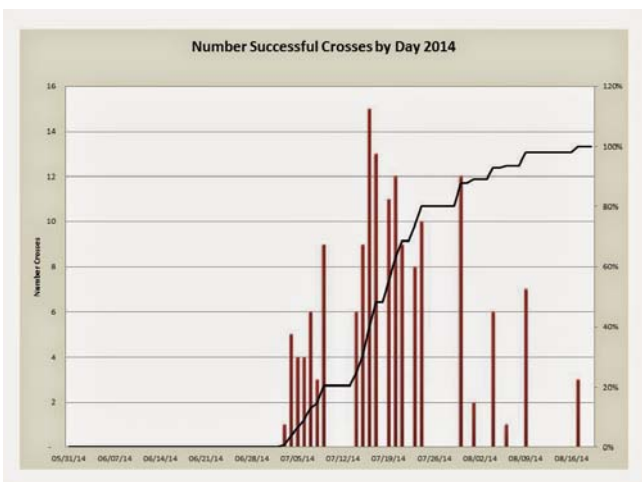




Now what we have plotted is the date of first bloom where the date is the number of days from January 1 until the bloom date. Thus the larger the number the colder the season. A downward sloping line means warming. H minor going back to 1990 shows warming. But last years was the 4th coldest in 25 years. Not the warmest. The same can be said of the other two species but H dumortierii shows little evidence of warming.

Why plants? Well plants integrate climate over a year. They reflect what is happening in an integrated manner. They are better than surface measurements.

Now I looked at the date of mid cross. This is the date when I had reached 50% of my total crosses. It is an integral of an integral if you will. It looks across all hybrids and tells when the peak blooming occurs. The results are below:



Again 2014 was not bad. The 50% point was about July 19th. In contrast 2013 had July 8th, almost 10 days earlier. Also 2012 showed a date of July 7th. Thus from my few thousands of plants perspective 2014 was one of the coldest years on record.

I guess one really should look at the data. Plants are great creatures. They use the sun more than

any other creatures so why not use them to tell us something. The reason is we really have so few Botanists. Perhaps we need a few at NASA.



Labels: [Climate Issues](#)

SUNDAY, JANUARY 11, 2015

[ENTREPRENEUR?](#)

The [Harvard Crimson](#) reports on a rather strange offer. Namely:

When edX courses Entrepreneurship 101 and 102 opened Friday, enrollees had an extra incentive to complete the courses: Users who pass either class will receive \$1,000 in credit to spend on Amazon Web Services.

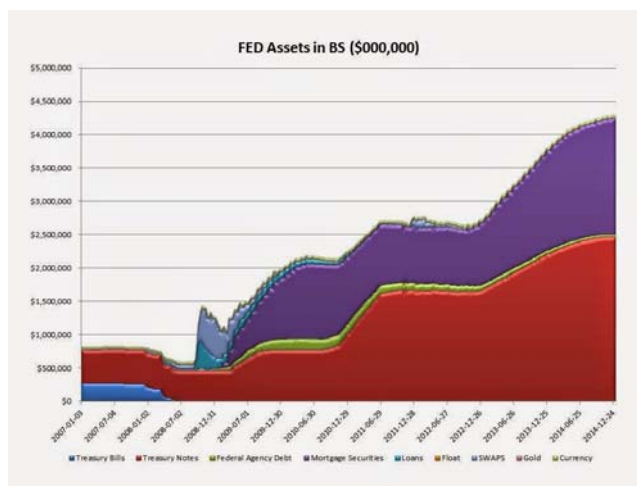
This is the ultimate in Millennial mindsets. Not only do they want to do something they like, or rather not work, but now they get "paid" to become an entrepreneur! You cannot make this up. Perhaps they should just skip everything and go directly to an IPO and cash out.



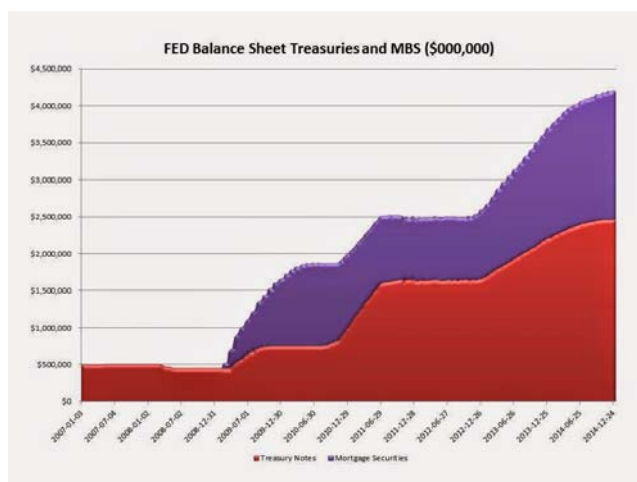
Labels: [Academy](#)

[FED BALANCE SHEET](#)

As of this week the [FED Balance](#) sheet is seen as below:



In some focus the two main items are Treasuries and MBS. This we show below:



Both seem to be flattening out as compared to a year ago. This is the case for the MBS, and the Treasuries have flattened. One expects some unwinding will occur. This will put pressure on rates although world conditions may keep them low.



Labels: [Economy](#)

[THE NEW MATH AS POLITICS](#)

The New Math, by Phillips, is subtitled as a “Political History”. The New Math movement was an attempt to rejuvenate the teaching of mathematics in secondary schools and ultimately in the Primary schools. To the proponents of this movement there was staleness in the teaching of mathematics which was reflected in their belief that it was merely an exercise in memorization and lacked any true understanding of the elements of mathematical thinking.

For example, most elementary school students had memorized multiplication tables, learned fractions and division as a mechanical process, and dealt with “word problems” with abject terror. Mathematics was taught as if it were some mechanical set of processes that one set to memory and the students failed to have an understanding of what they were doing.

On pp 13-15 the author provides some baseline information on the creation of the New Math. The intent was to imbue understanding of what they student was doing not just a set of rote manipulations to produce an answer. There was an abject fear that memorization was futile and that the expression of what the processes were became the goal. Students must learn why they could multiple 3×2 and then $3 \times 2+4$ and find an answer. They must understand the processes of manipulations, at the risk of never memorizing that 3×4 are 12.

On p 27 the authors also discusses some of the political movements pressing for improvement. It mentions Rickover and Doolittle as applying their influence to promote improved education due to the need seen in WW II to “educate” many enlistees to be able to perform what were technical tasks. For example, to train an enlisted sailor in Fire Control Systems or in Radio or Radar, there was a prerequisite in understanding Geometry, Algebra and Trigonometry. Many schools never

taught the skills to students, and thus the need to re-educate. Thus on one hand the need was to have a better baseline education and on the other hand to attempt to emphasize fundamentals as the core of that education.

What then were the principles? It all depended on whom one spoke with. What happened was that a group of “mathematicians” saw that they needed understanding of set theory, complex rules of algebra, base n systems of numbers and the like. This then changed the core of many of the courses.

The attack then also went to the teachers themselves. Teachers were all too often the product of teachers colleges, often state run institutions, to produce individuals to manage the utilization of the state mandated texts and managed by state mandated exams. The Regents of the State of New York was in many ways a classic example. Geometry was defined by them and each instructor taught that material.

The author on p 31 refers to Hofstadter and his book on “anti-intellectualism” and the argument that teachers had become “estranged” from academia. In reality the Hofstadter book is a polemic of a Columbia Professor against what he perceives is the “anti-intellectuals”, namely the Republicans, Catholics, and anyone opposed to his politics. In Hofstadter’s book on pp 138-141 is one of his many rants against Catholics and the Church, ironically because the intellectual were also strong supporters of Kennedy.

Thus the intellectualism at Columbia and of Hofstadter was at best problematic and use of the author of Hofstadter as a baseline is also problematic. Likewise, for example, on p 394 of the anti-intellectual treatise of Hofstadter, Hofstadter calls the Partisan Review the “house organ” of the “intellectuals”. It is in William Barrett’s writings of his time at the Partisan Review that he noted is strong Communist bent. Thus, using Hofstadter by the author is an attempt to set up the New Math as the “intellectual’s movement” and then subsequently to use this as the basis for arguing that its demise was the result of some right wing attempt to defeat it appears as a bit of a straw man strategy.

One of the problems I have is that the author fails to clearly identify what he means by New Math and what the New Math was. In a classic paper by Feynman in 1965 criticizing the New Math he states:

Many of the books go into considerable detail on subjects that are only of interest to pure mathematicians. Furthermore, the attitude toward many subjects is that of a pure mathematician. But we must not plan only to prepare pure mathematicians. In the first place, there are very few pure mathematicians and, in the second place, pure mathematicians have a point of view about the subject which is quite different from that of the users of mathematics. A pure mathematician is very impractical; he is not interested - in fact, he is purposely disinterested - in the meaning of the mathematical symbols and letters and ideas; he is only interested in logical interconnection of the axioms

This was the problem of the New Math. A radar technician does not need to understand set theory to understand the probability of a false alarm and the signal to noise ratio. Specifically Feynman states:

What is the best method to obtain the solution to a problem? The answer is, any way that works. So, what we want in arithmetic textbooks is not to teach a particular way of doing every problem but, rather, to teach what the original problem is, and to leave a much greater freedom in obtaining the answer - but, of course, no freedom as to what the right answer should be.

Feynman, a product of the New York City School System, and then MIT and Princeton, is correct. His own technique was to intuit the answer and then find the framework to support it. I doubt he ever used a single element of set theory. The conclusion even in 1965 was the core of the New Math was flawed as a pedagogical approach. It in fact was intellectualism gone astray.

On p 103 the author describes some of the texts which resulted from this effort. Take the Moise and Downs text on Geometry, and compare it to text by Wells in 1908. Wells was brief and to the point and one walked away understanding enough geometry to measure angles, understands triangles and the like. The Moise and Downs book makes the development of Proofs impossible. The simple example on pp 190-191 (of the 1982 edition) is a classic obfuscation of the obvious, a proof of the existence of a perpendicular line.

Kline also discussed the shortcomings in his superb book “Why Jonny Can’t Add” Mathematics is a tool for almost all of its users. It is “learned” by application. No user of an Excel spreadsheet would benefit from the New Math.

The author then proceeds to discuss the political opposition from the right to New Math and the Back to Basics movement. On p 145 he opens the Epilogue with the statement “Opponents of the new math won.” In reality the weaknesses of the New Math caused its own demise. With the like of Kline and Feynman against it than what chance would it have? It just did not work.

The last sentence is also worthy of comment:

“Yet math classroom will remain a political venue as long as learning math counts as learning to think. Debates about American math curriculum are debates about the nature of the American subject.”

It is not clear to me what he means by the phrase, “*nature of the American subject*”. Is subject the material taught, the individual, some broader idea not explained?

Overall this book has two tales. One is the intended one of the birth and death of the New Math. It has not totally died but still is found floating around a bit. It is also a tale of pedagogy in the state run schools and who decides what students must know and why they must know it. For most of us, mathematics is a tool, it is a way to express facts and explore reality. My day is often driven by mathematical realities, albeit those of an engineer, pedantic, utilitarian, and lacking in questioning principles. I assume solutions exist; I do not really pay attention to uniqueness theorems, and use them as a tool kit to gain knowledge. Almost all who rely on mathematics do

so. The pure mathematician asks fundamental questions, questions about fields, convergence, existence, measurability and the like. They do affect reality from time to time. But rarely, yet when they do the impact is significant, just look at the analysis of the Wiener Process in dynamic systems, and the Ito integral.

However, for the most part we want students to understand technique, to a point. Out of the mix will come the engineers, physicists, and yes the mathematicians, the very few mathematicians who have the unique capabilities to abstract thinking.

Overall the book is a reflection of the political processes surrounding education. This has been all too common especially since the advent of Dewey and the education movement he was so prominent in. This book is a useful exercise in grasping with the tendencies to make material relevant on the one hand and a facilitator to understand society for good citizens on the other. The book has certain weaknesses but it also has certain positive points. It allows one to see how the arguments can be made. One may then ask in a similar fashion; if these same arguments and this same process will follow through with Common Core?

The book also shows the break between the academic practitioners and the practitioners who teach the subjects. At the University level we still see a great deal of freedom. At MIT for example courses change on almost an annual basis as the technology and science progress. The need for "standards" is non-existent. At the secondary level this is hardly the case, due to the size and complexity. That perhaps is worthy of a similar study.

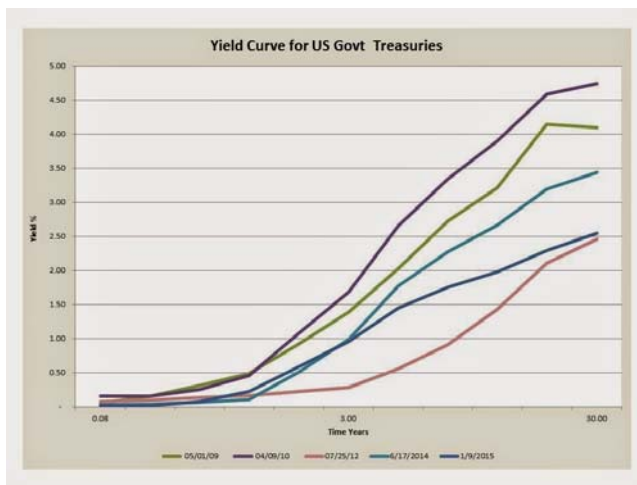
But one of the important observations here is the movement of "protected" groups like the "mathematicians" who may very well have been used by political operatives to gain deeper control in schools. As indicated colleges and universities are somewhat protected. But if the Government extends its control to Community Colleges we can easily see the movement of Washington control to move there. That may very well be the unintended lesson of this book. Namely, beware the Politician, they ultimately want to control everything,



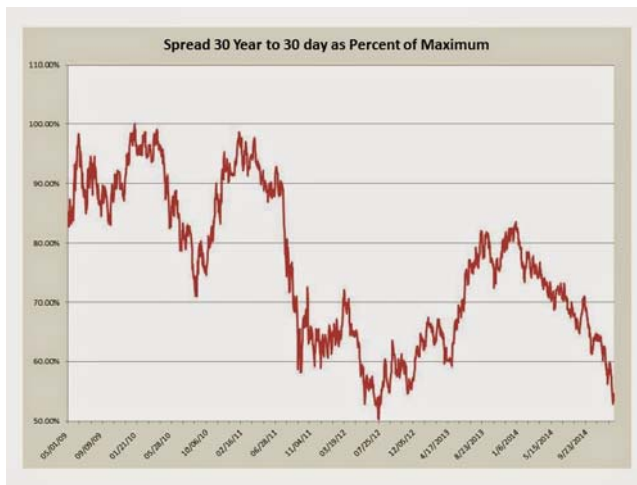
Labels: [Academy](#), [Books](#), [Politics](#)

SATURDAY, JANUARY 10, 2015

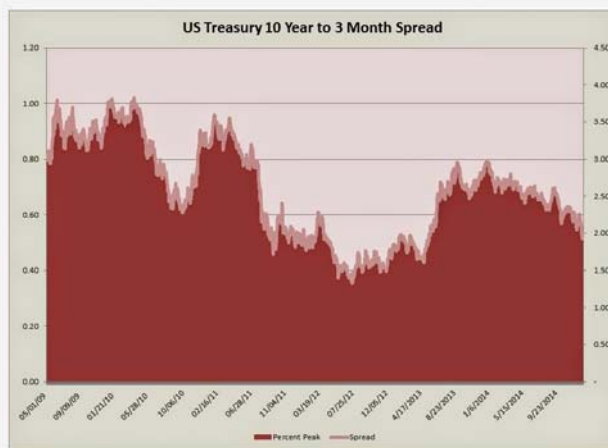
TREASURY SPREADS JANUARY 2015



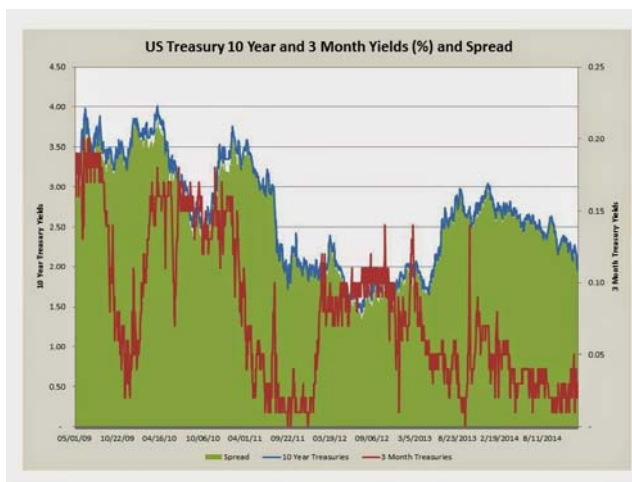
The above are a few yield curves from the past five years. Note that as of yesterday the yield is dropping to one its lows for 30 years. Also note that the curve is starting to slope upward, showing higher yields at lower durations. There is doubt of getting to an inverted yield curve again but one can wonder.



The above is the spread of 30 day to 30 year, the maximum spread. It is approaching a long term low again.



The above is the 90 day to 10 year spread. It is far from a low and this reinforces the above conjecture.



This shows the dynamics of the details of the previous curve. One suspects that with the employment rates we could see the FED making a change but again we must examine the FEDs Balance Sheet. We will do this tomorrow.



Labels: [Economy](#)

[MOOCS AND RESULTS](#)

In a recent article in [Science](#) there was a discussion about obtaining performance data from MOOCs. Two things struck me:

1. The fact that it seems that there was limited if any thought as to how well they MOOC performed. One suspects that performance measures would have been at the heart of the effort. Namely is all this money worth it, and worth what? Apparently not.
2. Also the article in my opinion seems to ramble almost everywhere except in articulating any semblance of content or context. One wonders what the purpose of all those words were.

For example:

Using engagement data rather than waiting for learning data, using data from individual courses rather than waiting for shared data, and using simple plug-in experiments versus more complex design research are all sensible design decisions for a young field. Advancing the field, however, will require that researchers tackle obstacles elided by early studies. These challenges cannot be addressed solely by individual researchers. Improving MOOC research will require collective action from universities, funding agencies, journal editors, conference organizers, and course developers. At many universities that produce MOOCs, there are more faculty eager to teach courses than there are resources to support course production. Universities should prioritize courses that will be designed from the outset to address fundamental questions about teaching and learning in a field. Journal editors and conference organizers should prioritize publication of work conducted jointly across institutions, examining learning outcomes rather than engagement outcomes, and favoring design research and experimental designs over post hoc analyses. Funding agencies should share these priorities, while supporting initiatives—such as new technologies and policies for data sharing—that have potential to transform open science in education and beyond.

OK, now try to parse this one. First what is engagement data? Second what is learning data? I have now played around with over a dozen MOOCs. Some are good, most are horrible. My last attempt was a Materials Science course at MIT. The lectures were spent watching the instructor write the lecture notes, which we had, on a large chalk board in total silence except for the clicking of the chalk. So why? Second the tests were really tests in reading comprehension, did you use the right units, and did you copy the value properly. Any errors were errors of transcription and not comprehension. How is that measured?

Frankly it seems that MOOC management has been stumbling around in some directionless manner. If there is no way to determine what the "return" on the investment is then why invest.

Now the biggest problem I have with MOOCs is the discussion functions. In my experience I saw anonymous discussants who were a few steps from shall we say rather anti-social actions. The article states:

The most common MOOC experimental interventions have been domain-independent "plug-in" experiments. In one study, students earned virtual "badges" for active participation in a discussion forum. Students randomly received different badge display conditions, some of which caused more forum activity than others.

My experience, and anyone seeking proof need look no further than any anonymous discussion on the web, is that it facilitates the worst and possible near real anti-social behavior. Why would anyone want to participate. I tried once to make an observation and some, in my opinion, socially in-adept person made comments that had me remove my remark. The remark from another made one shudder! Then there is the near diabolical "peer review" method of having people who know nothing from disparate cultures attack others work. One wonders who invented that scheme!

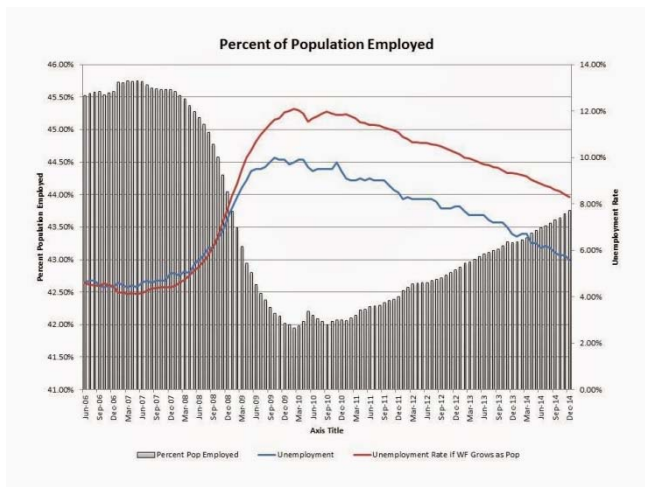
Thus one may wonder if the writer of the piece has had any hands on experience. Apparently from what is written the answer is they have not. Yet the ability to measure effectiveness is critical. When will someone credibly address that issue?



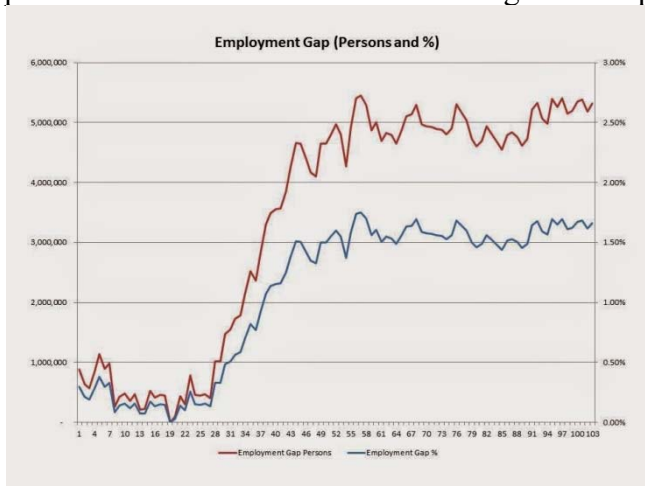
Labels: [MOOCs](#)

SATURDAY, JANUARY 10, 2015

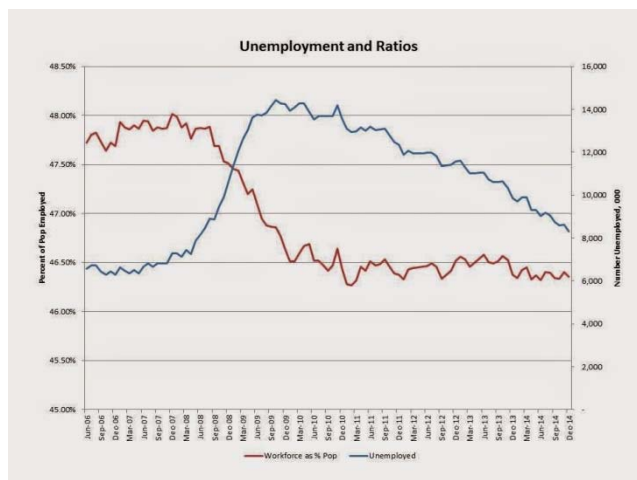
EMPLOYMENT JANUARY 2015



Let's start with the standard chart. Yes the DoL report says 5.6% but if one were to use the baseline of 2006 participation rates it is still above 8%. Although we see participation increasing.



The chart above should be the concern. We have a lower participation rate or higher gap, there are now millions permanently unemployed. That is and should be the concern. Frankly not only is there no change in that number but it appears to be increasing.



The above demonstrates that concern.

Thus overall things are getting better but the permanent gap is a real ongoing concern. It appears that at the older end we have lost people permanently and at the lower end the young millenials want meaningful work rather than a job. That is the real problem.



Labels: [Economy](#)

SUNDAY, JANUARY 4, 2015

WORDS MEAN SOMETHING

From today's NY Times weather map of 2014 they make the following statement:

The average temperature for the year was 54.5 degrees, 0.5 degrees below normal, which makes 2014 tied for the 56th-warmest year since 1869.

Now just think a bit:

1. The temperature was 54.5 and that was 0.5 below normal, call that average.
2. Then 2014 is tied for the 56th warmest year since 1869.
3. If it is below normal, say average, median or mean, then it means that half are above.
4. If it is since 1869 we have 145 years of data and assume that there are other ties, possibly even triplets.
5. Then if all were ties there would be 72 years of data and being 59th makes sense but calling it the warmest in any measure is nonsense. The words just do not match.
6. How does it rank as coldest? I guess it is politically incorrect to ask such a question in front of

the NYT readers?

This is a clear example of the duplicity in the discussion about climate, change or otherwise. Political correctness dominates facts. Pity.



Labels: [Global Warming](#)

[PROSTATE CANCER MARKERS](#)

The [MAC](#), has just announced reimbursement for three prostate cancer genetic tests. As [OneLive](#) states:

After months of delay, the Medicare Administrative Contractor (MAC), with jurisdiction over most molecular diagnostic tests used to treat cancer, made a series of decisions this fall that will allow Medicare reimbursement for several well-known tests, including 3 used in the treatment of prostate cancer.

Specifically the tests were:

1. [ConfirmMDx](#) by Oral Oncolytics which is a methylation test. We considered this in [WP 116](#).
2. [Prolaris](#) by Myriad which is a complex gene test which we considered in [WP 107](#).
3. [Decipher](#) by GenomeDx which is akin to Prolaris.

The methylation test has interesting merit and the others seem correlative at best. One of the problems of prognostic tests as to more aggressive PCa is just what does one do next?



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

SATURDAY, JANUARY 3, 2015

[A WORTHWHILE CONTRIBUTION](#)

[Medieval Christianity](#) by Madigan is a very readable and comprehensive book covering Western Europe from about 500 AD until 1400 AD, albeit edging down to 150 and up to 1500 at its extreme. The book is well balanced, well researched and accessible to all readers. The title also states it as “A New History” but just what is “new” and “well known” is not as clear perhaps as the author may have desired. Notwithstanding, what the author has presented is useful for the newly informed as well as the “well informed”.

The author starts with a brief discussion of early Christianity from 150 to 600. This has as its center piece Augustine and his writings. One of the most difficult problems with early Christianity is the complexity of Greek thought and the Eastern Church and the slow evolution of a Western Church. Southern has examined this in detail and it is the complexity of Eastern thought which in many ways was a departing point for the west and it was its abandonment by

Augustine via his Roman way of thinking that opened the Western Church and what we now think of Medieval Christianity. Augustine introduced many ideas in a manner that reformed Western beliefs. His battle with Pelagius is clearly one and his emphasis on grace another.

There is an interesting discussion on p 29-30 on when this stage of early Christianity ended. One way to pinpoint this change perhaps is the time of Gregory I. The reason is that at this time Gregory breached with Byzantium by severing with the ruler in Ravenna and taking both religious and political control in Rome.

The author's discussion on Gregory is very limited in scope and here I would fault the author for an opportunity to use this figure as a major break point for the establishment of the Western Church (see pp 45-62). It can be argued that it was Gregory who de factor created Medieval Christianity.

The Bishop of Rome in 600 was still just that, the Bishop of Rome. The Emperor in Constantinople was a de facto head of the Church, calling various Councils to discuss major religious issues. Gregory had been in the court in Constantinople, had been Mayor of Rome, had come from an old line Roman family and desired to be a monk along the lines of Benedict. However he was drawn to the Bishop of Rome slot by the people of Rome who required his leadership.

Also Gregory was looking westward, seeing Constantinople as an aging confluence of political intrigue. Thus by looking west his communications with the Merovingian queen Brunhilda is a classic example of Rome becoming *pari passu* with leaders and influencing them via religion and charm. On the other hand the likes of Brunhilda were brutal to the point of savagery and Gregory seems in his writing to have avoided discussion of these facts. Likewise he dealt with the Lombards as well as sending the Italian Bishop Augustine to England. This latter act however can be viewed as an affront to the Irish who were still adhering to the Eastern Church ways and saw Gregory as an equal in debate. In essence Gregory set up the conflict between Ireland and England. But it was Gregory and his looking westward rather than Eastward that made for the seminal start of the Medieval Church.

In this section it would have been useful to explore in some detail the lengthy discussions between Columbanus and Gregory I. There was but a brief mention on p 48 of Columbanus. First the Latin of Columbanus, the Irish monk, was dramatically different from Gregory. Gregory had evolved to almost a koine type Latin while Columbanus seems to have retained almost Ciceronian Latin. The Irish monks had learned Latin almost independently from Rome based upon classic texts and this in a way strongly influenced their style. In addition Columbanus and all the Irish monks had never been under the Roman yoke and thus in dealing with Rome they dealt with them as almost an independent thinker.

Chapter 4 introduces Charlemagne. Charlemagne was a follow on to the Merovingians, albeit the descendent of a Merovingian court official. Charlemagne in 800 gets coroneted by the Bishop of Rome, now viewed as both a religious figure and putative political player.

Chapter 5 deals with the parochial life. There was a local parish alongside the monastic monasteries. The local priests were typically less well educated than the monks who spent much of their time reading and writing. In contrast the local parish priest was dealing with local matters of lesser import. Chapter 6 deals with the Jews, an issue always made complex, especially in the West. Chapter 7 considers the Crusades and Islam. A great deal has been written on crusades and this presentation is brief. The complexity of the expansion and acceptance of Muslim beliefs was often seen by the Christians as another heretic sect, especially their belief in polygamy. There did not seem to be any attempt to “understand” their thought throughout this period.

Starting in Chapter 8 the author moves to what he calls the era of High Medieval Christianity. This is from 1050 through 1300. There is a discussion of the reforms to what had become a Church with many small faults, and this included Rome itself. By this time Rome had clearly become a Papacy in terms of its singular position. Chapter 10 discusses some of the heretical movements during this early period of the High Medieval Church.

Chapters 11 and 12 present the Dominicans and the Franciscans respectively. Whereas the Dominicans were always positioned as intellectually elite, Aquinas was a Dominican, the Franciscans presented a possible threat to Rome, and they advocated a return to early Christian belief of poverty. However Rome managed them quite well and the net result was a Franciscan order that was on a par with the Dominicans and in a sense often superior. One needs look no further than Ockham and his Franciscan followers.

The author then details many of the elements of religious life and affairs. At this time the Church was becoming a dominant part of the lives of the people.

On pp 262-266 the author presents Abelard and Heloise. This is one of the classic tales of this time. This is one of the best descriptions and one in context that I have seen. This alone is worth reading.

On pp 277-283 there is a brief discussion on Aquinas. I would have liked to see a more detailed presentation. Aquinas became a figure of the Aristotelian movement and after his death his works were banned by some but they came back in the 19th century and the basis of Church belief and doctrine. Some more detailed discussion of his work would have been useful. I felt his presentation was too brief in passing.

As noted, the author discusses Aquinas but fails to discuss Ockham, the Franciscan, albeit a brief note on the next to last page ((p434). Ockham was a nominalist, one who denied universals, and thus in contradistinction to Aquinas. Ockham also reinvigorated the idea of the Individual and as such was a catalyst for many works emanating from his. Also Ockham demonstrated confrontational intellectual opposition to the Avignon Popes resulting in his fleeing eastward and being supported by German Princes. Here is an example of quasi-national opposition to the non-Roman Pope, a conflict that was just starting to brew.

Late Medieval Christianity occurs from 1350 to 1500 and the author does a good job in details the key points. Again there are “heretical” movements such as Hus and Wyclif and the Lollards.

He discusses the changes and discusses Prague in some detail. Prague was a cauldron of religious dissent, as the statue to Hus demonstrates in the square of present day Prague, a statue I passed daily on my way to my office, ironically across from the house of Kafka! Understanding central Europe more would have been helpful in explaining this effect.

The Avignon papacy from 1309-1378 (pp 374-378) blends Middle and High Medieval Christianity and represents a clear distortion of the Bishop of Rome and the attempted, and in many ways total, control by the French throne over the Pope. Here we have most likely the first instance of having a Pope as a separate entity from the Bishop of Rome. For centuries before this, when the Pope qua leader of the Church was mentioned, the position was synonymous with the Bishop of Rome. In fact the true title should be Bishop of Rome, since that is the position of such a leader. It would have been helpful to have an expanded discussion on this topic. This period of fighting Popes has in my opinion left an indelible scar on the Western Church.

Overall this is a superb book and worth reading and rereading. The author builds upon Southern and his work as he indicates. However there are many other views of the issue he presents and space being limited his presentation is fair, well balanced, and exceptionally readable. In contrast one might also read, if available, the works of Henri Daniel-Rops (a pseudonym for Henri Tetiot) who albeit an apologist for the Church, has added insight on many of these issues discussed by the author.



Labels: [Books](#)

FRIDAY, JANUARY 2, 2015

[CANCER AND "BAD LUCK"](#)

I commented yesterday on the brief Science piece by Vogelstein and colleagues. In the past twenty four hours I have seen over two dozen news pieces from every continent, except Antarctica, pitching the "bad luck" tale. Even [China Daily](#) had the story on its front page! This is unfortunately now a typical response, no analysis, just repetition. The "bad luck" was in the abstract and they could not have chose a better phrase to get picked up globally.

Now the results are not ground shaking and "bad luck" is not a scientific phrase. In reality the authors just observed that certain cancers are most likely driven by specific genetic changes already known or by such personal life choices like smoking. The rest are really unknown.

We are learning more and more of epigenetic effects, such as methylation, that result from inflammation, which may be a result of some life style choice such as obesity. That has not been factored in, especially since breast and prostate cancers were not considered.

Thus the term "bad luck" may just be a "bad choice" but it does get Press. But is that what science it meant to do?



Labels: [Cancer](#)

THURSDAY, JANUARY 1, 2015

CANCER BY THE NUMBERS

There is always a novel attempt to garner information or patterns from data on cancer. In a recent [Science](#) paper Vogelstein and colleagues have done some interesting "back of the envelope" analysis. They did the following:

1. Collected data which provided the number of stem cells of a particular cells type in a typical lifetime of a person. For example they somehow determined from the literature the number of melanocyte stem cells in a lifetime. They did the same for many other cells. For example there are lots of basal cells per human lifetime, as one would expect. In contrast there were two orders of magnitude less melanocytes.

Let us call that NSC(i) where i equals a specific type of cell.

2. Then they plotted the incidence of cell related cancers versus the total lifetime stem cells by type. Thus we see that the incidence of basal cell cancer is high and so are the total number of lifetime stem cells of basal cells.

Let us call this INC(i) the incidence of a specific cancer related to the specific cell.

3. Then they created a normalized line through the incidence versus stem cell count curve and drew a chart of cancers how far below to how far above they were to the average line. This waterfall type chart then was the discussion point.

That is we have some generalized relationship:

$INC(i) = K \cdot NSC(i)$ where K is a common constant obtained from a regression type analysis. However the actual INC(i) may be above or below the regression line.

4. The cancers well above the norm were those driven by some putative genetic or environmental factor such as smoking and lung cancer. The rest are due the authors state to just having lots of stem cell mutations.

This if $INC \text{ actual } (i) > INC \text{ regression } (i)$ we attribute this excess to some genetic or environmental/lifestyle condition.

Interesting concept, but there are some issues:

1. Do they really mean stem cells? Melanocytes do not reproduce as quickly but it is not clear just what a melanocyte stem cell is. We have seen this in prostate cancers.
2. The authors admit epigenetic factors as well and one suspects that they could dominate.
3. The excess cancers such as smoking and lung are clearly environmental effects.

4. Some how there is no discussion of breast and prostate. One wonders why since they are so prevalent.

Otherwise this is interesting and worth the read. Their conclusion is:

These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes.

That is worth exploring. But, and this is a classic case, the Press has latched on to the "bad luck" phrase. We really do not know from this study what is the issue. Thus again we have a confluence of words by authors and the explosion of the press to enhance the piece. Frankly it is interesting but hardly conclusive of anything!



Labels: [Cancer](#)