12/1/2014

The Squirrel's Nest 2014

Terrence McGarty

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THE SQUIRREL'S NEST

MONDAY, DECEMBER 1, 2014

YOU HAVE TO PASS IT TO SEE WHAT'S IN IT!

As I bemoaned the ACA while it was in process, one of the things I was concerned about was the Law enabled Agencies to create the Rules. Most people think the Law is the Law, not really, the Rules are the Law and the ACA enabled the FDa, amongst other Agencies to come up with a real mess.

Take the FDA's own blog where they introduce the new food labeling law. They state:

The Affordable Care Act requires calorie and other nutrition information on menu and menu boards for consumers in chain restaurants and other "similar retail establishments" that sell restaurant-type food. In 2011, FDA issued a proposed rule (see our previous post here). FDA received 1,100 comments, many of which focused on the reach of the law. The final rule contains few of the accommodations that industry requested. Despite the many comments and legislative proposals to exempt certain categories of retail food establishments (see our previous post here), the final rule significantly broadens the definition of covered establishments by redefining "restaurants and similar retail establishments" and "restaurant-type food," and provides limited relief compared to the proposed regulation. The Federal Register publication of the final rule is 105 pages and will require careful analysis to assess its full impact and determine how compliance can be achieved. This blog post aims at identifying some of the notable aspects and differences between the proposed and final rule.

That 105 pages of Government speak detailing how restaurants must meet the labeling laws as promulgated under the FDAs reading of the ACA.

Will this reduce obesity? Hardly, ever see these porkys read the menus, just plop down and shovel it in. Go to any fast food place or better yet the chain restaurants prevalent at most highway drop offs.

What will this do? Increase the costs of food. Will it influence consumer food consumption? The answer is no, just look at the carriages of junk food at the markets which have had this information for decades.

The only thing to stop it is a financial cost. Namely those who are overweight or obese should pay a fine on a per pound or per BMI fraction. Take your pick.

But this is just a small example of how the ACA will seep like a pestilence into every pore of our existence, and to no positive effect, just increase Government control while costing us all more and taking money from the economy which could be better spent on creating jobs! Real jobs!

Labels: Health Care

SUNDAY, NOVEMBER 30, 2014

A GOOD IDEA DOES NOT A BUSINESS MAKE

Having spent the last couple of years amongst academic high tech folks, I have seen and heard about a lot of good ideas. However, what has surprised me, and it should not have, is that the "good idea" is believed to be all you need. Sales and operations, implementation and customer care are unheard of.

I think the cause of this is the rash of entrepreneurial help groups, on campus and off. The "shark tank" actors come up like carnival pitch men and have not a clue as to how the will build a full company.

In addition they also do not know that only 1% of the start ups are alive five years later and only 1% of them are a true financial success.

The best one I have seen is fathers taking "maternity leave" at the beginning of a start up! Two months leave and then restarting the process. Really, and that is just one of several of the antics we have seen.

The best thing I try to tell them is that a good idea is not a business. No matter how smart you are you have to have someone willing and able to buy it and more importantly you have to deliver it.

One would have thought with all the talk about the entrepreneur and creativity that the basic principles of the local candy store would apply. Sell the Dinky Twinkies to the kids, along with the grape soda....but make sure they have the money to pay for it. Having a store filled with stuff is not a business, unless you move the stuff...for money.

Labels: Commentary

THE INTERNET AND THE RIGHT

I am amazed how the right seems to totally miss the debate in Net Neutrality. Totally amazed. Take the Heritage Foundation, allegedly some form of conservative think tank. In a recent piece the author bemoans common carriage by saying:

He showed that earlier this month when — in an unusually deep wade into the decision-making process at the supposedly independent Federal Communications Commission — the president came out four-square in favor of imposing "common carrier," or public utility, regulation on America's Internet service providers. ... n spite of its style points, the president's policy fails on substance. Simply put, regulating the 21st century Internet under common carrier rules designed for railroads in the 19th century simply makes no sense.

First, common carriage goes back some 600 years, not 200 or less. Second common carriage does not demand regulation, just the opposite. It says the carrier must not discriminate. The

carrier sets a price for a capacity and that's that!

As it stands now Comcast sets the conditions and funds its political mouthpiece MSNBC! Are these guys at Heritage out of their minds! They want Comcast to decide what I see. The FCC would not do that under common carriage, just the opposite.

How dumb are some of these people....I forgot it is Washington...dumbness seems to be the condition of entry into the Beltway.

Please folks, try at the very least to understand what you propose!

Labels: Internet

THURSDAY, NOVEMBER 20, 2014

USE OF THE ENGLISH LANGUAGE, AND CANCER

I am always amazed at how a small bit of insight, perhaps well interpreted, may get presented by the Press as the be all and end all. It is especially true with cancer. The most recent case in point is a study by physicians at a Toronto Hospital as well as at MSKCC and other places that the existence of some CNV, copy number variants, can give some modest prognostic data on prostate cancer. Simply, using some 300 patients in toto, theu compared tumor cells to non tumor cells and determined what CNVs across the genome could possibly be prognostic. With the 300 patient sample they got an ROC with about a 70& AUC. Nice but no cigar frankly.

But now to the Press. A Canadian paper states:

Canadian researchers have developed a genetic test to identify which men are at highest risk for recurrence of prostate cancer following localized treatment with surgery or radiation therapy. The genetic test provides a quick and highly accurate tool to determine which men with prostate cancer would do well with only surgery or radiation, and those who would need additional treatment — chemotherapy and hormone therapy, say the researchers, whose findings are described in Wednesday's online edition of the journal Lancet Oncology. "Our findings set the stage to tackle the ongoing clinical problem of under-treating men with aggressive disease that will recur in 30 per cent to 50 per cent of patients due to hidden, microscopic disease that is already outside the prostate gland during initial treatment," said ...a clinician-scientist ... in Toronto. "This genetic test could increase cure rates in intermediate- to high-risk men by preventing progression to this metastatic spread of prostate cancer," said ... a scientist at the Ontario Institute for Cancer Research.

Now if one reads the opening sentence one could be led to believe that there is some massive discovery here. In my opinion, I will be delivering a more detailed analysis later, the following most likely are the results:

1. CNV are found everywhere in DNA. The fact that CNVs are more extensive in cancer cells may or may not be informative.

2. 300 patients is not a lot, especially not enough to in my opinion justify the first opening sentence. However in fairness the researcher did say "could".

3. There is the causative issue here. Why did these CNVs arise and why where they did. That seems to be the compelling issue.

4. Prognosis means that we can tell who after surgery or radiation will fare better or more poorly. But frankly so what if we have no way to mollify the negative results. We get to tell the patient that they are going to die at a greater odds ratio that someone else. We are not really certain but the odds are higher and yes we cannot do anything. Why even have that conversation?

5. There are already dozens of similar tests, genes, mRNAs, CNV, SNPs proteins, exosomes, endosomes, and the list goes on. What does one get by this test?

Yet the real issue is why does the Press make it appear that there is truly something here, here?

Labels: Cancer

MONDAY, NOVEMBER 17, 2014

WHY I DO NOT LIKE FOOTBALL

From an MIT Press release today they list the history of Football on Campus:

- ***1881:*** *The MIT football team, nicknamed the Techmen, defeats Exeter College, 2-0.*
- ***1885:*** *MIT trounces Amherst, 80-0, to tie Williams College for the Northeastern Intercollegiate Football Association (NIFA) league title. In perhaps the first playoff game in college football history, MIT loses to Williams, 18-10.*
- ***1886: MIT loses to Yale, 96-0.***
- ***1887-1888:*** *MIT wins back-to-back NIFA league titles.*
- ***1890:*** *With two games left, the football season is cancelled due to injuries.*
- ***1901:*** *MIT President Henry S. Pritchett holds a controversial student vote that eliminates the football program by a two-vote margin (119-117).*
- ***1940:*** *A non-varsity Junior-Senior team forms, plays four games, and Virginia Jewell is crowned "MIT Football Queen" before a football dance.*
- ***1941:*** *The non-varsity team disbands after two seasons.*
- ***1966:*** *A student survey indicates a desire for intercollegiate football, but the MIT Athletic Board votes unanimously against adding an MIT team.*
- ***1978:*** *The MIT football club forms and joins the National Club Football Conference (NCFC), thanks to the efforts of players including Walt Crosby '81, Bruce Wrobel '79, and Gary Spletter '79.*
- ***1978, cont.:*** *The Rochester Institute of Technology drops their football program, and the MIT club purchases their football equipment and uniforms for $2,000. The team wears orange and white jerseys during the 1978 season.*
- ***1978, cont.:*** *A crowd of 2,000 attends the club's only home game. The Engineers loses to Siena College, 30-14, and an Ugliest Man on Campus contest is held at halftime.* ***The team finishes the season 0-6.***

- ***1987:*** *The NCFC disbands. The club becomes a varsity program and joins the NCAA Division III.*
- ***1988:*** *The Engineers win their first varsity game of the modern era, beating Stonehill, 29-7.*
- ***2013:*** *The team wins a then-record six games and post back-to-back winning seasons (5-4 in 2012) for the first time in 124 years.*
- ***2014:*** *The Engineers finish the regular* ***season 9-0*** *and win their first NEFC title. The team will play in the NCAA Division III Football Championship tournament on November 22.*

The 78 season I recall, having walked across campus and seeing the "team" and the "cheerleaders". Now just where the "cheerleaders" came from was anyone's guess, but perhaps they were better at chemistry than cheerleading. Well they won with a perfect season and they did not play a single JV High School team to accomplish this. Not Harvard or Yale but not bad.

Labels: Academy

SATURDAY, NOVEMBER 15, 2014

IF ELEPHANTS HAD WINGS...

Economists imagine universes to which they can apply their tools, namely, and quite often, mathematics taken from engineers who have to deal with reality. As engineers we use mathematical tools to do things, we model reality and then test it out to be certain our models work. Economists have no such checks and balances. And as we have recently seen they also seem to have the tendency to promote their ideas via prevarication, namely saying one thing to push their belief while holding onto to a reality starkly different. There is no other occupation that allows no less encourage this other than magicians and circus acts. Oh, yes and of course politicians.

Now I read an article in Vox which focuses on the 1% and inequality. They conclude, regarding their proposed extortionary tax plan of some 90%+ marginal rate:

Overall we find that increasing tax rates at the very top of the income distribution and thereby reducing tax burdens for the rest of the population is a suitable measure to increase social welfare. As a side effect, it reduces both income and wealth inequality within the US population. Admittedly, our results apply with certain qualifications. First, taxing the top 1% more heavily will most certainly not work if these people can engage in heavy tax avoidance, make use of extensive tax loopholes, or just leave the country in response to a tax increase at the top. Second, and probably as importantly, our results rely on a certain notion of how the top 1% became such high earners. In our model, earnings 'superstars' are made from luck coupled with labour effort. However, if high income tax rates at the top would lead individuals not to pursue high-earning careers at all, then our results might change. Last but not least, our analysis focuses solely on the taxation of large labour earnings rather than capital income at the top 1%. Despite these limitations, which might affect the exact number for the optimal marginal tax rate on the top 1%, many sensitivity analyses in our research suggest one very robust result – current top marginal tax rates in the US are lower than would be optimal, and pursuing a policy aimed at increasing

them is likely to be beneficial for society as a whole.

You see they assume that the rich just got rich by luck. There seems to be little hard work involved. But they do seem to admit that perhaps they could avoid taxes by moving, that they may possibly not work as hard.

This is a classic example of some thought based upon no knowledge. But unfortunately our current Government policies are all too often based upon academic advice from these people.

Labels: Economics

TUESDAY, NOVEMBER 11, 2014

MORE THOUGHTS ON INTERNET NEUTRALITY

It seems that the Progressives are taking the fore in the argument of Internet Neutrality. They have managed to rephrase it as a means to have the Government protect people who use the Internet. In reality it should be a scheme whereby a user pays for local transport, and all users are the same for the same service. Namely if I choose not to have Netflix downloaded then I should not have to pay for that capacity. It is akin to my arguments against paying for football and funding the debauched lives of its players.

If however I want Netflix and whatever else that requires broadband then I should pay, not everyone else. That is Net Neutrality.

However, the prices are another issue. You see the Internet is really cheap at least per household. The real problem is why do the carriers charge so much? That is where the argument should be.

I fear that the Progressives have turned the argument around so that it now allows Government regulation. What a mess. The should reread Coll's book, The Deal of the Century.

As noted in the New Republic:

Under Title II, Internet service—and in the president's plan, that means through computer, mobile or tablet—would become a "common carrier," much like your phone line. And just as phone providers like AT&T or Verizon cannot deliberately slow down particular phone calls or charge certain businesses more money to connect faster, those standards would apply to the Internet under Title II. That means no "fast lanes," where companies pay for quicker load times for their Web sites. It means no deliberate throttling of any content. It effectively means no special treatment for anyone, from Netflix and Google to photos of your cat.Broadband providers have argued that Title II authority would subject their businesses to all sorts of cumbersome and costly regulations, and potentially even price-setting. But Obama made clear in his statement that the FCC should exclude the industry from those kinds of rules, focusing on only those "relevant to broadband services."

Being a Common Carrier means two things: everyone is treated equally, and the carrier has de

minimis liability. Queen Elizabeth I created this in 1602. It allowed British ships to sail and created a world shipping power. The same can be done with the Internet, common carriage in a de minimis manner, meaning all are treated equally.

Labels: FCC

VETERANS DAY; NOW AND THEN

To the men and women in the Military, then and now, and yes to the dogs! Happy Veterans Day

The USS Albert W Grant at Manus under repair.

Some of the men relaxing.

The CPOs and the crew.

Officers under the 5" gun.

Labels: Commentary

HAVE THEY NO SHAME?

While the ACA was being debated I was deeply concerned by the statements of an MIT Economics Professor who was saying things that were just not correct. I wrote extensively about this and lo and behold I was right. As this Professor has acknowledged (from Reason):

"This bill was written in a tortured way to make sure CBO did not score the mandate as taxes. If CBO [Congressional Budget Office] scored the mandate as taxes, the bill dies. Okay, so it's written to do that. In terms of risk rated subsidies, if you had a law which said that healthy people are going to pay in – you made explicit healthy people pay in and sick people get money, it would not have passed… Lack of transparency is a huge political advantage. And basically, call it the stupidity of the American voter or whatever, but basically that was really really critical for the thing to pass....Look, I wish Mark was right that we could make it all transparent, but I'd rather have this law than not."

Well some of us were not that stupid. First he is he is an economist, and that knocks off a few IQ points anyhow. However the obfuscation, sadly seemingly supported by the publication in the New England Journal of Medicine (NEJM), is, in my opinion, on the verge of being conspiratorial. We are now all suffering from this massive mess.

One wonders if any of this is ever taken into account in the Academic world. From time to time I am reminded of Heidegger, and his academic foibles.

The tale gets even better when reading Forbes which states:

The new ..... comments come from a panel discussion that he joined on October 17, 2013 at the University of Pennsylvania's Leonard Davis Institute of Health Economics. He was joined on the panel by Penn health economist ..... was the first to flag .... remarks. In fairness to.....American voters are not the only people whose intelligence he questions; elsewhere in the discussion, he describes New York Sen. ..... as someone who "as far as I can tell, doesn't understand economics" and calls a staffer for .....—presumably .....—an "idiot."

This an amazing statement. Here we have the alleged self-proclaimed architect saying that it was an attempt to deceive the American voters. Well frankly many were not fooled, as I had indicated many times. But institutions were used. In my opinion, MIT was used, NEJM was used, and the consequence is what? If this were a physician who did this, most likely he or she would be banned. But as a Professor of Economics, well what does one expect?

Yes, they have no shame. Nor, quite frankly, it seems to appear in my opinion, do the institutions who have seemingly supported them.

Now consider if this were a biologist who had devised a putative cure for say Ebola, but was just posing as such and then admitted publicly that what was done was just a way to deceive the public to sell the drug. What would that persons Institution do? Most likely send them packing. The same would apply to any scientist, physician, or engineer. But apparently not to an Economics Department instructor, and that says something about business. Would Harvard allow

this? Possibly not. In fact most likely not.

Consider the classic case of David Baltimore, the brilliant and revered Biologist, who was attacked by Congress with Congressman Dingell at the fore. He had a student make a sloppy entry in a lab notebook and after the bemoaning of another post-doc it started a Federal case. Where is the Federal case here. One assumes the good Professor was compensated by the Government so why not the same level of outrage. Baltimore actually did great deeds for mankind. Rarely if ever does one see this in an Economist.

Academic freedom permits the investigation of ideas not the promoting of error. In my view, it does not permit the propagation of known falsehoods. Back to Heidegger.

Labels: Health Care

MONDAY, NOVEMBER 10, 2014

THE INTERNET, PRIORITY AND NEUTRALITY

I heard a presentation by some Law Prof at U Penn this weekend where I believe he claimed that the IP protocol has a priority code so this justifies Comcast discriminating against providers and deciding what customers can see. Now here I have a problem. In the 70s when I was heading part of the Internet implementation in DC, I had the satellite side of the ARPA Net, I had an MIT student do a thesis that looked at priority queuing. Why? Simple the Internet was a DoD network and when a General needed to communicate the General needed priority. It had nothing to do with Comcast. Lawyers know less of technology and even less of history than any others I have ever seen!

Now to today's announcement by the current President. He is apparently supporting the FCC taking the position of supporting Common Carriage. He stated:

.....*said that new rules under consideration by the F.C.C. should adhere to several key principles: No website or service should be blocked by an Internet service provider; no content should be purposefully slowed down or sped up; there should be more transparency about where traffic is routed; and no paid deals should be made to provide a speed advantage to some providers over others in delivering content.*
Of course the monopolistic cable and telco companies replied:

"Imposing antiquated common carrier regulation, or Title II, on the vibrant mobile wireless ecosystem would be a gross overreaction," said Meredith Attwell Baker, president and chief executive of the trade association and a former Republican commissioner for the F.C.C.

As we had written a few years back regarding Internet Neutrality :

Internet Neutrality is a term which means many things to many people. In this paper we look at the Internet from a technical, legal, and economic perspective. We look at the ways the various players are trying to position their view and we attempt to apply the factual elements of what actually exists as a set of tests and tools to analyze the options. We as a result of this detailed

analysis have come up with a set of conclusion and principles which re -interpret the concepts of Internet neutrality and present a set of principles which are based on the technological facts, the market realities, and legal precedents which go back more than a thousand years. Our concern is that some of the proposal are so self-serving that if accepted of if implemented will do irreparable harm to what has been created in the Internet.

Hopefully the FCC has some modicum of backbone to ensure that individual rights are preserved.

Labels: FCC

SUNDAY, NOVEMBER 9, 2014

MOOCS AGAIN

There is a piece in the New Yorker on MOOCs. The author states:

The other major problem is that MOOCs tend to be set up in a way that minimizes frustration for students (who might drop out at any moment). There often aren't pop quizzes or the kinds of challenges that can alienate students in traditional settings. The problem here is that easy learning does not make good learning. In fact, the very tools that we believe make for better education may also make students more likely to quit. More frequent testing, for instance, can improve memory, learning, and retention. And, sometimes, the best test of all is the test that you fail: recent work from the cognitive psychologist Elizabeth Ligon Bjork has shown that pre-testing on never-before-seen materials helps students perform better in a subsequent course covering that material. In general, Bjork has found, speed bumps in learning are good—desirable difficulties, she calls them. MOOCs would likely be more effective if they didn't shy away from challenging students, rather than presenting a fluid experience which gives the false impression of the learning and retention.

Frankly the problem with MOOCs is that those who do so in English do not know English. For example in a recent MIT exam for a materials course they asked a question which required height and width. Except they stated:

a width, b, of 20μm and a depth, h, of 1μm

Now what is depth? One was given the length and allegedly the width but one needed height. Is depth a new word for height? Words mean something. Now I am facile in six languages, so I tried translating into each but came to the same conclusion, there must be some language wherein depth equals height. I think.

This is the problem of MOOCs, students and teachers who don't read what the wrote, at least in the language it is taught!

As to the above suggestion, my response is clap trap! The MOOCs maximize frustrations. Again in the same course one must enter equations in a format that is hidden in the bowels of the course. One spends hours finding out how to do the computer side of the course, NOT the

material taught.

In addition the approach to grading is an all or none approach. One must go through all the equations, convert them to a program, run the numbers and then make certain the the units are consistent. To complicate things the units in the problems are disparate to say the least.

Finally the New Yorker shows Lander at MIT, strangely the only existing MOOC instructor who has a course that works. One wonders if the New Yorker writer had the slightest clue!I suspect as a psychology major she does not!

Then there is the Harvard Medical School course on Anatomy. Apparently the TAs has disappeared. The answers are wrong and the students in the discussion group are running wild. The overhead on a good MOOC is significant, and costly. Lander has figured it out, as he has with everything he touches. Almost all the others have not. Some seem clueless.

UPDATE: Well I just found out that depth=height. Amazing what people will come up with.

Labels: MOOCs

TUESDAY, NOVEMBER 4, 2014

INSIGHT INTO EBOLA AS A PUBLIC HEALTH ISSUE

Amid all the turmoil of Ebola the interview in Science with the Nigerian President of their Academy of Sciences is the most telling. It should be mandatory reading for all politicians.

For example he states:

People say African countries are poor. But it's not poverty. It's misuse of what we have. As we are talking, with all the crises that are going on, the presidents of our countries are still traveling in the best of conditions. Some will come to New York in their private jets, although their national airlines collapsed years ago; in addition, they will bring along a long retinue of private, personal, and public assistants, all lodged in the best hotels. I am not saying the president should not be treated well, but these are issues we need to look at. Take my country: We do not have a national airline, but the number of private jets we have is more than all the airlines in Africa have together.

Almost sounds like a Secret Service trip.

But the point is that the solution must be enacted by the country. The west alone cannot always take the burden and responsibility. Nigeria acted, almost as an afterthought. The others, if one reads this correctly, failed at the beginning and are continuing to do so.

Labels: Health Care

TUESDAY, NOVEMBER 4, 2014

POLAND

Poland is now some 25 years free of Soviet domination. I entered Poland to work in 1995, and my partner, Peter Mroczyk, a former Solidarity leader had come back and we created a pan Central European business, from the Baltic to the Balkans. I saw the potential of Poland through the eyes of Peter and of those other Poles who saw that they could recreate Poland to its former glory.

It was hard work, some politics, but it lacked the cronyism of Russia and the rigid controls of France. In a sense Poland was allowed to expand because they did what was necessary, and have pulled together splendidly.

In Project Syndicate there is a laudatory article on Poland well worth reading. He states:

Last month, Donald Tusk, Poland's former prime minister, was appointed President of the European Council, thus becoming one of Europe's three top leaders. This decision not only reflected Tusk's successful leadership in Poland, where he ensured political stability and oversaw impressive economic progress; it was also a clear signal that EU leaders fully acknowledge Poland's political and economic importance. It also signaled to the other new member states that they are true equals in European decision-making. Again, it was Poland that paved the way, reminding the old member states from the outset of the accession process that it was not an outsider or a poor relative in need of charity, but rather a source of inspiration in the European integration process, its impact delayed only by World War II and its aftermath. Now, after ten years of EU membership, a new Golden Age for Poland may be on the horizon. Poland has the potential to become a European leader again. Firmly anchored in the community of Western democracies, its role transcends the technical aspects of the European integration process, for it bears the responsibility of ensuring that no new barrier excludes our Eastern neighbors from taking part in this process.

Poland is what Russia could have become. The irony is that the tower in downtown Warsaw built as a "gift" of Stalin to the Polish people still stands in all is Soviet "beauty" while across the street is the Marriott, a western hotel built by Russian investors. In between springs forth a new Poland, looking westward and growing economically as an example to the rest of the Free World.

Labels: Economics

A FANTASTIC BOOK

There is a draft of a book, Cell Biology by the Numbers, also see dropbox, by Milo and Phillips, that is just amazing! It is a set of questions with answers briefly given, such as how fast is translation and transcription. Also how big is a cell. It is really a fantastic amalgam of questions, answers, and technique. It is not yet published but I would argue that it should be on the desk of anyone trying to do real work in the life sciences. The questions and answers alone are a gold mine but the way they arrive at them and explain them are sine qua non.

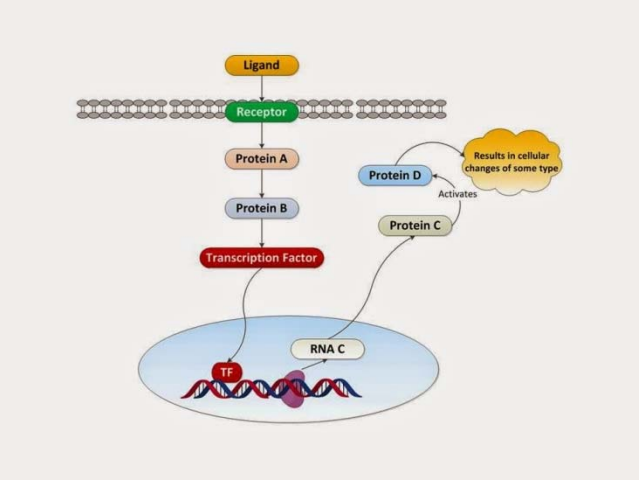
Keep a watch out for this one, it is a true gem!

Labels: Commentary, Genetics

SUNDAY, NOVEMBER 2, 2014

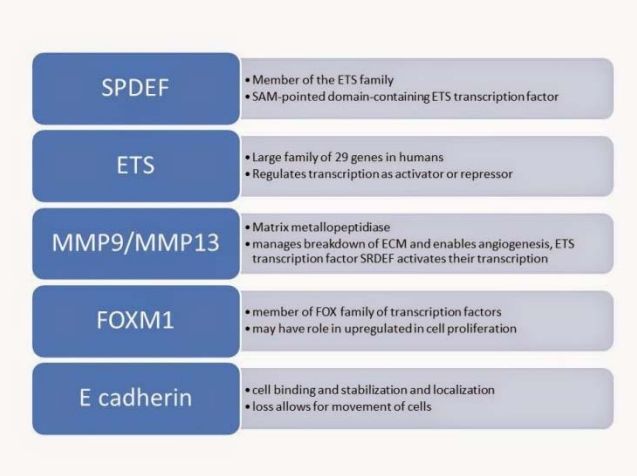
SPDEF AND PROSTATE CANCER

In a recent White Paper we examine some recent results regarding a class of transcription factors and Prostate Cancer. SPDEF is one of the 30-40 transcription factors found in the ETS family. Recall that transcription factors can be promoters (activators) or repressors of gene expression and that depending where they act than can dramatically change the expression of genes in the cell. The general paradigm is shown below:

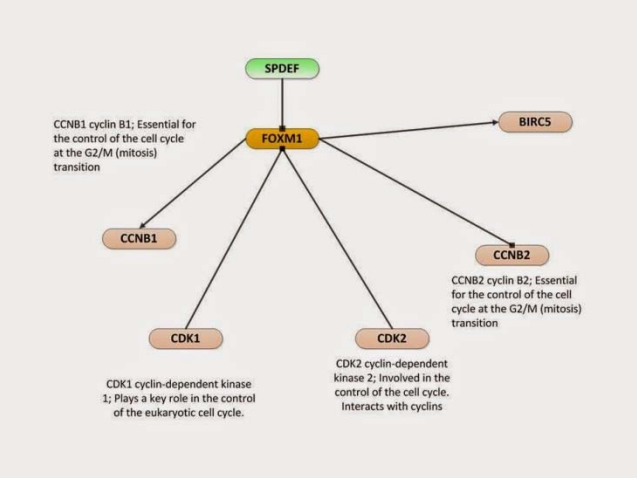


The ETS family is a powerful family of transcription factors and they are often found altered in prostate cancer. In this section we examine a specific subset of these transcription factors.

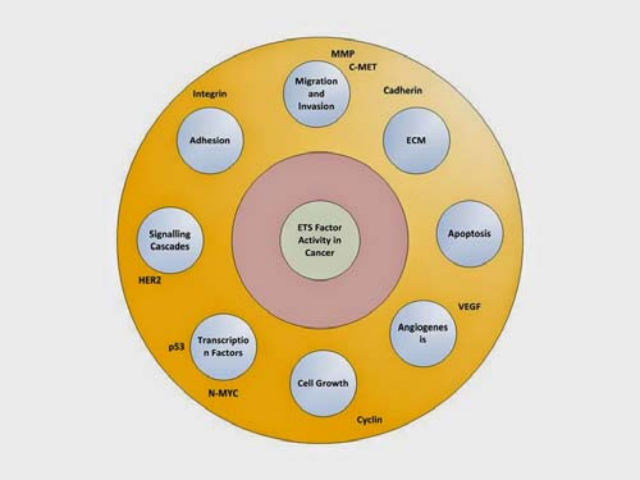
The chart below displays the specific factors we discuss herein. The driver for this discussion is a recent paper by Cheng et al which discusses SPDEF and the regulation of FOXM1 oncogene. The paper is interesting in that if examines a transcription factor and the specific influence on an oncogene expression. SPDEF is in the ETS family and thus the interest in ETS. SPDEF is the SAM pointed domain containing ETS transcription factor. Thus, the acronym was formed. It is distinct from another ETS gene the PDEF which the prostate derived epithelial factor. As they indicate it is not clear what the role of SPDEF is in PCa and it is not clear whether its expression suppresses or enhances PCa development. Yet the analysis of this process does present an alternative view of a complex PCa development mechanism.



As Cheng et al have postulated the increase in SPDEF results in a suppression of FOXM1 which is a known oncogene, especially for PCa. As in Gellmann et al (pp 328-333) FOXM1 is a known oncogene. It drives the cell cycle and thus leads to uncontrolled cell proliferation. We show this below:



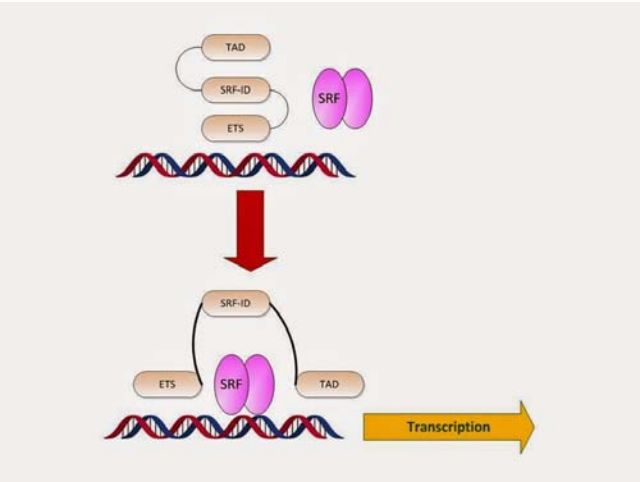
The ETS ("E26 transformation specific") family has some 30-40 genes and many relate to prostate cancer. For example the ERG (the "ETS related gene") gene is often found translocated with TPRSS in a fused state and this translocation is a clear indication of an aggressive form of PCa. From Watson et al we have the following breath of structure for the ETS family:



Let us begin with a brief overview of ETS family and specifically the inclusion of SPDEF. As Wasylyk et al state:

The Ets family of transcription factors includes nuclear phosphoproteins that are involved in cell proliferation, differentiation and oncogenic transformation. The family is defined by a conserved DNA-binding domain (the ETS-DBD), which forms a highly conserved, winged, helix-turn-helix structural motif. As targets of the Ras-MAPK signaling pathway, Ets proteins function as critical nuclear integrators of ubiquitous signaling cascades. To direct signals to specific target genes, Ets proteins interact with (other) transcription factors that promote the binding of Ets proteins to composite Ras-responsive elements.

We demonstrate the winged or "butterfly" operation of ETS transcription factors as shown below[1][1]:



In a 2012 report in Science Daily they state[2][2]:

[1][1] See Marks et al p 405. As adapted.
[2][2] http://www.sciencedaily.com/releases/2012/07/120706164422.htm

Prostate cancer doesn't kill in the prostate -- it's the disease's metastasis to other tissues that can be fatal. A University of Colorado Cancer Center study published this week in the Journal of Biological Chemistry shows that prostate cancer cells containing the protein SPDEF continue to grow at the same pace as their SPDEF- cousins, but that these SPDEF+ cells are unable to survive at possible sites of metastasis.

"It's as if these cancer cells with SPDEF can't chew into distant tissue and so are unable to make new homes," says Hari Koul, PhD, investigator at the CU Cancer Center and director of urology research at the University of Colorado School of Medicine, the study's senior author.

Koul and his group discovered the homesteading power of cancer cells that have lost SPDEF by introducing a gene into cells that makes them glow in the presence of a dye, and then introducing them into the bloodstream of animal models. Cells without SPDEF traveled through the blood and successfully attached to tissue, surviving and so fluorescing many weeks later when dye was introduced. However, cells with SPDEF flowed through the blood but were unable to successfully establish new colonies and so soon died out.

***In fact, the protein SPDEF doesn't act directly to allow cells to attach at possible metastasis sites, but is a transcription factor that controls the production (or lack thereof) of two other proteins MMP9 and MMP13**. These two downstream proteins work to break down tissue, like a dissolving agent -- they are the cleaning crew that clears space for new and different growth, and in the case of prostate cancer metastasis they chip the tissue footholds that cancer cells need to create micrometastases.*

There has been a great deal of work on MMPs especially MMP9[3][3]. We will expand this discussion later.

"Given that MMP9 and perhaps MMP13 are also involved in metastasis of several other cancers including lung, ovarian, breast and colon to name a few, our findings could potentially have far-reaching consequences outside prostate cancer," adds Koul

The group's continuing work points in two directions.

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[3][3] See Jamaspishvili et al, *Matrix metalloproteinases (MMPs) have been implicated in invasion and metastasis of human malignancies. Moses et al. used substrate gel electrophoresis (zymography) to determine MMPs in the urine of patients with a variety of cancers. MMP9 yielded better sensitivity (64%) than MMP2 (39%) for CaP whereas specificities (84 and 98%, respectively) were calculated from controls of both sexes. The same group also detected several unidentified urinary gelatinase activities with molecular weights 4125 kDa and recently used chromatography, zymography and mass spectrometry for their identification. The approximately 140, 4220 and approximately 190 kDa gelatinase species were identified as MMP9/TIMP1 complex, MMP9 dimer and ADAMTS7, respectively. MMP9 dimer and MMP9 were independent predictors for distinguishing between patients with prostate and bladder cancer.*

"First, we hope that the presence of SPDEF could help doctors recognize prostate cancers that don't require treatment." If future studies confirm the group's initial findings, the presence of SPDEF could predict prostate cancers that are unable to metastasize and so unable to kill. These cancers could be left to run their course without the use of treatments that sometimes carry difficult side effects.

"And second," Koul says, "we hope to regulate expression of this protein to remove prostate cancers' ability to metastasize."

Koul points to small molecules, gene therapy or nanodelivery as possible mechanisms for introducing SPDEF into cells that lack the protein.

"With this discovery we have opened a hopeful door into a future in which prostate and potentially other cancers are unable to metastasize," Koul says.

However it appears that this work has been withdrawn in several venues. It is not clear where the problem was that caused the withdrawal.

We will now consider a recent paper by Cheng et al which we referred to in the Introduction. The interest here is the collecting together of multiple elements in this SPDEF chain and the effects of ETS transcription factors.

In the recent paper by Cheng et al the authors state[4][4]:

SAM-pointed domain-containing ETS transcription factor (SPDEF) is expressed in normal prostate epithelium. While its expression changes during prostate carcinogenesis (PCa), the role of SPDEF in prostate cancer remains controversial due to the lack of genetic mouse models. In present study, we generated transgenic mice with the loss- or gain-of-function of SPDEF in prostate epithelium to demonstrate that SPDEF functions as tumor suppressor in prostate cancer. Loss of SPDEF increased cancer progression and tumor cell proliferation, whereas over-expression of SPDEF in prostate epithelium inhibited carcinogenesis and reduced tumor cell proliferation in vivo and in vitro.

Transgenic over-expression of SPDEF inhibited mRNA and protein levels of Foxm1, a transcription factor critical for tumor cell proliferation, and reduced expression of Foxm1 target genes, including Cdc25b, Cyclin B1, Cyclin A2, Plk-1, AuroraB, CKS1 and Topo2alpha.

Deletion of SPDEF in transgenic mice and cultures prostate tumor cells increased expression of Foxm1 and its target genes. Furthermore, an inverse correlation between SPDEF and Foxm1 levels was found in human prostate cancers. The two-gene signature of low SPDEF and high FoxM1 predicted poor survival in prostate cancer patients. Mechanistically, SPDEF bound to, and inhibited transcriptional activity of Foxm1 promoter by interfering with the ability of Foxm1

[4][4] http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1004656

to activate its own promoter through auto-regulatory site located in the 2745/2660 bp Foxm1 promoter region. Re-expression of Foxm1 restored cellular proliferation in the SPDEF-positive cancer cells and rescued progression of SPDEF-positive tumors in mouse prostates. Altogether, SPDEF inhibits prostate carcinogenesis by preventing Foxm1-regulated proliferation of prostate tumor cells.

The present study identified novel crosstalk between SPDEF tumor suppressor and Foxm1 oncogene and demonstrated that this crosstalk is required for tumor cell proliferation during progression of prostate cancer in vivo.

The relationship between SPDEF and Foxm1 are significant and could become a possible therapeutic target. They continue:

Development of prostate cancer is a multistep process that involves the loss of tumor suppressor functions and activation of oncogenes. SPDEF transcription factor is expressed in normal prostate epithelium and its expression changes during prostate carcinogenesis (PCa). Since the role of SPDEF in PCa remains controversial, we generated transgenic mice with loss- and gain-of-function of SPDEF to demonstrate that SPDEF functions as a tumor suppressor in PCa. In animal models, the loss of SPDEF promoted PCa and increased the levels of Foxm1, a well-known oncogenic protein.

Overexpression of SPDEF in prostate epithelium decreased PCa and reduced Foxm1 levels. Proliferation defects in SPDEF-containing tumor cells were corrected by re-expression of Foxm1, providing direct evidence that SPDEF inhibits tumor cell proliferation through Foxm1. We further showed that SPDEF directly bound to Foxm1 promoter and prevented its autoregulatory activation. In prostate cancer patients, the low SPDEF and high Foxm1 were found in most aggressive prostate tumors that were associated with poor prognosis. The combined two-gene signature of low SPDEF and high Foxm1 was a strong predictor of survival in prostate cancer patients. The present study identified novel molecular mechanism of prostate cancer progression, providing a crosstalk between SPDEF tumor suppressor and Foxm1 oncogene.

The Figure below details a putative pathway element showing how the AR[5][5] interacts with SPDEF[6][6]:

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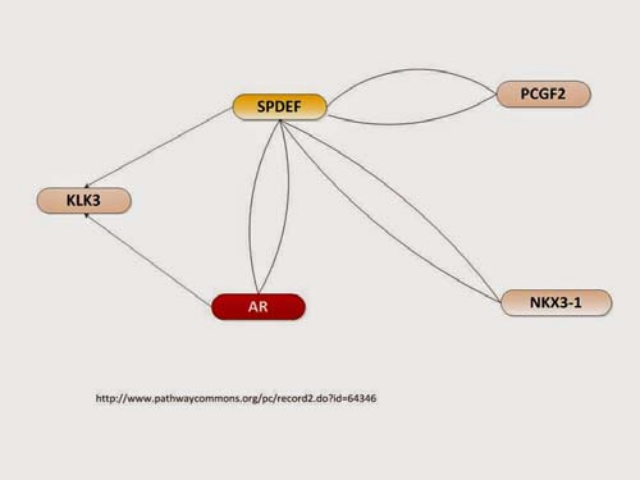
[5][5] From NCBI: T*he androgen receptor gene is more than 90 kb long and codes for a protein that has 3 major functional domains: the N-terminal domain, DNA-binding domain, and androgen-binding domain. The protein functions as a steroid-hormone activated transcription factor. Upon binding the hormone ligand, the receptor dissociates from accessory proteins, translocates into the nucleus, dimerizes, and then stimulates transcription of androgen responsive genes. This gene contains 2 polymorphic trinucleotide repeat segments that encode polyglutamine and polyglycine tracts in the N-terminal transactivation domain of its protein.*

[6][6] See also: https://targetexplorer.ingenuity.com/gene/EG/25803/pathways



Furthermore, Pal et al in a paper, that has been subsequently withdrawn, had stated:

Loss of E-cadherin is one of the key steps in tumor progression. Our previous studies demonstrate that SAM pointed domain-containing ETS transcription factor (SPDEF) inhibited prostate cancer metastasis in vitro and in vivo. In the present study, we evaluated the relationship between SPDEF and E-cadherin expression in an effort to better understand the mechanism of action of SPDEF in prostate tumor cell invasion and metastasis.

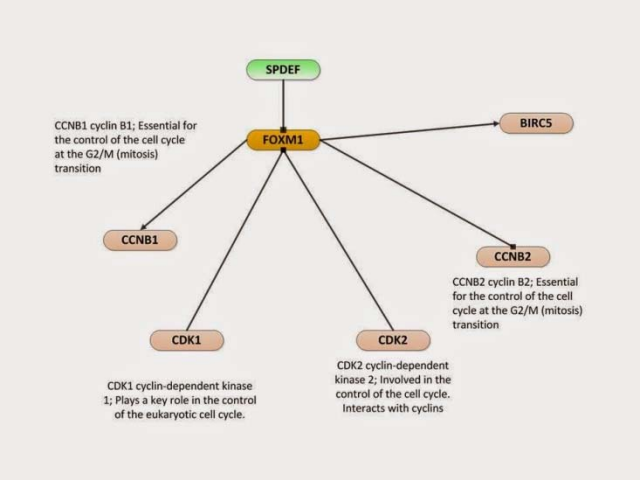
The results presented here demonstrate a direct correlation between expression of E-cadherin and SPDEF in prostate cancer cells. Additional data demonstrate that modulation of E-cadherin and SPDEF had similar effects on cell migration/invasion. In addition, siRNA-mediated knockdown of E-cadherin was sufficient to block the effects of SPDEF on cell migration and invasion. We also show that stable forced expression of SPDEF results in increased expression of E-cadherin, whereas down-regulation of SPDEF decreased E-cadherin expression.

In addition, we demonstrate that SPDEF expression is not regulated by E-cadherin. Moreover, our chromatin immunoprecipitation and luciferase reporter assay revealed that SPDEF occupies E-cadherin promoter site and acts as a direct transcriptional inducer of E-cadherin in prostate cancer cells. Taken together, to the best of our knowledge, these studies are the first demonstrating requirement of SPDEF for expression of E-cadherin, an essential epithelial cell junction protein. Given that loss of E-cadherin is a central tenant in tumor metastasis, the results of our studies, by providing a new mechanism for regulation of E-cadherin expression, could have far reaching impact.

The SPDEF capability to deal with adhesion via the paths shown is a significant factor in its overall importance in metastasis.

Foxm1 is a transcription activator and can be silenced by SPDEF. However when SPDEF is deficient then Foxom1 can act as an aggressive oncogene and can press metastatic growth. From NCBI we have[7[7]]:

7[7] http://www.ncbi.nlm.nih.gov/gene/2305



The protein encoded by this gene is a transcriptional activator involved in cell proliferation. The encoded protein is phosphorylated in M phase and regulates the expression of several cell cycle genes, such as cyclin B1 and cyclin D1. Several transcript variants encoding different isoforms have been found for this gene.

The Foxm1 gene may be a therapeutic target. It pushes the cell through the cell cycle and can kick off aggressive metastatic growth. This simple connection between the regulatory role of SPDEF and the aggressive cell cycle capabilities of Foxm1 is an important observation.

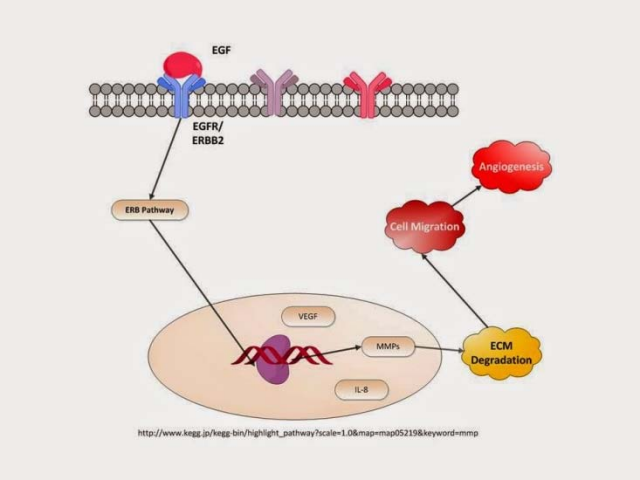
MMP genes have been found to assist metastatic growth by degrading the ECM structures. As Chiang et al state:

Various members of the matrix metalloproteinase (MMP) family (e.g., MMP-2 and MMP-9) are also implicated in cancer cell invasion. Independent screens for genes that mediate bone or lung metastasis in breast cancer have identified MMP-1 as being necessary for spread to the bone and lungs.

As noted in NCBI:

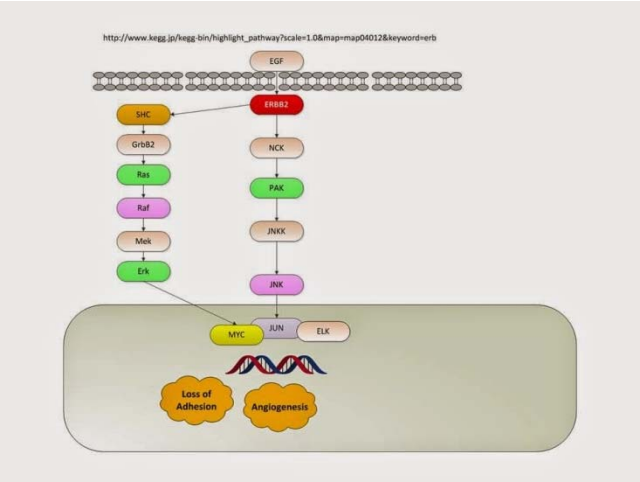
Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. Most MMP's are secreted as inactive proproteins which are activated when cleaved by extracellular proteinases. The enzyme encoded by this gene degrades type IV and V collagens. Studies in rhesus monkeys suggest that the enzyme is involved in IL-8-induced mobilization of hematopoietic progenitor cells from bone marrow, and murine studies suggest a role in tumor-associated tissue remodeling.

MMP actions are shown below in general terms depicting the activation via the ERB pathway:



MMPs initiate their actions via ECM degradation first and then enable cell migration and sustainability via angiogenesis. Thus the evidence of MMP-9 and MMP-14 are significant. As Marks et al note (p 242) there is no known ligan for ErbB2 but it does form an active heterodimer with either ErbB1 or ErbB4. We examine that pathway shortly. Also Marks et al note (p 243) that the organization of the ErbB network is quite complex and demands a systems based approach. This "systems based approach" is essential as we consider the interaction of all of these elements.

The details of the ErbB2 pathway are shown below:



Although the paper in question regarding SPDEF does read onto the MMPs directly the discussing surrounding it does.

In a 2012 paper by Stefan et al[8][8]:

[8][8] http://www.jbc.org/content/early/2012/07/02/jbc.M112.379396.abstract?sid=d84a3600-887d-4147-88e8-debf7bc61fd8

The role of SPDEF in tumor biology remains hotly debated. SPDEF suppressed tumor metastasis in-part by modulating MMP9 and MMP13. SPDEF is a modifiable therapeutic target in prostate tumors. This is the first study directly implicating SPDEF as a tumor metastasis suppressor in any system in vivo. Emerging evidence suggests that SAM Pointed Domain Containing ETS Transcription Factor (SPD

EF), plays a significant role in tumorigenesis in prostate, breast, colon, and ovarian cancer. However, there are no in vivo studies with respect to the role of SPDEF in tumor metastasis. The present study examined the effects of SPDEF on tumor cell metastasis using prostate tumor cells as a model. Utilizing two experimental metastasis models, we demonstrate that SPDEF inhibits cell migration and invasion in vitro and acts a tumor metastasis suppressor in vivo.

Using stable expression of SPDEF in PC3-Luc cells and shRNA-mediated knockdown of SPDEF in LNCaP-Luc cells, we demonstrate for the first time that SPDEF diminished the ability of disseminated tumors cells to survive at secondary sites and establish micrometastases. These effects on tumor metastasis were not a result of the effect of SPDEF on cell growth as SPDEF expression had no effect on cell growth in vitro, or subcutaneous tumor xenograft-growth in vivo. Transcriptional analysis of several genes associated with tumor metastasis, invasion, and the epithelial-mesenchymal transition demonstrated that SPDEF overexpression selectively down-regulated MMP9 and MMP13 in prostate cancer cells.

Further analysis indicated that forced MMP9 or MMP13 expression rescued the invasive phenotype in SPDEF expressing PC3 cells in vitro, suggesting that the effects of SPDEF on tumor invasion are mediated, in part, through the suppression of MMP9 and MMP13 expression. These results demonstrate for the first time, in any system, that SPDEF functions as a tumor metastasis suppressor in vivo.

From Science Daily they state[9][9]:

Prostate cancer doesn't kill in the prostate -- it's the disease's metastasis to other tissues that can be fatal. A University of Colorado Cancer Center study published this week in the Journal of Biological Chemistry shows that prostate cancer cells containing the protein SPDEF continue to grow at the same pace as their SPDEF- cousins, but that these SPDEF+ cells are unable to survive at possible sites of metastasis.

"It's as if these cancer cells with SPDEF can't chew into distant tissue and so are unable to make new homes," says Hari Koul, PhD, investigator at the CU Cancer Center and director of urology research at the University of Colorado School of Medicine, the study's senior author.

Koul and his group discovered the homesteading power of cancer cells that have lost SPDEF by introducing a gene into cells that makes them glow in the presence of a dye, and then introducing them into the bloodstream of animal models. Cells without SPDEF traveled through the blood

[9][9] http://www.sciencedaily.com/releases/2012/07/120706164422.htm

and successfully attached to tissue, surviving and so fluorescing many weeks later when dye was introduced. However, cells with SPDEF flowed through the blood but were unable to successfully establish new colonies and so soon died out.

In fact, the protein SPDEF doesn't act directly to allow cells to attach at possible metastasis sites, but is a transcription factor that controls the production (or lack thereof) of two other proteins MMP9 and MMP13.

These two downstream proteins work to break down tissue, like a dissolving agent -- they are the cleaning crew that clears space for new and different growth, and in the case of prostate cancer metastasis they chip the tissue footholds that cancer cells need to create micrometastases. "Given that MMP9 and perhaps MMP13 are also involved in metastasis of several other cancers including lung, ovarian, breast and colon to name a few, our findings could potentially have far-reaching consequences outside prostate cancer," adds Koul

The group's continuing work points in two directions. "First, we hope that the presence of SPDEF could help doctors recognize prostate cancers that don't require treatment." If future studies confirm the group's initial findings, the presence of SPDEF could predict prostate cancers that are unable to metastasize and so unable to kill.

These cancers could be left to run their course without the use of treatments that sometimes carry difficult side effects.

"And second," Koul says, "we hope to regulate expression of this protein to remove prostate cancers' ability to metastasize." Koul points to small molecules, gene therapy or nanodelivery as possible mechanisms for introducing SPDEF into cells that lack the protein.

"With this discovery we have opened a hopeful door into a future in which prostate and potentially other cancers are unable to metastasize," Koul says.

From Stefan et al (2011) the authors had stated the following about another ETS transcription factor, PDEF, not to be confused with SPDEF. :

The prostate-derived ETS factor (PDEF) is the latest family member of the ETS transcription factor family, although it is unique in many aspects. PDEF was first described as an mRNA transcript highly expressed in prostate tumor cells where it regulates prostate-specific antigen gene expression and is an androgen receptor co-regulator.

PDEF expression is highly restricted to epithelial cells and has only been found in prostate, breast, colon, ovary, gastric, and airway epithelium. Strong preclinical evidence is emerging that PDEF is a negative regulator of tumor progression and metastasis. PDEF expression is often lost in late-stage, advanced tumors.

The induction of tumor aggressiveness in response to the loss of PDEF is thought to be due to the plethora of PDEF-regulated gene targets, many of which are known players in tumor

progression including tumor cell invasion and metastasis. These data have led to the hypothesis that PDEF may function as a tumor metastasis suppressor.

In this review, we summarize what is known about PDEF since its discovery over a decade ago and give a detailed overview of PDEF-regulated gene products and the expression profiles of PDEF in clinical tumor samples.

Thus many other ETS transcription factors have similar roles. The therapeutic targeting of these factors may be of significant merit.

The analysis of SPDEF is interesting especially because it raises so many other issues.

1. SPDEF deals with multiple other pathway elements from receptors to promoter factors and the resulting complex pathway interactions demonstrate the need for having a complete systems model.

2. No clear therapeutic targets seem to be evident. Although the results are compelling the complexity of the pathways and their interactions lead one to examine more specific control points, since SPDEF by itself seems to be a multiple set of paths leading to metastasis.

3. There is the question of whether SPDEF can be prognostic and/or therapeutic. Many of the prognostic tests use large banks of gene expressions to develop a single metric. Oftentimes this metric can be useful but it also does not per se reflect what process is defective and what cells are the most of concern. The problem is that all too often when one samples a section of tumor that the cells may have substantially different gene expression profiles. We have examined technologies that allows the sampling of individual cells and creating a profile of the tumor in broad profile terms, namely how many cells express what genes (mRNA or proteins) and from that ascertaining prognostic measures.

4. The complexity of the relationships between the ETS transcription factor SPDEF, the oncogene Foxm1 and the MMD metastatic facilitators is of interest. It demonstrates a “system” view of the cancer. The key questions are; when does this occur, in what percent of the cells does this occur, and what is its prognostic value?

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Labels: Cancer

HEDGEHOGS AND FOXES

In an old New York Review of Books commentary on a release of Richard Feynman's letters the author states:

Great scientists come in two varieties, which Isaiah Berlin, quoting the seventh-century-BC poet Archilochus, called foxes and hedgehogs. Foxes know many tricks, hedgehogs only one. Foxes are interested in everything, and move easily from one problem to another. Hedgehogs are interested only in a few problems which they consider fundamental, and stick with the same problems for years or decades. Most of the great discoveries are made by hedgehogs, most of the little discoveries by foxes. Science needs both hedgehogs and foxes for its healthy growth, hedgehogs to dig deep into the nature of things, foxes to explore the complicated details of our marvelous universe. Albert Einstein was a hedgehog; Richard Feynman was a fox.

I like foxes, they are inquisitive, friendly, and nosy. There is a fox, or family probably, that inhabit Island Beach Park, a pristine piece of land on the coast in New Jersey. Every time one goes there the red fox sits aside the road and in a style of begging and investigation examines each human as the drive down the road. We see the hedgehogs everywhere else, getting down deep into their holes. Staying put and digging deeper. The fox just openly roams about in an almost fearless manner.

Interesting thought for any budding scientist.

Labels: Commentary

THURSDAY, OCTOBER 30, 2014

EBOLA SCIENCE

There is a limited set of papers in the literature regarding Ebola transmission to guide the policy making people. A recent NEJM paper presents data on the current outbreak and it is of substantial merit. Their discussion of viral load is on point:

We determined the viral load of EBOV at the time of presentation in 65 patients with a known outcome by means of quantitative RT-PCR. A positive correlation was noted between the viral load and the risk of death. Patients who presented with fewer than 100,000 EBOV copies per milliliter of serum had a case fatality rate of 33%, whereas those with a viral load of 10 million EBOV copies per milliliter or more had a significantly higher case fatality rate of 94% (P=0.003) Viral loads were quantified for a limited number of patients at multiple times during their hospitalization, with results suggesting that an inability to clear the virus was a risk factor for death, even though some patients with prolonged viremia survived

What seems still to be missing is a detailed progression analysis. Namely what is the minimal load for infection and where on the body and how quickly do the virions reproduce.

In an earlier article in the Journal of Infections Diseases they have performed an analysis of actual contagion. They state:

We conclude that EBOV is shed in a wide variety of bodily fluids during the acute period of illness but that the risk of transmission from fomites in an isolation ward and from convalescent patients is low when currently recommended infection control guidelines for the viral hemorrhagic fevers are followed.

They conclude:

Taken together, our results support the conventional assumptions and field observations that most EBOV transmission comes from direct contact with blood or bodily fluids of an infected patient during the acute phase of illness. The risk of casual contacts with the skin, such as shaking hands, is likely to be low. Environmental contamination and fomites do not appear to pose a significant risk when currently recommended infection control guidelines for the viral hemorrhagic fevers are followed. Prospective studies with the collection of a greater number of clinical samples from patients at different stages of EHF, as well as environmental samples analyzed with an assay validated for EBOV detection in such samples, should be performed to confirm our results.

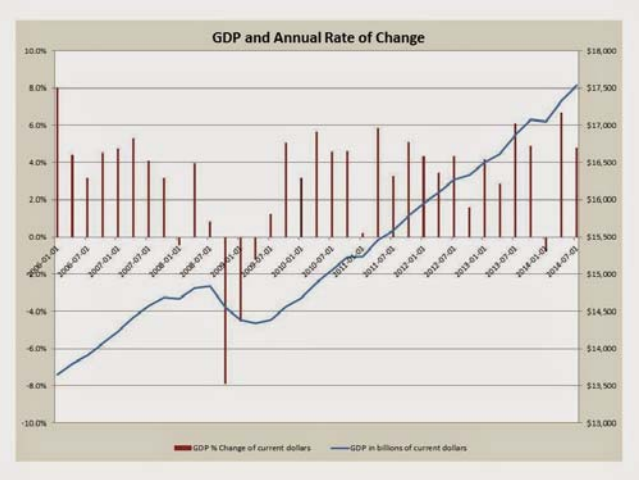
The actual mechanism and the growth mechanics is still unknown. Thus the science is reflective on cases but not prescriptive on putative cases. It is still problematic as to the risk of those "exposed" since the definition of being exposed is still a work in progress.

Thus the problem for policy people is that the "science" is still in a development stage and does one err on the side of caution or assume that transmission is highly unlikely. Also the time from exposure to time of symptoms seems to be about 12 days, and the proposed quarantines are 21. This may or may not make sense.

The "bottom line" is that despite what some say, the "science" is still in a state of flux and reliance on anecdotal evidence is useful but not definitive.

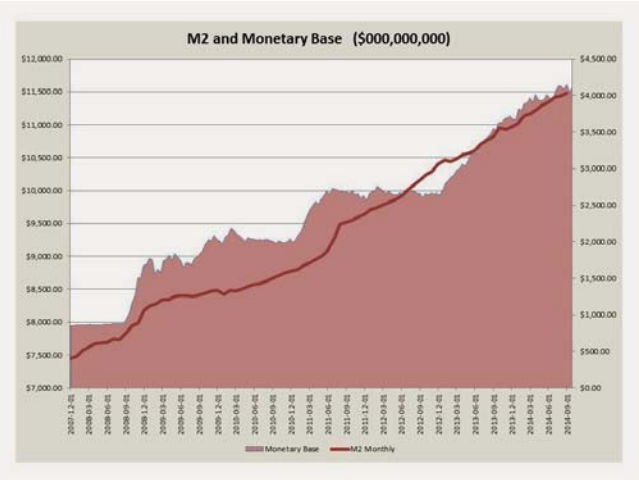
Labels: Health Care

GDP, M2 AND MONETARY BASE



The GDP is growing at a reasonable rate. The details will also be important as well as employment in a week. Two Quarters of positive growth and the rate is fine.

The Monetary Base also is growing but its rate has slowed as would be expected based upon the FED actions.

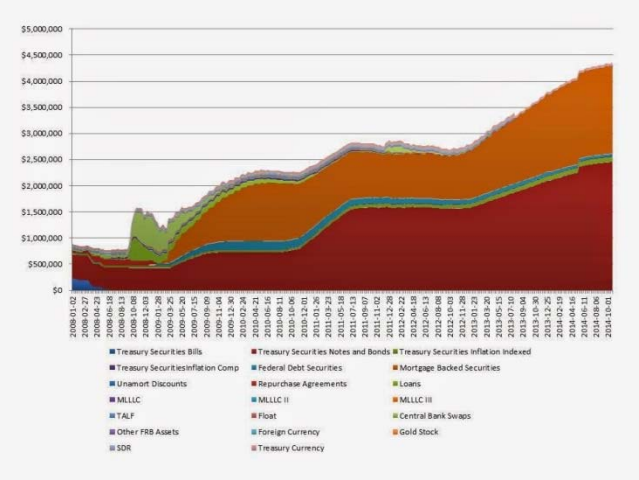


M2 also is growing. Note that in seven years we have seen almost a 50% increase in M2 and under normal terms this should have resulted in higher inflation. Perhaps the $4.5 trillion on the FED's BA may push that along, perhaps not.

Labels: Economy

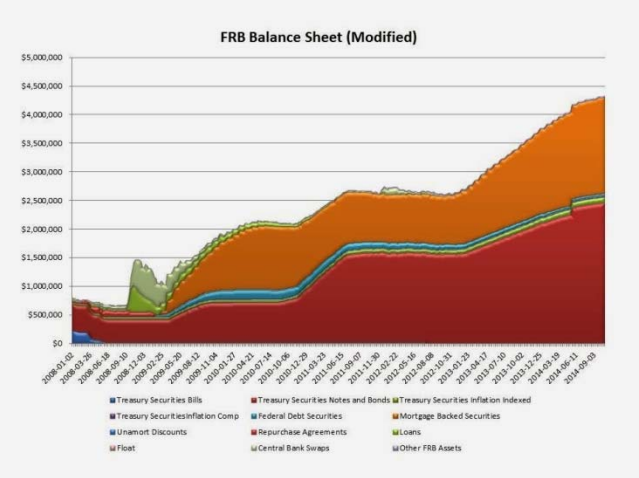
WEDNESDAY, OCTOBER 29, 2014

FED BALANCE SHEET OCTOBER 2014

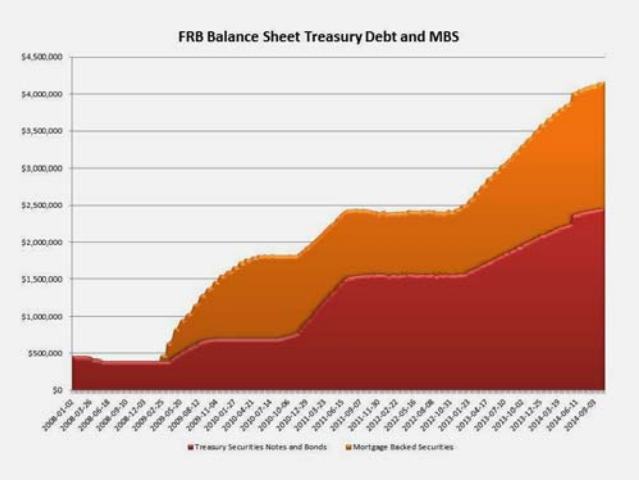


It is worth reviewing the FED Balance Sheet to see where things are. They are well above $4.4Trillion but growing at a slower rate. As the FED stated today:

The Committee judges that there has been a substantial improvement in the outlook for the labor market since the inception of its current asset purchase program. Moreover, the Committee continues to see sufficient underlying strength in the broader economy to support ongoing progress toward maximum employment in a context of price stability. Accordingly, the Committee decided to conclude its asset purchase program this month. The Committee is maintaining its existing policy of reinvesting principal payments from its holdings of agency debt and agency mortgage-backed securities in agency mortgage-backed securities and of rolling over maturing Treasury securities at auction. This policy, by keeping the Committee's holdings of longer-term securities at sizable levels, should help maintain accommodative financial conditions.



The above is a slightly modified version of the BS. Finally below we show the two dominant elements:



Thus we have $4 trillion + in Treasury and Mortgage securities they have to unload. Just what that will do is uncertain. The bigger concern is that if the FED is no longer "buying" Treasury stuff, then who will and at what price.

This is clearly an issue to watch closely. Two things: (i) unwinding the stuff above, (ii) getting people to buy US Treasury debt.

Labels: Economy

TUESDAY, OCTOBER 28, 2014

EBOLA AND FACTS

Let me lay out some facts that we know about Ebola. Then examine a conclusion:

1. Ebola is a highly contagious viral disease.

2. Ebola spreads via transfer by bodily fluids.

3. Sweat is one of the bodily fluids that contain the Ebola RNA virus.

4. The specific mechanism of spreading via bodily fluids is unclear.

5. The current outbreak in West Africa is the first time Ebola has broken out in a higher density area.

6. The rate of spread in a higher density area appears to be greater and lacks the natural self containment of previous outbreaks which were geographically quarantined.

7. The specific mechanism of infection of US based individuals is uncertain other than having had some form of proximity to an Ebola infected patient. In almost all cases the actual mechanism of transfer is unknown.

8. Ebola RNA titers in the blood and urine last about 20 days after initial symptoms. The Ebola RNA titers are still quite high and measurable in sweat after 40 days from start of symptoms.

9. New York subways are high contact transportation systems having hand rails and the like which are a source for sweat transfer.

10. If sweat is a carrier of Ebola RNA, and if an infected patient uses the subway in New York, then there is a likely probability of a transfer of RNA and interaction by third parties with that RNA.

11. To minimize such a potentially lethal exposure the only solution is a quarantine of exposed individuals in some appropriate manner.

Now in a recent NEJM piece the authors write:

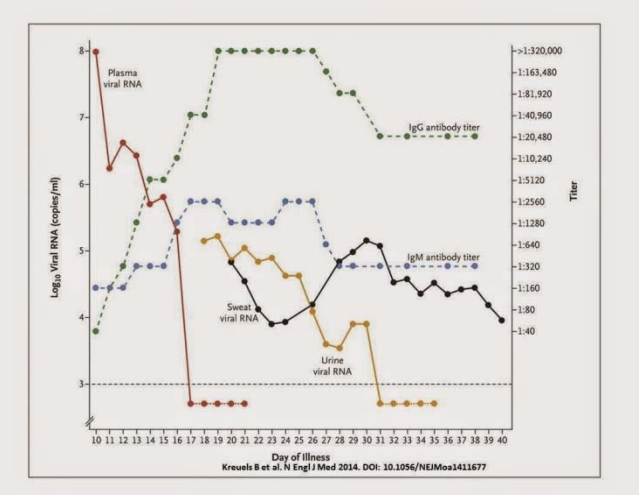
The governors of a number of states, including New York and New Jersey, recently imposed 21-day quarantines on health care workers returning to the United States from regions of the world where they may have cared for patients with Ebola virus disease. We understand their motivation for this policy — to protect the citizens of their states from contracting this often-fatal illness. This approach, however, is not scientifically based, is unfair and unwise, and will impede essential efforts to stop these awful outbreaks of Ebola disease at their source, which is the only satisfactory goal.

If one follows the "scientific facts" or observables then conclusion seems correct. Admittedly placing anyone in a tent in some lot in Newark is cruel and unusual punishment but after all it was Newark,
If it is unscientifically based then one wonders where the above logic fails based upon facts.

Now the NY Times has stated:

However, some public health professionals say that the governors are letting politics guide their decision making in a way that could prove dangerous. "The governors' action is like driving a carpet tack with a sledgehammer: it gets the job done but overall is more destructive than beneficial," according to the editorial in the journal. The article lays out the science behind the spread of the disease, as it is currently understood. "We have very strong reason to believe that transmission occurs when the viral load in bodily fluids is high, on the order of ***millions of virions per microliter****," according to the editorial. "This recognition has led to the dictum that an asymptomatic person is not contagious; field experience in West Africa has shown that conclusion to be valid. Therefore, an asymptomatic health care worker returning from treating patients with Ebola, even if he or she were infected, would not be contagious."*

Let us return to the NEJM Ebola data from Germany as we show below.



Now this starts at day 10, and the concentration is virions per ml in log base 10. Thus in sweat at day 40 we have 10,000 virions per ml or only 10 per micro l. But likewise we have at day 10 in serum about 100,000 per micro liter, or an order of magnitude below the above contagion level. However we also know that such a patient is contagious. Thus we really do not have adequate data. At least in the public domain.

Also the authors of the NEJM editorial have no references to facts, The NEJM editorial states:

A cynic would say that all these "facts" are derived from observation and that it pays to be 100% safe and to isolate anyone with a remote chance of carrying the virus. What harm can that approach do besides inconveniencing a few health care workers? We strongly disagree. Hundreds of years of experience show that to stop an epidemic of this type requires controlling it at its source.

One need not be a cynic. One need to be certain they have the duty of care to the public and absent any definitive evidence that care must be extreme, not based on conjecture. Even the German case is a one of data point. Why, for example, do we not now have a set of such data for all the Ebola cases in the US? Then we start to deal with data.

Oftentimes Medicine is a "what and how" profession. Namely diagnose and then use the standard treatment. It is becoming a "why" profession as well, and the ability to answer the way depends on data, and there now is a significant set of it available and it should become a key element of the conversation.

For example, it we have but 10,000 virions per ml at day 40 and we have a patient then exposing others to that concentration, is that ethically acceptable? Since the minimal viral load is not known, do we best err on the side of public safety?


Labels: Health Care

MONDAY, OCTOBER 27, 2014

VITAMIN D AND PROSTATE CANCER

Introduction

There has been a significant amount of confusion as to the role of Vitamin D in either preventing or in controlling prostate cancer, PCa. The results are often conflicting and have lacked details on why this may be the case. In some cases it is seen as beneficial and in others it is actually seen as having a deleterious effect. Just what the answer is may very well still be uncertain. We focus here on a recent paper by Lambert et al.

We begin with a recent paper by Boland et al state the authors summarize their clinical trial which demonstrates a negative correlation between Vitamin D levels and the incidence of PCa. Specifically they state[10[1]]:

Vitamin D insufficiency is associated with many disorders, leading to calls for widespread supplementation. Some investigators suggest that more clinical trials to test the effect of vitamin D on disorders are needed. We did a trial sequential meta-analysis of existing randomized controlled trials of vitamin D supplements, with or without calcium, to investigate the possible effect of future trials on current knowledge.

We estimated the effects of vitamin D supplementation on myocardial infarction or ischemic heart disease, stroke or cerebrovascular disease, ***cancer****, total fracture, hip fracture, and mortality in trial sequential analyses using a risk reduction threshold of 5% for mortality and 15% for other endpoints. The effect estimate for vitamin D supplementation with or without calcium for myocardial infarction or ischemic heart disease (nine trials, 48 647 patients), stroke or cerebrovascular disease (eight trials 46 431 patients),* ***cancer (seven trials, 48 167 patients)****, and total fracture (22 trials, 76 497 patients) lay within the futility boundary, indicating* ***that***

[10[1]] http://www.thelancet.com/journals/landia/article/PIIS2213-8587%2813%2970212-2/fulltext

vitamin D supplementation does not alter the relative risk of any of these endpoints by 15% or more.

Vitamin D supplementation alone did not reduce hip fracture by 15% or more (12 trials, 27 834 patients). Vitamin D co-administered with calcium reduced hip fracture in institutionalized individuals (two trials, 3853 patients) but did not alter the relative risk of hip fracture by 15% or more in community-dwelling individuals (seven trials, 46 237 patients). There is uncertainty as to whether vitamin D with or without calcium reduces the risk of death (38 trials, 81 173). Our findings suggest that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15%. Future trials with similar designs are unlikely to alter these conclusions.

Thus the above makes a clear assertion that the use of excess Vitamin D does not alter end points in cancer cases.

Even more so, the work by Wong et al states:

Lower levels of vitamin D may reduce prostate cancer risk in older men. By contrast, levels of vitamin D did not predict incidence of colorectal or lung cancers. Further studies are needed to determine whether a causal relationship exists between vitamin D and prostate cancer in ageing men…. As illustrated …, every 10 nmol/l decrease in 25(OH)D concentration was associated with a 4% reduction in prostate cancer incidence, after adjustment for age, education, living circumstance, smoking status, physical activity, CCI, BMI, creatinine, seasonality and previous diagnosis of cancer (other than prostate) (SHR 0.96, 95% CI 0.92–1.00). Similarly, every halving of 25(OH)D concentration was associated with a 21% reduction in incident prostate cancer after adjustment for other risk factors.

In this study in Australia they clearly note that there is a strong indication that lower Vitamin D blood levels yield lower PCa incidence. However the authors (Wong et al) also note the conflicting results on those with existing PCa. They write:

Whilst there is lack of conclusive evidence on the benefit of vitamin D supplementation in the development of prostate cancer, previous studies on the effect of pre-existing prostate cancer have so far produced ambiguous results. A research team in the United States explored the influence of vitamin D3 supplementation at 4000 IU daily for one year on the outcome of early stage, low-risk prostate cancer ... More than half of the study subjects remained stable or improved with supplementation, compared to a fifth of the control group who did not receive supplementation (p= 0.025).

Conversely, vitamin D3 supplementation did not benefit 40% of the subjects in this open-label clinical trial. Another study involves the randomization of 37 patients with histologically proven adenocarcinoma of the prostate who had selected prostatectomy as primary therapy. Calcitriol was administered to the treatment group at 0.5 mg/kg per week for a 4-week period prior to surgery. When prostatectomy specimens were processed and analyzed, VDR expression was significantly reduced in samples from calcitriol treated patients (p = 0.004) but there was no

statistically significant difference in the fraction of cells expressing the specific molecules involved with cell-cycle regulation and proliferation

Thus with evidence of reduction with lower Vitamin D and conflicting results with existing PCa patients it is useful to have some baseline model of what Vitamin D does and why it may be effective.

In a NEJM paper by Hollick, the author states regarding cancers:

In a study of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors. … Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin's lymphoma and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.

The conundrum here is that since the kidneys tightly regulate the production of 1,25-dihydroxyvitamin D, serum levels do not rise in response to increased exposure to sunlight or increased intake of vitamin D.1-3 Furthermore, in a vitamin D– insufficient state, 1,25-dihydroxyvitamin D levels are often normal or even elevated. The likely explanation is that colon, prostate, breast, and other tissues express 25-hydroxyvitamin D-1α- hydroxylase and produce 1,25-dihydroxyvitamin D locally to control genes that help to prevent cancer by keeping cellular proliferation and differentiation in check. It has been suggested that if a cell becomes malignant, 1,25-dihydroxyvitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive.

Once 1,25-dihydroxyvitamin D completes these tasks, it initiates its own destruction by stimulating the CYP24 gene to produce the inactive calcitroic acid. This guarantees that 1,25-dihydroxyvitamin D does not enter the circulation to influence calcium metabolism. This is a plausible explanation for why increased sun exposure and higher circulating levels of 25-hydroxyvitamin D are associated with a decreased risk of deadly cancers.

The issue with the above set of observations is that they lack causative linkages which can be carried through in the cellular analysis.

GDF-15 and PCa

It is always useful to have a clear understanding of what effect a molecule like Vitamin D has on specific pathways and particularly regarding cellular control.

As Lambert et al have noted[11][2]:

Accumulating evidence suggests that chronic prostatic inflammation may lead to prostate cancer development. Growth differentiation factor-15 (GDF-15) is highly expressed in the prostate and

[11][2] http://www.ncbi.nlm.nih.gov/pubmed/25327758

has been associated with inflammation and tumorigenesis. To examine the relationship between GDF-15 and prostatic inflammation, GDF-15 expression was measured by immunohistochemical (IHC) staining in human prostatectomy specimens containing inflammation. The relationship between GDF-15 and specific inflammatory cells was determined using non-biased computer image analysis. To provide insight into a potential suppressive role for GDF-15 in inflammation, activation of inflammatory mediator nuclear factor of kappa B (NFκB) was measured in PC3 cells.

GDF-15 expression in luminal epithelial cells was decreased with increasing inflammation severity, suggesting an inverse association between GDF-15 and inflammation. Quantification of IHC staining by image analysis for GDF-15 and inflammatory cell markers revealed an inverse correlation between GDF-15 and CD3+, CD4+, CD8+, CD68+, and inos+ leukocytes. GDF-15 suppressed NFκB activity in luciferase reporter assays. Expression of the NFκB target, interleukin 8 (IL-8), was downregulated by GDF-15. The inverse relationship between GDF-15 and inflammation demonstrates a novel expression pattern for GDF-15 in the human prostate and suppression of NFκB activity may shed light on a potential mechanism for this inverse correlation.

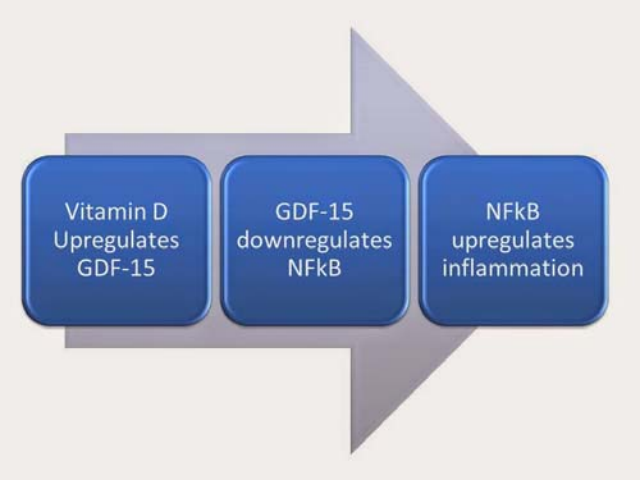
Note from the above:

1. GDF-15 suppressed NFκB
2. GDF-15 downregulates IL-8
3. GDF-15 concentration is inversely related to inflammation

and also shown below:

4. Vitamin D upregulates GDF-15

We summarize this below:



From Newswise we have the following report[12][3]:

A University of Colorado Cancer Center study recently published in the journal Prostate offers compelling evidence that inflammation may be the link between Vitamin D and prostate cancer. Specifically, the study shows that the gene GDF-15, known to be upregulated by Vitamin D, is notably absent in samples of human prostate cancer driven by inflammation.

"When you take Vitamin D and put it on prostate cancer cells, it inhibits their growth. But it hasn't been proven as an anti-cancer agent. We wanted to understand what genes Vitamin D is turning on or off in prostate cancer to offer new targets," says James R. Lambert, PhD, investigator at the CU Cancer Center and associate research professor in the CU School of Medicine Department of Pathology.

Since demonstrating that Vitamin D upregulates the expression of GDF-15, Lambert and colleagues, including Scott Lucia, MD, wondered if this gene might be a mechanism through which Vitamin D works in prostate cancer. Initially it seemed as if the answer was no.

"We thought there might be high levels of GDF-15 in normal tissue and low levels in prostate cancer, but we found that in a large cohort of human prostate tissue samples, expression of GDF-15 did not track with either normal or cancerous prostate tissue," Lambert says.

But then the team noticed an interesting pattern: GDF-15 was uniformly low in samples of prostate tissue that contained inflammation.

This observation is an interesting nexus. It is well known that inflammation is a driver of PCa. It is seen increased in patients with Type 2 Diabetes and obesity, two conditions with co-incident inflammatory responses. The authors continue:

"Inflammation is thought to drive many cancers including prostate, gastric and colon. Therefore, GDF-15 may be a good thing in keeping prostate tissue healthy – it suppresses inflammation, which is a bad actor potentially driving prostate cancer," Lambert says.

The study used a sophisticated computer algorithm to analyze immunohistochemical (IHC) data, a task that in previous studies had been done somewhat subjectively by pathologists. With this new technique, Lambert, Lucia and colleagues were able to quantify the expression of the GDF-15 protein and inflammatory cells by IHC staining on slides taken from these human prostate samples.

Additionally encouraging is that the gene GDF-15 was shown to suppress inflammation by inhibiting another target, NFkB. This target, NFkB, has been the focus of many previous studies in which it has been shown to promote inflammation and contribute to tumor formation and

[12][3] http://www.newswise.com/articles/finally-a-missing-link-between-vitamin-d-and-prostate-cancer

growth; however, researchers have previously been unable to drug NFkB to decrease its tumor-promoting behavior.

As we shall further show, this may be a bit contradictory to other evidence. As we had speculated before, increases in GDF-15 reduced NF-κB, and thus reduced inflammatory factors. They then argue that it is the inflammation and not the excess NF-κB that is the problem. However one must ask what the cause of the inflammation is. They conclude:

"There's been a lot of work on inhibiting NFkB," says Lambert. "Now from this starting point of Vitamin D in prostate cancer, we've come a long way toward understanding how we might use GDF-15 to target NFkB, which may have implications in cancer types far beyond prostate."

Now from a second report, Prostate Cancer News, they state[13][4]:

"GDF-15 may be a good thing in keeping prostate tissue healthy – it suppresses inflammation, which is a bad actor potentially driving prostate cancer," explained Dr. Lambert.

We must note this statement since we will show some contrary versions later. They continue:

The road to understanding was not as clear in the beginning. At first, Dr. Lambert's group tested the theory that vitamin D itself could be protective against prostate cancer in general. "When you take Vitamin D and put it on prostate cancer cells, it inhibits their growth. But it hasn't been proven as an anti-cancer agent. We wanted to understand what genes Vitamin D is turning on or off in prostate cancer to offer new targets."

After the group identified GDF-15 upregulation as a downstream result of vitamin D stimulation, they looked for GDF-15 in human prostate cancer tissue samples. "We thought there might be high levels of GDF-15 in normal tissue and low levels in prostate cancer, but we found that in a large cohort of human prostate tissue samples, expression of GDF-15 did not track with either normal or cancerous prostate tissue."

Then they turned to immunohistochemistry and noticed a pattern: GDF-15 protein expression was greater in samples with inflammatory cells. It seemed GDF-15 was acting to suppress inflammation by inhibiting the transcription factor NFkB. "There's been a lot of work on inhibiting NFkB," said Dr. Lambert.

Since NFkB is well-studied, there may be a few new potential treatments to explore for prostate cancer. "Now from this starting point of vitamin D in prostate cancer, we've come a long way toward understanding how we might use GDF-15 to target NFkB, which may have implications in cancer types far beyond prostate."

Now as NCBI states:

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[13][4] http://prostatecancernewstoday.com/2014/10/24/cu-cancer-center-study-strengthens-prostate-cancer-vitamin-d-link/

(GDF-15 is one of the) bone morphogenetic proteins are members of the transforming growth factor-beta superfamily and regulate tissue differentiation and maintenance. They are synthesized as precursor molecules that are processed at a dibasic cleavage site to release C-terminal domains containing a characteristic motif of 7 conserved cysteines in the mature protein

In a similar fashion:

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of DNA. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens

From Zimmers et al we have a description of GDF-15:

The immunoregulatory cytokine macrophage inhibitory cytokine-1 (MIC-1), a divergent TGF-beta family member, and its murine ortholog, growth/differentiation factor-15 (GDF-15) are induced in hepatocytes by surgical and chemical injury and heat shock. To better understand the in vivo role this factor plays in organ injury, we examined the regulation of GDF-15 in murine models of kidney and lung injury.

We demonstrate herein induction of GDF-15/MIC-1 after surgical, toxic/genotoxic, ischemic, and hyperoxic kidney or lung injury. Gdf15 induction was independent of protein synthesis, a hallmark of immediate-early gene regulation. Although TNF induced GDF-15 expression, injury-elicited Gdf15 expression was not reduced in mice deficient for both TNF receptor subtype. Furthermore, although the stress sensor p53 is known to induce GDF-15/MIC-1 expression, injury-elicited Gdf15 expression was unchanged in p53-null mice. Our results demonstrate that GDF-15 induction after organ injury is a hallmark of many tissues. These data demonstrate that GDF-15/MIC-1 is an early mediator of the injury response in kidney and lung that might regulate inflammation, cell survival, proliferation, and apoptosis in a variety of injured tissues and disease processes.

The GDF factor regulates the inflammatory and apoptotic pathways in cells. Zimmers et al demonstrates several specific issues regarding it regulatory effects.

As Vanhara et al state:

Deregulation of expression and function of cytokines belonging to the transforming growth factor-β (TGF-β) family is often associated with various pathologies. For example, this cytokine family has been considered a promising target for cancer therapy. However, the detailed functions of several cytokines from the TGF-β family that could have a role in cancer progression and therapy remain unclear.

One of these molecules is growth/differentiation factor-15 (GDF-15), a divergent member of the TGF-β family.

This stress-induced cytokine has been proposed to possess immune-modulatory functions and its high expression is often associated with cancer progression, including prostate cancer (PCa).

Now the above is possibly in contradiction to the observation made in the most current paper. However, this work was done earlier and the statement made is perhaps speculative at best.

However, studies clearly demonstrating the mechanisms for signal transduction and functions in cell interaction, cancer progression and therapy are still lacking. New GDF-15 roles have recently been identified for modulating osteoclast differentiation and for therapy for PCa bone metastases.

Moreover, GDF-15 is as an abundant cytokine in seminal plasma with immunosuppressive properties. We discuss studies that focus on the regulation of GDF-15 expression and its role in tissue homeostasis, repair and the immune response with an emphasis on the role in PCa development.

As Bruzzese et al note about the upregulation of GDF-15[14][5].

The tumor stroma is vital to tumor development, progression, and metastasis. Cancer-associated fibroblasts (CAF) are among the abundant cell types in the tumor stroma, but the range of their contributions to cancer pathogenicity has yet to be fully understood.

Here, we report a critical role for upregulation of the TGFβ/BMP family member GDF15 (MIC-1) in tumor stroma. GDF15 was found upregulated in situ and in primary cultures of CAF from prostate cancer. Ectopic expression of GDF15 in fibroblasts produced prominent paracrine effects on prostate cancer cell migration, invasion, and tumor growth.

Notably, GDF15-expressing fibroblasts exerted systemic in vivo effects on the outgrowth of distant and otherwise indolent prostate cancer cells. Our findings identify tumor stromal cells as a novel source of GDF15 in human prostate cancer and illustrate a systemic mechanism of cancer progression driven by the tumor microenvironment. Further, they provide a functional basis to understand GDF15 as a biomarker of poor prognosis and a candidate therapeutic target in prostate cancer.

Perhaps one may interpret the above in either way. Namely GDF-15 upregulated may have been an attempt by the cell to reduce the imputed inflammation of PCa. Now McCarty notes in the review of multiple targets for PCa. First he discusses NF-κB:

Constitutive activation of the transcription factor NF- κB has been observed in a high proportion of androgen-independent prostate cancers. Presumably, the ability of NF-κB to promote transcription of the prominent antiapoptotic protein Bcl-2aids the survival of cells that otherwise

[14][5] http://cancerres.aacrjournals.org/content/74/13/3408.long

would be at risk owing to loss of androgen activity. This constitutive activation reflects increased activity of the IκB kinase (IKK) complex, but why IKK is activated remains unclear. A report that dominant negative NF-κB-inducing kinase (NIK) and tyrosine kinase inhibitors suppress the constitutively elevated NF-κB activity in various prostate cancer cell lines suggests that NIK, possibly downstream from a tyrosine kinase, may mediate the constitutive activation of IKK.

Other factors suggested to play a role in the constitutive activation of NF-κB in prostate cancer include 12-(S)-HETE, Id-1, bombesin, and RhoA. In addition to suppressing apoptosis, NF-κB promotes malignant behavior in other ways: stimulating transcription of cell cycle progression factors (c-myc, cyclin D1), proteolytic enzymes (MMP-9, uPA), and angiogenic factors (VEGF, IL-8). Thus, it is not surprising that nuclear localization of NF-κB in prostate cancer biopsies has been shown to correlate with poor clinical prognosis….

This is consistent with what we have shown before.

Normal prostate epithelium expresses vitamin D receptors, and calcitriol, the natural agonist for these receptors, exerts a growth-inhibitory effect.390-392 These cells also express 1-α-hydroxylase activity and thus can generate their own calcitriol from circulating 25-hydroxycholecalciferol.391,393,394 Since the serum level of 25-hydroxycholecalciferol is determined largely by exposure of skin to ultraviolet light, these findings have encouraged the speculation that good vitamin D status might reduce prostate cancer risk. Although epidemiological studies correlating assessed sunlight exposure with subsequent prostate cancer risk are reasonably supportive of this thesis,395-401 prospective studies examining serum levels of calcitriol or 25- hydroxyvitamin D have been much less so.402-407 Thus, the role of vitamin D status in prostate cancer induction remains unclear. Since supra-physiological concentrations of calcitriol have been employed in most in vitro studies, it is conceivable that the growth inhibitory impact of this hormone on prostate epithelium is pharmacological rather than physiological.

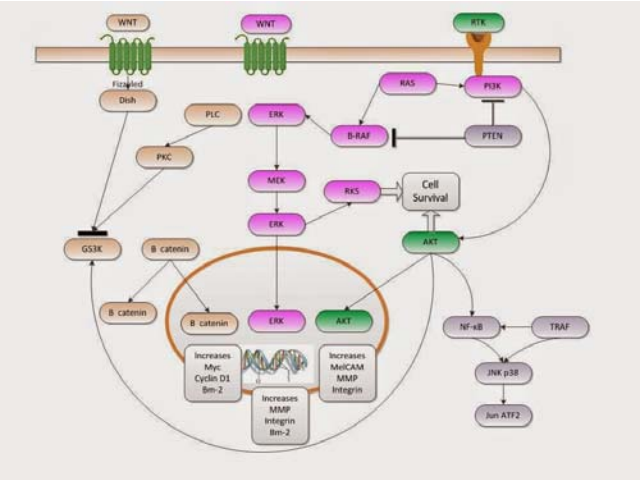
In the above by McCarty there is no clear nexus drawn between NFκB and Vitamin D. The work in question regarding the nexus through GDF-15 may have some promising results therefore.

Finally in a paper by Jeet the authors discuss Vitamin D in murine models. They state:

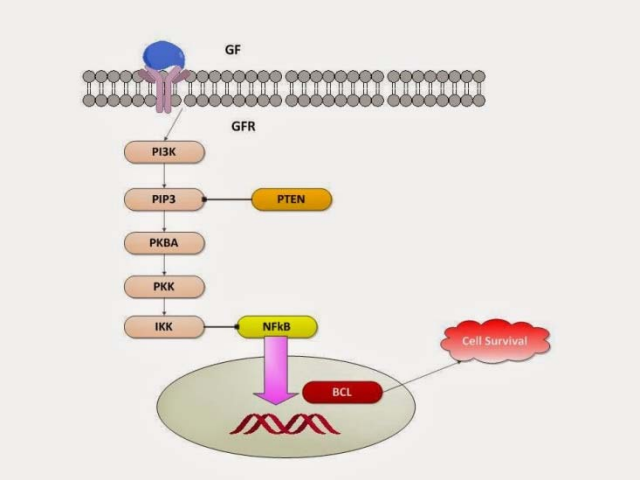
The potential efficacy of vitamin D as a chemopreventive agent for PC has been observed in large cohort studies of human patients with PC [153, 154]. Based on these studies, precancerous and cancerous cohorts of Nkx3.1; Pten compound mutant mice have been treated with 1α, 25 dihydroxyvitamin D3 (biologically active form of vitamin D3) for 4 months continuously [155]. This results in a significant reduction in the occurrence of HGPIN only in the precancerous cohort, whereas mice with already established PIN lesions do not respond to this treatment. However, cancerous cohorts display a less aggressive phenotype with small and focal lesions compared to the wild type controls. Another study has used androgen-independent Gγ/T-15 transgenic mice to test the efficacy of EB1089 (a vitamin D3 analog) in preventing prostate carcinogenesis [156]. Treatment of these mice with EB1089 at three different time points does not cause any significant reductions in tumor onset or delay; however, tumor growth is adversely

affected by 60% at a higher dose of the compound albeit with attendant hypercalcemia and weight loss.

We now show some of the pathways:



Now the specific pathway for what we have been discussing:



Now the presence of GDF-15 is as a specific activating growth factor, GF, as shown in the above. Namely the activation moves down through to NF-κB to activate cell survival and allow for proliferation.

Warburg Effect

The Warburg effect was proposed by Warburg in 1922 when studying cancer. As Vender Heiden et al state in a recent review paper:

In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed "the Warburg effect." Aerobic glycolysis is an

inefficient way to generate adenosine 5'-triphosphate (ATP), however, and the advantage it confers to cancer cells has been unclear.

Namely the alternate pathway is powerful yet confusing. As Wang et al state in examining this effect in PCa:

The Warburg effect, the inefficient metabolic pathway that converts glucose to lactate for rapid energy generation, is a phenomenon common to many different types of cancer. This process supports cell proliferation and promotes cancer progression via alteration of glucose, glutamine and lipid metabolism. Prostate cancer is a notable exception to this general process since the metabolic switch that occurs early during malignancy is the reverse of the Warburg effect. This "anti-Warburg effect" is due to the unique biology of normal prostate cells that harbor a truncated TCA cycle that is required to produce and secret citrate.

In prostate cancer cells, the TCA cycle activity is restored and citrate oxidation is used to produce energy for cancer cell proliferation. 1,25(OH) 2 D 3 and androgen together modulates the TCA cycle via transcriptional regulation of zinc transporters, suggesting that 1,25(OH) 2 D 3 and androgen maintain normal prostate metabolism by blocking citrate oxidation. These data demonstrate the importance of androgens in the anti-proliferative effect of vitamin D in prostate cancer and highlight the importance of understanding the crosstalk between these two signaling pathways

Thus much of the analysis we have been discussing is good science with some excellent observation based conjecture. However there is also the dynamics of the Warburg effect that can be drawn into the analysis.

Observations

We can now make several observations about this continuing investigation into Vitamin D and PCa. Lambert et al present an interesting paradigm to consider in our understanding of PCa.

We leave with a few observation:

1. No clear benefit of Vitamin D enhancements seems to be present. The data is still a bit confusing. On the one hand we have a trial that says the lower the better the chance of not getting PCa and on the other hand we have the statement that Vitamin D helps people with lesions as least in murine models and petri dishes.

2. A logical pathway is presented. The GDF-15 path seems to have a good logical basis and one approachable by targeted therapeutics. That is always a benefit and can be helpful for many who have the problem.

3. Inflammation is a strong and viable source of a precipitating event. This is a well-known observation and the relationship between inflammation and PCa has always been strong. The use of NASIDS has been observed as a putative preventive. The actual biochemical processes leading to this need to be better understood.

4. HGPIN is reversible and this model should include such an observation. Why does it reverse is an open question but its existence is without question.

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Labels: Cancer

ARCHITECTURE AND USE

This is not something out of an Alice in Wonderland script, it is the Stata Center at MIT for EECS. I spent a few years in there and got to know the place a bit. I also spent years in its predecessor, Building 20, the old MIT Rad Lab, the wooden shacks used during WW II to house the radar development group. The old wooden building gave one a sense of past and connection. The new one is a mess. Just look at the above entry, it snows in Cambridge, often quite a lot. The entry ways pile up with ice and snow and then when it is sunny it comes down like a guillotine on whoever is walking by.

The rest rooms are designed to have several stall for women and one for men. Now that is not really important at say 3 in the AM but it could cause a problem during the flu season. The windows leak, and you must bring bread crumbs to find one's way about.

So why the ranting, well its designer seems to be lashing out at his critics. In an article in the New Yorker it states:

"Let me tell you one thing," (the architect) said, according to the Guardian: "In this world we are living in, ninety-eight per cent of everything that is built and designed today is pure shit. There's no sense of design, no respect for humanity or for anything else." He added, pleading, "Once in a while, however, a group of people do something special. Very few, but God, leave us alone."

Well as one who has used his design shown above, it may fall into his set of human waste designs in my opinion. Form follows function, or something like that. But I also wonder who washes the windows and at what cost. Frankly it is monstrosities like this that drive up university costs. MIT actually sued him for the design. But it remains.

Labels: Academy

SUNDAY, OCTOBER 26, 2014

I GUESS WE MUST DEPEND ON WASHINGTON FOR EVERYTHING!

In a statement by the Wellesley grad she states:

"Don't let anybody tell you that its corporations and businesses that create jobs. You know that old theory, trickle-down economics. That has been tried, that has failed. It has failed rather spectacularly. One of the things my husband says when people ask him what he brought to Washington, he says I brought arithmetic."

Yes, those of us who started companies, took risks, used our own capital, in many countries did not create those jobs, Washington did! This perhaps is why we have such a mess in Washington, not only a lack of understanding of those who create jobs, but almost abject hatred for anyone outside of the DC machine.

This statement I gather was made at a Massachusetts whistle stop of one of the State local Pols. One wonders about all of those start ups in Cambridge, did Washington create them?

The logic is amazing, in the past six years we have seen a near collapse of the economy, international respect and the like and now in order to create jobs we must rely on Washington. To do what!

Labels: Government, Politics

SATURDAY, OCTOBER 25, 2014

FACTS NOT FEAR

As we noted yesterday the report by German physicians in NEJM has shown that the Ebola RNA remains active and well above measurable and most likely transferable levels well beyond 40 days after showing symptoms in sweat. At that point the blood and urine are unmeasurable. However transfer by sweat can be significant especially in for example the New York Subways.

In a Guardian piece the current president takes umbrage with the New York and New Jersey Governors who have mandated a quarantine. The paper says:

(the current president) urged Americans to base their response to domestic Ebola cases on "facts, not fear" on Saturday, as signs of a rift emerged between city and state officials over the handling of the diagnosis of the virus in a doctor from New York. In New Jersey, a health worker returning from west Africa, stopped at Newark airport under a new policy hurriedly put in place by that state and New York, remained in hospital quarantine on Saturday despite testing negative in a preliminary test. Civil liberties activists, meanwhile, raised concerns about the constitutionality of the new rules, warning they could discourage health workers from volunteering to fight Ebola in Africa.

Thus will all due respect the "facts" seem to indicate a significant and lasting effect. It is not just

blood, urine, and feces that one worries about but sweat, a readily transferable body fluid. This is especially the case of New York and large metropolitan areas with mass transit. The Governors may very well be dealing with facts, whereas Washington seems to deal in its own brand of fiction.

Labels: Health Care

SATURDAY, OCTOBER 25, 2014

SAINT CRISPIN'S DAY

Today October 25 is the 70th anniversary of the Battle of Leyte, and above is a picture of the crew of the USS Albert W Grant just about that time. It is also the 599th anniversary of the Battle of Agincourt, that of Henry V of which was written:

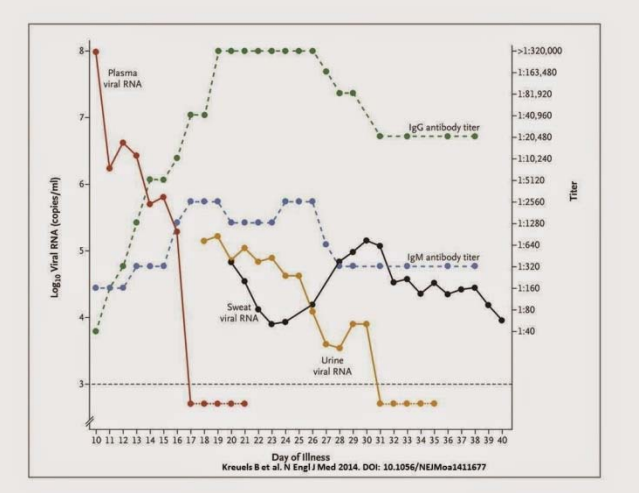
We few, we happy few, we band of brothers;
For he today that sheds his blood with me
Shall be my brother; be he ne'er so vile,
This day shall gentle his condition.
And gentlemen in England, now abed,
Shall think themselves accursed they were not here;
And hold their manhoods cheap whiles any speaks
That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

Labels: Commentary

FRIDAY, OCTOBER 24, 2014

INTERESTING EBOLA CURVE

An interesting curve of Ebola RNA has been presented from a German study in NEJM.



What is worrisome is the viral load in sweat well into the 40th day after exhibiting symptoms. Frankly that is one of the easiest bodily fluids transferred and one especially the case in the New York City exposure. It seems to remain at a measurable level even though the patient is considered free based upon urine and serum. Ebola is a single stranded RNA virus that appears as a crosier with its crooked neck. Having this data makes one wonder what Public Health Officials are basing their judgements upon.

Labels: Health Care

COASE AND EBOLA

The Coasean approach generally is one that if there is a cost to a second party as a result of a first party then the most efficient remedy if transaction costs are zero is to litigate. That is my rephrasing anyhow. This is in contrast to the Government trying to create a law that covers everyone. This of course assumes that the act and actor can be defined and that the damages quantified. We have many such minor cases arise all the time. They generally get settled.

Now to horses. If one has a horse, a very health horse, and one wants to use it in some event in another country then one must quarantine it in the departing country and have it examined before it is allowed to enter the other country. Just look at the Olympics equestrian events. We test for TB on incoming visitors from certain regions.

Now to plants. A couple of decades ago I spent time collecting bryophytes all over Hawaii. From the top of the mountains to the lowest levels. Then before I could bring them back to the mainland I had to wash them in isopropyl alcohol and declare them at the airport to the Department of Agriculture inspector. Made sense.

Yet one can come back to the US having been exposed to the greatest degree to Ebola, heroic as

it may have been, and then wander all over New York. Now to Coase. Perhaps if it results in some cost then perhaps one may then seek a Coaseian remedy. Yet in this case it truly requires a Government response. Respect the great efforts but use common sense. A form of quarantine is essential, if for no other reason than to stop the mass concern.

Now to the truly striking, the New York Police dumping their protective Ebola garb into a trash can. In MedCity News they write:

New York City's Health Commissioner Mary T. Bassett said Spencer "was transported by a specially trained HAZ TAC unit wearing Personal Protective Equipment." Instead of going to the emergency room, the man was taken directly to an isolation unit. But what's also disturbing is a video posted by The Daily Mail showing police officers outside of Spencer's apartment throwing away their gloves and masks in a street trash can. It's unlikely that these guys had any direct contact with Spencer's belongings or the inside of his apartment, but regardless, this doesn't look good.

Not only does it not look good but it clearly demonstrates a clear lack of command control. Where is the Precinct Lieutenant, or better the Captain, and why did this happen! Would this have happened with a New York born Police Commissioner, very doubtful? Or just one from Boston?

Update:

As expected there is now a quarantine. States seem to be more concerned about their citizens than the Feds. As Medscape reports:

New York Governor Andrew Cuomo and New Jersey Governor Chris Christie announced the decision to impose quarantines this afternoon. Calls for this stringent measure have grown louder since Craig Spencer, MD, tested positive for the Ebola virus yesterday after he returned to New York City on October 17 from an assignment with Doctors Without Borders in Guinea. "Since taking office, I have erred on the side of caution when it comes to the safety and protection of New Yorkers, and the current situation regarding Ebola will be no different," Cuomo said in a news release. Christie added, "By demanding these enhanced measures, we are ensuring that any suspected cases are identified quickly and effectively, and that proper safeguards are executed."

Over a hundred years of common sense kicks in finally.

Labels: Health Care

WEDNESDAY, OCTOBER 22, 2014

WHY UNBUNDLING IS GOOD FOR SOCIETY

CATV bundles packages. Often they do it because they have to if they want any of the content providers channels. In addition certain bundles like those carrying sports channels charge exorbitant rates and any subscriber is forced to pay whether they watch it or not.

Then what happens. This massive charge is some $20 per month per HH, or about $2B per month, goes to the teams, most to football teams. Then the money flows to players who it appears then go out and beat their female associates. Thus we poor folks who are forced to fund this assault on women have no voice in denying it.

Along comes some writer for the NY Times and takes the content providers position and argues:

It would be great if you could pay just for the channels you actually use, right? That's the idea behind "unbundling," which some consumer groups have advocated. Cable companies would sell you individual channels rather than vast packages of them. It's an easy idea to get behind when cable companies, never the most lovable of service providers, are raising prices and merging. But surprisingly, unbundling cable channels wouldn't make consumers materially better off. The most likely result would be people paying about the same amount for fewer channels.

He seems not to understand the fundamental law of content. It goes where the money is. Just look at CBS going rogue on the Internet with a subscription service. Even the Times is subscription. The author continues:

And consider how the cable channels would react to losing so many subscribers. The networks make money in two main ways: They get per-subscriber carriage fees from the cable companies that distribute them, and they sell advertising. Ad revenue would fall a little, as some viewers would drop channels they used to watch occasionally. The number of customers subject to carriage fees would plummet as consumers chose to order fewer channels. Meanwhile, each cable channel would know its remaining subscribers are mostly people who actually watch the channel, meaning they have a high willingness to pay. Knowing this, they would raise carriage fees — a lot.

Sorry, but perhaps he has not heard of the free market. It does work if compulsion is removed. If people get to choose and if the channels do raise the price then there is a clearing of the market. People will stay until the price exceeds the value. It works in every other market, so why not content. It works in something we call "the movies". People go and pay to see a film, been doing so for over a hundred years. Forces better content, perhaps. But the above argument in my opinion is worthless, has no merit, and fails both on fact and on logic.

Unfortunately I have the distinct disadvantage of experience. I spent five years in Cable, the early years, 80-84. I still have close friends there and in a manner the rule that "content follow the money" most likely change cable as well. Namely other distribution channels will evolve, the most challenging is 5G wireless, a Gbps distribution network. That will upset the apple cart. Unfortunately the author of the Times piece seem to be a Psychology major turned business analyst, should have stayed with the rat experiments. "Content follow the money".

Labels: CATV, FCC

BURN YOUR BOATS!

Cortes actually sunk his boats but the reminder of burning the boats and moving forward still remains. The counter to this is the "Wing Walker" Rule' do not let go of something until you have a firm hold of something else. The problem in a start up is the latter and not the former. In the many companies I have done, "Burn your boats" is essential. It is akin to joining a religious order, you have one loyalty, to the new company.

Now in contrast I just read an MIT piece praising those who stay at MIT and also start a company. Frankly it violates the "Burn your boats" mantra. In fact, unless you are consulting or a Board member it is in violent contradiction to what is necessary. You are either one or the other.

The MIT piece says:

Not only is it possible to found one's first company while at MIT, says Bill Aulet SM '94 — it's ideal. Aulet is co-director of the Martin Trust Center for MIT Entrepreneurship, along with MIT Sloan faculty member and Innovation Initiative co-director Fiona Murray. Founded in 1990 by Professor Edward Roberts, the Trust Center provides the expertise, support, and connections MIT students need to become effective entrepreneurs — including an extremely popular start-up accelerator capstone program and access to a rotating roster of entrepreneurs in residence. Up-and-coming founders can also avail themselves of the center's workspace, which is equipped with such essentials as videoconferencing systems and floor-to-ceiling dry-erase walls.

Frankly dry-erase walls is the last thing one needs. A start up need focus and leadership, and execution, not a nice room. The article continues:

"When I say our students shouldn't drop out of school to found a company, people always bring up Mark Zuckerberg. Well, you know what — that's like saying Lebron James didn't go to college, so you don't need to. Some people are extreme cases. What about the MIT alumni who cofounded Qualcomm [Irwin Jacobs SM '57, SCD '59 and Andrew Viterbi '56, SM '57]? Their education at MIT gave them the foundation to start that company, not just in technology and engineering and math and science, but also in this carbon-based life form called humans. How do you communicate with people? How do you get along with people?

Andy and Irwin did the start up at a totally different time. This is a strange and contradictory statement. I was there, Irwin was my Faculty Advisor and we worked together while he had Linkabit and I provide funding for Qualcomm when at NYNEX. The facts contradict what he says. They burned their boats and left academia to do the Qualcomm deal, again I was there.

Thus this article does a great dis-service in my opinion. MIT is a fantastic training ground for technology, and now gives some exposure to business.

But, and this is key, I am reminded by a statement by my students a few years back, "We did not know a MIT PhD could run a company?" My response, "Do I look like chopped liver!" They thought you needed some MBA or attorney from Harvard. You hire them, they do not employ you! But you must be ready to "Burn your boats". You must leave academia, and move forward. Beware quasi-academics who seem to be justifying their existence. The only way to learn how to be an entrepreneur is to do it. I guess it is kind of like sex.

Labels: Academy

TUESDAY, OCTOBER 21, 2014

TAKE THE MONEY AND RUN!

Economists are a strange breed and European ones are the most strange. In a recent Think Progress posting they discuss a paper written by a German post-doc and a German Prof at U Penn. The article states:

A 90 percent tax rate on the top 1 percent of American earners wouldn't just significantly reduce income and wealth inequality and boost government tax revenues. It would also be the optimal level for Americans' welfare, according to a new paper from economists ... They find that the top marginal tax rate that maximizes government revenues before being so high as to discourage the wealthiest from earning more is very high, or 95 percent on those who are among the top 1 percent of earners. They also find that a 90 percent tax rate on the richest 1 percent could significantly reduce the Gini index, a measure of income inequality, and wealth inequality would also steadily decline.

Now being in the top 1% does not mean a great deal if one lives in New York City or in almost all of California. In New York City one's marginal tax rate is 39% Federal, plus 14% City and State, plus 3.5% Medicare. That is 56.5% out the gate, well on the way to the above proposed target.

But the real question one should ask is who best redistributes money. Often those in the top 1% are major donors to Universities and Medical Centers as well as the Arts. For example one need only look at the Hospitals on First Avenue above 61st Street and see what the donors have done. Then compare that to a VA Hospital. It shows that the top 1% create much better outcomes in their redistribution. They really pay attention to what happens with what they give. Unlike the Federal Government whose "gifts" honor former politicians and enrich donors to campaigns. A second example is the New York Botanical Garden, supported by the top 1% and open to all who

can come in and explore nature in a pristine location within the confines of New York City.

The question then simply is: who is the best re-distributor of others hard earned wealth, a collection of individuals or the Government. The answer is obvious, especially after examining the Government in the past six years. Individuals make better decisions than any Government official.

Furthermore it seems clear that some German economist most likely will never truly understand the way individualism would and has worked to make the United States what it is today. In my experience they have already two strikes against them; first they are economists and second they are Germans. As economists they see the world through often false paradigms, and from that they develop mathematical models to justify their views. Second, as Germans, based upon my decades of experience, they come from a culture of collectivism and with no inkling of individualism. As individualism was a discovery for de Tocqueville, at least he saw it in action, there never has been such a German equivalent.

Thus what we see coming from these economists in my opinion is their world view, which is reflective more of them than any reality that may exist in Nature.

Labels: Economy

MONDAY, OCTOBER 20, 2014

EBOLA AND POLITICS

Ebola has been around for decades, and most likely longer albeit hidden in small communities in Central Africa. The current outbreak is most likely due to a failure of local Health Care systems to manages its spread. What makes Ebola and its sister viruses so worrisome if the way they cause mortality, they just decompose the body's cells at surfaces so that there is bleeding from every possible location in the victim. It is nasty, and highly contagious in the right circumstances. Nigeria seems to have controlled it, the other three countries seem to have let it run loose, most likely due to lack of infrastructure and leadership.

Now to the US. Clearly Texas has been a clear case of "dumb and dumber". All those who touched this issue demonstrated their ineptness and lack of preparedness. Yet it seems that certain commentators want to make this even more political. Take for example the Left wing blog, Syndicate, whose commentator states:

But, as recent events have illustrated, robust health agencies should not be taken for granted. In fact, over the past decade, the government has slashed budgets at several top health agencies, including the CDC, the National Institutes of Health (NIH), and state and local health departments. Between 2005 and 2012, for example, the CDC lost 17% of its funding, and officials recently reported that funding allocated for Ebola-type health emergencies is $1 billion less than it was in 2003.

Now if we go back a century to the early 20th we see such massive outbreaks of TB and Influenza, much less of a budget but highly competent Public Health people. I recall my grandmother's tales of Seaview Hospital on Staten Island, the NY City TB sanatorium, the City was prepared, the professionals trained and the outbreak controlled. Massive numbers in New York were subject to a plethora of deadly diseases which were handled locally. New York survived. There was no Federal help since it did not exist, it was Harding and Coolidge.

Yet this author in classic Progressive manners take on the budget cuts as the cause of the problem. The problem arose by what appears to be a deficit in Medical expertise, mistakes, and mishandling. In addition the Federal authorities exacerbated the problem.

This same author continues:

The NIH, which funds important advances in our understanding and treatment of diseases like Ebola, has also suffered cutbacks. Its budget has stagnated for most of the past decade, except for years when it was dramatically reduced, such as in 2013. This has forced productive research laboratories to close, putting potentially life-saving research – like that on an Ebola vaccine – on the back burner.

Now the problem with Ebola was that it just was not a problem. There were small outbreaks and all generally were controlled. Here in the current situation we have a different problem, one of massive defects in the US system, for which no more money would ever solve. It is akin to just washing one's hands.

This Syndicate piece lacks in my opinion any credibility and just adds more political gasoline to the fire. It is a shame.

Labels: Health Care

WEDNESDAY, OCTOBER 15, 2014

MICROSOFT MUST REALLY HATE ITS CUSTOMERS

It appears again that Microsoft demonstrates its contempt for its customers. The issue is a re-release of an update package that results in crashes. A UK Blogger says:

This KB 2952664 update for Windows 7 has been continually pushed out by Microsoft almost every month since April 2014 with various tweaks and revisions. Most have had some degree of install problems or have caused some degree of system instabilities. The October 2014 version appears to be the most problematic. It isn't needed so don't install it. It is for reasons like this that I now recommend ***NOT*** *to use automatic updates for windows and do a manual update on 2nd and 4th Tuesdays of the month and check what updates are being installed. Updates are supposed to secure the system and improve it, not cause problems. There have been far too many broken, damaged and unnecessary windows updates forced on a computer recently and it breaks the trust we have with Microsoft updates, that we expect to protect us and only give us automatic updates we need and that are relevant to the computer. Updates like this one should be optional and should not ever be pushed down the regular automatic update channel.*

It appears that Microsoft keeps sending out this rather dangerous item and the only solution is as noted above, stop the auto updates and only selectively update.

After the apparent anti-woman outburst by the current CEO one wonders how long this collection of overblown egos will survive.

Remember, if all else fails listen to the customer. This is something that Microsoft has always failed to do.

Labels: Microsoft

TUESDAY, OCTOBER 14, 2014

MORE ON SNPS AND PCA

Introduction

The problem often found in examining PCa patients with Gleason 7 lesions is to assess whether they are aggressive or indolent. There has been an explosion of putative markets ranging from SNPs, Genes, promoters, miRNAs, methylations and any combination thereto. We generally understand on a cell by cell basis what is occurring in many malignancies and the logic to such changes. But examining cells in a broad spectrum basis, say from any part of the body, to ascertain what a specific tumor portends is highly problematic. The reason is that

Some researchers have argued that SNPs are highly useful. For example Yonggang et al argue:

A major advantage of using SNP data over microarray data to study genetic predisposition is that, unlike microarray data, a person's SNP pattern is unlikely to change over time. Loosely stated, the SNP pattern collected from a person with a disease is likely to be the same pattern that would have been collected from that person at birth or early in life. Thus, we can use SNP data from patients at any stage of their life and at any stage of their disease progression.

However there is no fully accepted basis of that assertion. For example if the lesion is initiated by some methylation resulting from some excess inflammation, and the methylation induces some resulting transcription blockage, then the SNP is irrelevant unless it can be expressly shown to be causative. The mechanisms for such are problematic. Admittedly a SNP in a promoter region may demonstrate blockage of the promoter but most likely must do so on both chromosomes.

A second major advantage of using SNP data is that the data can be collected from any tissue in the body. With microarray data, the mRNA samples for cancer patients are taken from tumor tissue (e.g., from the colon), and the mRNA samples for healthy donors are taken from healthy tissue of the same type (e.g., colon again). SNP data, on the other hand, is not taken directly from tumor samples, but from any tissue in the body. The benefit of this is that, in addition to being faster to obtain, SNP data is also easier to obtain since less invasive procedures can be

used. On the other hand, when using SNP data, we do not expect to have predictors of as high accuracy as we get with microarray data.

Again one must examine this assertion in detail. Does every cell reflect all others in the body? In PCa for example we know that as the tumor progresses the cells express differently, for example look at PTEN, and also in the case of a PCa stem cell we again may have a substantially different expression.

Thus each time we see a result promoting SNPs we must be somewhat cautious.

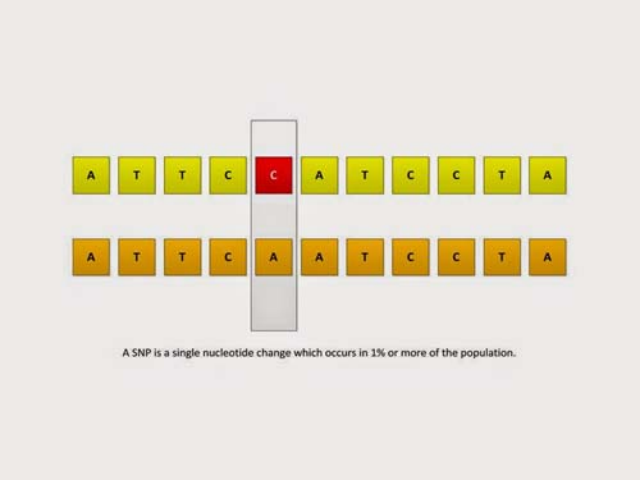
For example in a paper by Lin et al we have an interesting and supportive developed in a causative manner. They state:

However, in many disorders including prostate cancer, the balance between stimulators and inhibitors is tilted to favor stimulators, resulting in an ‘‘angiogenic switch’’. The so- called ‘‘angiogenic switch’’ may result from changes in the expression levels of genes in the angiogenesis pathway. Single nucleotide polymorphisms (SNP) in angiogenesis genes may alter gene expression and influence the process of angiogenesis in prostate cancer and inhibited tumor growth in animal models. Indeed, several SNPs in angiogenesis genes that affect gene expression have been identified. These variants may potentially contribute to inter-individual variation in the risk and progression of prostate tumors. Furthermore, angiogenesis is shown to be associated with the Gleason score, tumor stage, progression, metastasis and survival among prostate cancer patients. Although the number of studies for evaluating the role of SNPs in angiogenesis genes is limited, several of the studies support the association between angiogenesis and prostate cancer aggressiveness. So far, results from several candidate gene and genome-wide association (GWA) studies suggest that SNPs in the angiogenesis pathway may be important in prostate cancer progression and aggressiveness.

Here the authors have not only a correlative connection but a causative one, perhaps.

SNPs Again

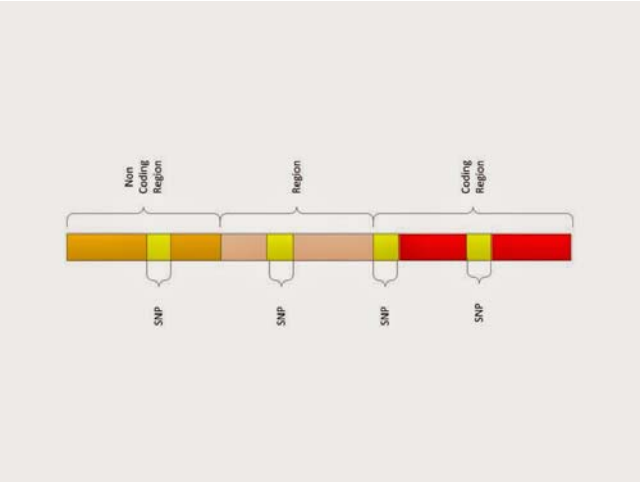
SNPs are single nucleotide changes in a chromosome. There are millions and the clinical significance is at best problematic. The impact of a SNP on the



As Yonggang et al state:

A significant contribution to the genetic variation among individuals is the cumulative effect of a number of discrete, single-base changes in the human genome that are relatively easy to detect. These single positions of variation in DNA are called single nucleotide polymorphisms, or SNPs. While it is presently infeasible to obtain the sequence of all the DNA of a patient, it is feasible to quickly measure that patient's SNP pattern – the particular DNA bases present at a large number of these SNP positions.

The statement of SNPs being substantial elements of genetic variation is not all that obvious. We do observe that some clusters of SNP individuals have a higher propensity for a disease but that may be correlative rather than causative.



SNPs can appear anywhere in a chromosome. As shown above they can be in coding regions, non-coding regions and across promoter regions. What are the effects of these changes? That has been a driving question and it is the issue that must be addressed before correlative effects are used.

Recent Reports

In a paper by Yonggang et al they report:

Gleason score (GS) 7 prostate cancer is a heterogeneous disease with different clinical behavior. We sought to identify genetic biomarkers that may predict the aggressiveness of GS 7 diseases. We genotyped 72 prostate cancer susceptibility SNPs identified in genome-wide association studies in 1,827 white men with histologically confirmed prostate adenocarcinoma. SNPs associated with disease aggressiveness were identified by comparing high-aggressive (GS ≥8) and low-aggressive (GS ≤6) cases. The significant SNPs were then tested to see whether they could further stratify GS 7 prostate cancer.

Three SNPs—rs2735839, rs10486567, and rs103294—were associated with biopsy-proven high-aggressive (GS ≥8) prostate cancer (P < 0.05).

Furthermore, the frequency of the variant allele (A) at rs2735839 was significantly higher in patients with biopsy-proven GS 4+3 disease than in those with GS 3 + 4 disease (P = 0.003). In multivariate logistic regression analysis, patients carrying the A allele at rs2735839 exhibited a 1.85-fold (95% confidence interval, 1.31–2.61) increased risk of being GS 4 + 3 compared with those with GS 3 + 4.

The rs2735839 is located 600 base pair downstream of the KLK3 gene (encoding PSA) on 19q13.33 and has been shown to modulate PSA level, providing strong biologic plausibility for its association with prostate cancer aggressiveness. We confirmed the association of the rs2735839 with high-aggressive prostate cancer (GS ≥8).

The question is how does it modulate the activity and if it does then why does a malignancy occur all too often late in life if that SNP has been sitting there for so long. They continue:

Moreover, we reported for the first time that rs2735839 can stratify GS 7 patients, which would be clinically important for more accurately assessing the clinical behavior of the intermediate-grade prostate cancer and for tailoring personalized treatment and post-treatment management.

In effect the above mentioned SNP, which modulates KLK3 or the PSA gene somehow, can be used as a monitor itself. One could then argue that changes in PSA are reflective of changes in the SNP modulation effect and this have a further basis for continuing PSA measurements.

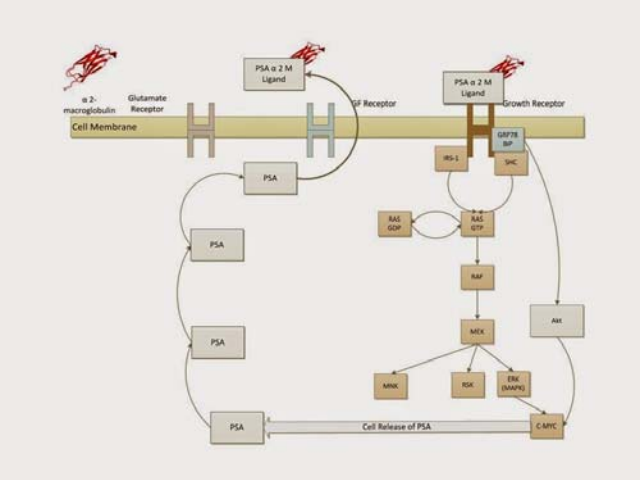
From NCBI we have the following summary discussing KLK3[15][1]:

Kallikreins are a subgroup of serine proteases having diverse physiological functions. Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers. This gene is one of the fifteen kallikrein subfamily members located in a cluster on chromosome 19. Its protein product is a protease

[15][1] http://www.ncbi.nlm.nih.gov/gene/354

present in seminal plasma. It is thought to function normally in the liquefaction of seminal coagulum, presumably by hydrolysis of the high molecular mass seminal vesicle protein. Serum level of this protein, called PSA in the clinical setting, is useful in the diagnosis and monitoring of prostatic carcinoma. Alternate splicing of this gene generates several transcript variants encoding different isoforms.

The PSA process is shown below:



The above demonstrates the normal process for PSA production.

From Waltering[16][2]:

Kallikrein related peptidase 3 (KLK3), better known as prostate specific antigen (PSA), is located in chromosome 19q13.41. KLK3 encodes a single chain glycoprotein with a molecular mass of 33 kDa and functions as a serine protease. It belongs to the family of the fifteen kallikrein members located in a cluster in the same chromosomal region. All kallikrein genes encode five exons of similar size and have high sequence homology with other family members. Many of these peptidases also have several alternative splice variants and are known to be regulated by androgens. KLK3 was cloned in 1987. KLK3 expression has been shown to be elevated in BPH and in highly differentiated PCs, but it is decreased during PC progression.

The use of KLK3 as a PC biomarker (the so-called PSA test) began in the mid-1980s. In a recent European study, which included more than 160,000 men aged 55 to 69; it was found that PSA based screening reduced PC mortality by 20%. However, there was a high risk of overdiagnosis. Androgen regulation of KLK3 includes both the proximal promoter and the enhancer ARE located 4 kb upstream from the TSS. Recruitment of AR and its co-regulators create a chromosomal loop from the enhancer to the core promoter. Kallikrein family members have also

[16][2] Waltering, K., Androgen Receptor Signaling Pathway in Prostate Cancer, PhD Thesis, Univ Tampere, Sept 2010.

been suggested to play a putative role in PC progression. For example, KLK3 has been suggested to directly degrade extracellular matrix glycoproteins and facilitate cell migration.

From a Eureka report on this work they state[17][3]:

Researchers at The University of Texas MD Anderson Cancer Center have identified a biomarker living next door to the KLK3 gene that can predict which GS7 prostate cancer patients will have a more aggressive form of cancer.

The results reported in the journal of Clinical Cancer Research, a publication of the American Association of Cancer Research, indicate the KLK3 gene – a gene on chromosome 19 responsible for encoding the prostate-specific antigen (PSA) – is not only associated with prostate cancer aggression, but a single nucleotide polymorphism (SNP) on it is more apparent in cancer patients with GS7.

Researchers have linked Gleason score, an important predictor of prostate cancer outcomes, to several clinical end points, including clinical stage, cancer aggression and survival. There has been much research associated with prostate cancer outcomes as well as GS7 prostate cancers, which is an intermediate grade of cancer accounting for 30 to 40 percent of all prostate cancers.

"This is the first report that I am aware of that indicates a genetic variant can stratify GS7 prostate cancer patients," said Jian Gu, Ph.D., associate professor at MD Anderson, and a key investigator on the study. "This is important because this group with heterogeneous prognosis is difficult to predict and there are no reliable biomarkers to stratify this group."

In this study, researchers investigated inherited genetic variants to see if there would be any promising biomarkers for prostate cancer patients. The investigators studied the genetic makeup of 72 SNPs identified from the genome-wide association studies (GWAS) in 1,827 prostate cancer patients. They analyzed associations of these SNPs with disease aggression, comparing them in clinically defined high and low aggressive cases. They found a SNP on the KLK3 gene that can predict an aggressive form of GS7 disease.

"Treatment options for the GS7 disease are controversial because the burden of combined treatment modalities may outweigh the potential benefit in some patients," said Xifeng Wu, M.D., Ph.D., professor and chair of Epidemiology, and lead investigator on the study. "It is critical that we develop personalized treatments based on additional biomarkers to stratify GS7 prostate cancers. Additional biomarkers may help us achieve personalized clinical management of low and intermediate risk prostate cancer patients."

Wu also said her team are expanding the study and taking a pathway-based approach to systemically investigate genetic variants in microRNA regulatory pathways as biomarkers for the prognosis of prostate cancer patients. "We are also working on circulating biomarkers.

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[17][3] http://www.eurekalert.org/pub_releases/2014-10/uotm-rdg100214.php also see http://medicalxpress.com/news/2014-10-gene-aggressive-prostate-cancer-diagnosis.html

Eventually, we will incorporate all biomarkers, epidemiological and clinical variants into nomograms to best predict the prognosis of prostate cancer patients at diagnosis."

Now many others have studies SNPs and PCa[18][4]. In a recent paper by Mikropoulos et al on Medscape the authors provide an excellent up to date summary[19][5]:

Several SNPs associated with PrCa risk in the 8q24 locus were among the earliest identified. The 8q24 region is a gene-poor region located upstream of the MYC proto-oncogene and this suggested an association with its expression, which was later proven to occur in a tissue-specific manner. Another important SNP is rs10993994 in the region containing the MSMB gene on chromosome 10. This risk allele associates with reduced MSMB protein expression. MSMB expression is high in normal and benign prostate tissue and low in PrCa. MSMB regulates cell growth and when lost, tumor cells grow in an uncontrolled manner. The odds ratio (OR) for this SNP's association to PrCa was established as 1.61. This is a potential biomarker since urine MSMB assays have been developed and their role in screening is being evaluated.

The Myc region is always a sensitive region. Myc controls cell proliferation and as such needs close control. They continue:

SNP rs2735839 was identified between the KLK2 and KLK3 genes on chromosome 19 where there is a kallikrein gene cluster. Kallikreins are serum proteases and the most well-known member of this group is the prostate-specific antigen (PSA), which is widely used for screening and monitoring PrCa. SNPs were also identified in the intronic region areas of the LMTK2 gene, which codes for cdk5, the SLC22A3 gene, which codes for an organic cation transporter and NUDT10, which regulates DNA phosphorylation.

Again the proximity to PSA gene expression is noted. This has been the case for many previous works not just the one we have focused on herein.

In proximity to the TERT gene (encoding TERT) on 5p15, a further susceptibility SNP was identified (rs2242652). Telomerase is important in counterbalancing telomere-dependent replicative aging. SNPs in this region have been associated with numerous cancers, such as basal cell carcinoma, lung cancer, bladder cancer, glioma and testicular cancer. This SNP showed an association with high PSA levels, as well as increased risk of developing PrCa. Fine-mapping analysis identified a total of four loci independently associated with PrCa risk in the TERT region, one of which was associated with changes in gene expression.

rs2121875 is a SNP located at 5p12 within the FGF10 locus associated with an increased risk of PrCa. FGF10 is often overexpressed in breast carcinomas, and encodes a FGF essential for a range of developmental processes, which also has an important role in the growth of normal prostatic epithelial cells.

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[18][4] We had written extensively on this in July 2013.
http://www.telmarc.com/Documents/White%20Papers/99%20SNPs.pdf

[19][5] http://www.medscape.com/viewarticle/830689

In 2013, we reported on 23 new susceptibility alleles associated with PrCa, 16 of which were also associated with aggressive disease.. A SNP located at 1q32 (rs4245739) in proximity to the MDM4 gene is of potential clinical significance. MDM4 inhibits cell cycle arrest and apoptosis, via p53 downregulation.[30] Another SNP (rs11568818) with a potential prognostic value is situated at 11q22 within a region containing the gene MMP7. MMP7 encodes for a matrix metalloproteinase, which is pivotal for tumor metastasis and overexpression of MMP7 is a potential biomarker for PrCa aggressiveness and risk of metastatic disease. Finally, SNP (rs7141529) at 14q24 is an intronic SNP within the RAD51B gene, which is an important DNA repair gene involved in homologous recombination, also associated with PrCa risk.

From this report we also present below the detailed tabular results on a wide variety of SNPs.

SNP	***Nearby gene***	***Gene function***
rs1218582	*KCNN3*	Calmodulin binding
rs4245739	*MDM4* and *PIK3C2B*	Negative TP53 regulator and therefore inhibits cell cycle arrest and apoptosis and positive regulation of cell proliferation
rs10187424	*GGCX/VAMP8*	SNARE interactions in vesicular transport
rs721048	Intronic in *EHBP1*	Eps15 homology domain binding protein
rs1465618	Intronic in *THADA*	Complex locus
rs13385191	*C2orf43*	Catalytic activity
rs11902236	*TAF1B*:*GRHL1*	TBP-associated factor
rs12621278	Intronic in *ITGA6*	Integrins-cell adhesion cell surface-mediated signaling
rs2292884	*MLPH*	Exophilin subfamily of Rab effector proteins
rs3771570	*FARP2*	Rac protein signal transduction
rs2055109	–	
rs2660753	–	
rs7611694	*SIDT1*	Unknown
rs10934853	Intronic in *EEFSEC*	GTP binding, GTPase activity, nucleotide binding, translation elongation factor activity
rs6763931	Intronic in *ZBTB38*	Transcriptional activator that binds methylated DNA
rs10936632	*CLDN11/SKIL*	CNS myelin
rs1894292	*AFM* and *RASSF6*	Structurally-related serum transport proteins
rs17021918	Intronic in *PDLIM5*	Cytoskeleton organization, cell lineage specification and organ development oncogenesis
rs12500426	–	

rs7679673	*TET2*	Metal ion binding, oxidoreductase activity
rs2121875	*FGF10*	Important role in the growth of normal prostatic epithelial cells
rs2242652	*TERT*	Telomerase is important in counterbalancing telomere-dependent replicative aging†
rs12653946	*IRX4*	Regulation of transcription, DNA dependent
rs6869841	*FAM44B (BOD1)*	Encoding biorientation of chromosomes in cell division 1
rs130067	Missense coding in *CCHCR1*	Protein binding
rs1983891	*FOXP4*	FOX transcription factor family
rs3096702	*NOTCH4*	Notch signaling network
rs2273669	*ARMC2* and *SESN1*	*ARMC2*
rs339331	*RFX6*	RFX family of transcription factors
rs9364554	Intronic in *SLC22A3*	Cation transporter gene
rs1933488	*RSG17*	
rs10486567	Intronic in *JAZF1*	Transcriptional repressor
rs12155172	*SP8*	Transcription factor
rs6465657	Intronic in *LMTK2*	Tyrosine kinase
rs2928679	*SLC25A37*	Mitochondrial carrier proteins
rs1512268	*NKX3.1*	Homeodomain-containing transcription factor NKX3–1†
rs11135910	*EBF2*	Regulation of transcription
rs10993994	*c-MYC* oncogene	Transcription factor activity controlling cell cycle progression, apoptosis and cellular transformation†
rs1447295	–	
rs6983267	–	
rs16901979	–	
rs10086908	–	
rs12543663	–	
rs620861	–	
rs1571801	Intronic in *DAB2IP*	GAP tumor suppressor
rs817826	*RAD23B-KLF4*	Nucleotide excision repair
rs1571801	*DAB2IP*	Ras GAP tumor suppressor
rs10993994	*MSMB* gene	MSMB regulates cell growth†
rs3850699	*TRIM8*	Ligase activity
rs4962416	Intronic in *CTBP2*	Wnt signaling pathway and Notch signaling pathway
rs2252004	–	
rs7127900	–	
rs1938781	*FAM111A*	Proteolysis
rs7931342	–	

rs11568818	*MMP7*	Matrix metalloproteinase associated with metastatic potential
rs902774	*KRT8*	Cellular structural integrity
rs10875943	*TUBA1C/PRPH*	Protein binding, GTP binding, GTPase activity, nucleotide binding and structural molecule activity
rs1270884	*TBX5*	Transcription factors involved in the regulation of developmental processes
rs9600079	–	
rs8008270	*FERMT2*	Actin cytoskeleton organization, cell adhesion, regulation of cell shape
rs7141529	*RAD51*	DNA repair
rs684232	*VPS53* and *FAM57A*	Protein transport
rs7210100	*ZNF652*	Transcription regulation
rs11650494	*HOXB13*	Encoding transcription factor homeobox B13
rs4430796	Intronic in *HNF1B*	Homeodomain-containing superfamily of transcription factors†
rs11649743	–	
rs1859962	–	
rs7241993	*SALL3*	Regulation of transcription†
rs2735839	*KLK2* and *KLK3* regions	Serine proteases†
rs8102476	–	
rs11672691	–	
rs103294	*LILRA3*	Immunoreceptors expressed predominantly on monocytes and B cells
rs11672691	–	
rs6062509	*ZGPAT*	Transmembrane adaptor phosphoprotein
rs2427345	*GATAS* and *CABLES2*	Cyclin-dependent protein kinase regulator activity
rs2405942	*SHROOM2*	Amiloride-sensitive sodium channel activity beta-catenin binding
rs5945619	*NUDT11*	Diphosphoinositol-polyphosphate diphosphatase activity, hydrolase activity and metal ion binding†
rs591943	Androgen receptor	Androgen receptor regulation

Observations

This paper that we have been discussing presents a SNP analysis which has some logical nexus to PSA and pathways often found aberrant in PCa. We are left asking a few questions:

1. What is the controlling mechanism between the SNP and the PSA production?

There seems at best closeness to PSA and an argument that the proximity is reflective of the aggressiveness of the malignancy. There must be a clearer understanding of the entire process before arguing as is done above.

2. Why if the SNP is in the gene does it not cause a PCa effect earlier? What then is the precipitating sequence of events?

This is the key question. If these SNPs are pandemic in all cells then why is PCa specific and why does it take so long? What is truly occurring here?

3. What are the pathway effects?

There appears to be a great deal of inferential data but no clear definitive linkages. The problem with SNPs all too often is the correlative and non-causative relationships.

4. Can one examine a means to block the deleterious effects of this modulation and if so what are they?

This is the therapeutic question. Again one needs the details and not just single nucleotide suggestions.

5. How cell specific is this SNP and as we have seen, many SNPs have broader imputed effects.

We have examined many of the ROC curves and they are interesting but not conclusive. One may not want to bet one's patient's lives on these specific markers

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TUESDAY, OCTOBER 14, 2014

EARLY DETECTION OF PCA

The arguments about the use of PSA screening and the like should also be viewed in actual mortality changes. In a recent paper in Nature Prostate Cancer the authors note:

During the last 30 years, there has been a major shift in initial staging in prostate cancer (CaP) in Western countries, with the incidence of metastases at diagnosis decreasing from over 50% in the 1970s to currently less than 10%. Yet, CaP is still the second cause of cancer death in men. We used two monthly curated databases of patients with castration-resistant prostate cancer (CRPC) to describe the natural history of patients dying of CaP in the modern era. In the modern era, approximately half of the patients who die from CaP have metastases at diagnosis. The paradigm of progression from localized disease to metastasis and eventually death is only represented in the other half, although possible initial screening and staging errors ought to be taken into consideration. More efforts are needed to conduct trials in patients with newly diagnosed metastatic Ca.

Thus the conclusion should be clear; early detection, no matter what the discomfort, should be the goal.

Labels: Cancer

PLANTS, CO2 AND WARMING

A recent NAS paper demonstrates that trees and other plants absorb substantially more CO2 than estimated before. The BBC reports on this effort as follows:

Global climate models have underestimated the amount of CO2 being absorbed by plants, according to new research. Scientists say that between 1901 and 2010, living things absorbed 16% more of the gas than previously thought. The authors say it explains why models consistently overestimated the growth rate of carbon in the atmosphere. But experts believe the new calculation is unlikely to make a difference to global warming predictions.

The paper states:

This increase represents a 16% correction, which is large enough to explain the persistent overestimation of growth rates of historical atmospheric CO_2 by Earth system models. Without this correction, the CFE for global GPP is underestimated by 0.05 PgC/y/ppm. This finding implies that the contemporary terrestrial biosphere is more CO_2 limited than previously thought.

There are several observations that should be made.

1. On the negative side the Equatorial forests are often being defoliated at a rapid rate.

2. The Temperate lands are being reforested at a significant rate. New Hampshire is almost 90% forested and is more than during the Colonial daya of 300 years ago.

3. Temperate trees have a much wider region for growth, from Zone 9 through Zone 3. Thus Pinus rigida can survive from San Diego to Northern Canada. The classic Palm trees cannot.

4. 16% is not a small number especially when compounded. Just think of 1.16 to the 100th power. That is a big number.

The issue is one that states that change is a natural phenomenon and that our knowledge of that process is miniscule at this stage.

Labels: Global Warming

MONDAY, OCTOBER 13, 2014

ECONOMICS AND THE NOBEL

The Nobel Committee today awarded a French Economist the Prize in Economics for the work done in regulation theory. The NY Times states:

The Royal Swedish Academy of Sciences said that (he) had helped governments tame such firms by analyzing when and how regulators should intervene to constrain activities, and when to stand back. (he) helped show "what sort of regulations do we want to put in place so large and mighty firms will act in society's interest," (said) the chairman of the prize committee, said after the award announcement. His work focuses on markets that lack the perfect competition portrayed in textbooks, where the push-and-pull among firms keeps prices low and quality high. In reality, many markets are dominated by a small number of firms that have the power to keep prices artificially high, and may lack incentives to improve quality. Furthermore, these firms tend to know much more than their regulators.

Now this is a topic that I have some firsthand knowledge. The winner for example addressed the issue of interconnection fees, best discussed in his book entitled Competition in Telecommunications. One need read no more than pp 100-133 to see that although he is good at mathematics he has failed in my opinion to understand the business. His arguments are

repositioning of the Baumol-Willig Theorem on interconnect. The theorem justifies the incumbent charging the new entrant an interconnect fee, thus maintaining the monopoly.

In this case it was the interconnection between long distance or wireless carriers and the incumbent wire line carrier. In my analysis in the early 1990s I indicated that they were separate services and that they should be priced to reflect their costs not costs bearing unacceptable cross subsidies. It was this person's studies that through complex mathematics he argued for the cross subsidies to maintain the existing monopoly incumbent.

The essence of the argument is simple. If one buys a pair of socks, must one pay the shoe maker a fee for interconnecting your foot to the shoe via the sock? The logical real life answer is no! However to this person he sets up an argument to minimize consumer costs but subject to the incumbent monopolist not losing any money. Ad hoc propiter hoc. The true fact is that a consumer should pay for each piece from the provider of that piece and there should be no interconnection. This false concept took consumer monies in the hundreds of billions if not trillions over decades. If one places a long distance wireless call then one should select the local carriers and the long distance carriers. It was a nice idea in 1982 with the Judge Green decision but it has been lost in my opinion due to sophistry of the type we see in the above arguments.

It is a shame that his analysis failed to see and understand the need for separation and that wireless was and would become a dominant player as we clearly understand today. I had written a paper for the White House Staff in 2002 depicting the changes in telecom having just battled the issue in the trenches in 22 countries. There is a need to do "bench work" in economics, namely to understand the technology and actual cost structures, not just expansive mathematical analyses.

Unfortunately this award, to a highly competent mathematical manipulator of economics issues, in my opinion lacks the factual underpinnings which all too often are lacking in the political swamp of regulatory proceedings.

Labels: Regulation, Telecom

SUNDAY, OCTOBER 12, 2014

THE ACA, POLICY, AND WHO GETS TO LIVE

There was a set of discussions regarding the ACA and the limiting of services under Medicare regarding those over 65. Of course those in the Administration voiced their objections to such an assertion yet there were members of the White House staff who actually discussed such options in detail.

In a recent article by a former White House adviser on the ACA the individual states[20[1]]:

[20[1]] http://www.theatlantic.com/features/archive/2014/09/why-i-hope-to-die-at-75/379329/

This means colonoscopies and other cancer-screening tests are out—and before 75. If I were diagnosed with cancer now, at 57, I would probably be treated, unless the prognosis was very poor. But 65 will be my last colonoscopy. No screening for prostate cancer at any age. (When an urologist gave me a PSA test even after I said I wasn't interested and called me with the results, I hung up before he could tell me. He ordered the test for himself, I told him, not for me.) After 75, if I develop cancer, I will refuse treatment. Similarly, no cardiac stress test. No pacemaker and certainly no implantable defibrillator. No heart-valve replacement or bypass surgery. If I develop emphysema or some similar disease that involves frequent exacerbations that would, normally, land me in the hospital, I will accept treatment to ameliorate the discomfort caused by the feeling of suffocation, but will refuse to be hauled off.

What about simple stuff? Flu shots are out. Certainly if there were to be a flu pandemic, a younger person who has yet to live a complete life ought to get the vaccine or any antiviral drugs. A big challenge is antibiotics for pneumonia or skin and urinary infections. Antibiotics are cheap and largely effective in curing infections. It is really hard for us to say no. Indeed, even people who are sure they don't want life-extending treatments find it hard to refuse antibiotics. But, as Osler reminds us, unlike the decays associated with chronic conditions, death from these infections is quick and relatively painless. So, no to antibiotics.

As we had noted previously, this same author has written that the young and old should be left to perish for the best interest of all[21][2]. In this paper he promulgated the proposal that when a severe expansive disease explodes that the young and old could or should be allowed to perish and maximize the benefit of the most productive to society. This he has termed the Complete Lives System. He states:

Because none of the currently used systems satisfy all ethical requirements for just allocation, we propose an alternative: the complete lives system.

This system incorporates five principles: youngest-first, prognosis, save the most lives, lottery, and instrumental value. As such, it prioritizes younger people who have not yet lived a complete life and will be unlikely to do so without aid. Many thinkers have accepted complete lives as the appropriate focus of distributive justice: "individual human lives, rather than individual experiences, [are] the units over which any distributive principle should operate."

Although there are important differences between these thinkers, they share a core commitment to consider entire lives rather than events or episodes, which is also the defining feature of the complete lives system. Consideration of the importance of complete lives also supports modifying the youngest-first principle by prioritizing adolescents and young adults over infants.

Adolescents have received substantial education and parental care, investments that will be wasted without a complete life. Infants, by contrast, have not yet received these investments. Similarly, adolescence brings with it a developed personality capable of forming and valuing

[21][2] http://www.factcheck.org/UploadedFiles/emanuel_lancet.pdf

long-term plans whose fulfilment requires a complete life. As the legal philosopher Ronald Dworkin argues, "It is terrible when an infant dies, but worse, most people think, when a three-year-old child dies and worse still when an adolescent does"; this argument is supported by empirical surveys.

Importantly, the prioritization of adolescents and young adults considers the social and personal investment that people are morally entitled to have received at a particular age, rather than accepting the results of an unjust status quo. Consequently, poor adolescents should be treated the same as wealthy ones, even though they may have received less investment owing to social injustice. The complete lives system also considers prognosis, since its aim is to achieve complete lives. A young person with a poor prognosis has had few life-years but lacks the potential to live a complete life.

Considering prognosis forestalls the concern that disproportionately large amounts of resources will be directed to young people with poor prognoses. When the worst-off can benefit only slightly while better-off people could benefit greatly, allocating to the better-off is often justifiable. Some small benefits, such as a few weeks of life, might also be intrinsically insignificant when compared with large benefits.

Saving the most lives is also included in this system because enabling more people to live complete lives is better than enabling fewer. In a public health emergency, instrumental value could also be included to enable more people to live complete lives. Lotteries could be used when making choices between roughly equal recipients, and also potentially to ensure that no individual—irrespective of age or prognosis—is seen as beyond saving. Thus, the complete lives system is complete in another way: it incorporates each morally relevant simple principle.

When implemented, the complete lives system produces a priority curve on which individuals aged between roughly 15 and 40 years get the most substantial chance, whereas the youngest and oldest people get chances that are attenuated

Namely in his analysis those between 15 and 40 are deemed worthy of treatment and those younger or older are left by the wayside. This paper was a clear predecessor of his proclamation of 75 as a maximum lifetime, no matter what. This not only goes beyond rationing it enters the field of state based euthanasia.

Again one must remember that this person has been and continues to be a spokesperson for the current Administration. Are these pure academic musings or are they a recipe for the future of health care. Clearly the first academic paper attracted some attention but it may have been dismissed as the musings of a pure academic. On the other hand and in my opinion the second outcry demanding a death at a certain age is almost an affirmation of adherence to this policy.

The overall objections to this type of thought are as follows:

1. The very personal discussion is perhaps in my opinion beyond the norm. This is most likely a very private and personal issue and frankly one does not then take your personal description of

life and then expose it publicly as a mandate for all. Between excess ego and limited social skills perhaps a better approach would apply.

2. However, it should be noted that this same person had examined and proposed an option of allowing early or late life death by the process of selection based on metrics adjudged by the State.

3. Individuals who bring this type of thought process may find a home in the academy but when they enter the arena of public policy then there is a demand for closer scrutiny and analysis, if not outright rejection.

Labels: Health Care

WEDNESDAY, OCTOBER 8, 2014

MOOCS: THERE HAS TO BE A BETTER WAY

I am again examining the MOOCs and their approach to education. One recent course is an MIT course on what used to be called Strength of Materials. Some observations:

1. The instructor spends well more than half the time writing her note on the board without any real additional insight. The board should be a stage prop, not a means to re-write the notes. If you have them thus why re-write them?

2. The exam questions are interesting. Let me explain.

a. Some fifty plus years ago, with paper, pencil and slide rule, students attacked the same issues. Most likely it was done that way for a few centuries. One received an exam question on paper and then the student used what was called Engineering paper, a grid like sheet of paper, upon which you prepared the solution. You restated the givens, you then drew whatever diagrams you needed, then you proceeded through the equations in the analysis, then you inserted the numbers, used your slide rule, underlined the answers and so on. You interacted with the problem so as to get to know and understand it in a linear and proximate fashion. The pencil, paper and slide rule became an integrated whole.

b. In today's world the approach is dramatically different. The computer gives the problem on the screen, you must somehow capture that and convey it to whatever mode of processing you choose. I first started out with paper but bad mistake. It appears that using Excel spread sheets as a substitute for your Engineering paper works better. But beware, you must copy exactly. For example a 1.59 may appear as a 1.50 or even get copied that way. Then the answer is inserted into the same screen from which you got the information. Watch as you units and what I have found essential is to copy from Excel into the computer screen. The problem is that the computer never understands your level of thought and your only feedback is the right or wrong mark. There is no way to understand a mistake, say a sign, and remedy it. The exam measure more the

ability to copy in correctly and copy out correctly and to be correct in one's units! It does not measure understanding and it does not facilitate understanding.

Thus the change from half a century ago to today actually may defeat the purpose of education.

3. The Discussion groups are oftentimes chaotic. It is a mass of often divergent cultural approaches to learning, or worse, the participants may be actually assuming they are getting an MIT education. In reality this may be a move to checking reading skills and short term memory. Any mild dyslexia could and does cause havoc, one always writes the wrong number, close but not exact. Thus one spends time checking the transcriptions. One is not learning the material but fine tuning the process. The participants do not seem to understand that, unless they come from a world in which that is the way they are educated, which many do.

Labels: Academy, MOOCs

SUNDAY, OCTOBER 5, 2014

DESTROYING AMERICAN EXCELLENCE

In a piece in today's NY Times some Business School instructor suggests we abandon the current method of selecting college students and using Psychologist interviews. The writer suggests:

Sending student applicants to assessment centers would solve at least three problems for college admissions. First, colleges have traditionally relied on recommendation letters from different teachers and interviews with different alumni who evaluate students in different situations. These idiosyncrasies create a great deal of noise: Reports reveal as much about the teachers, interviewers and situations as they do about the students. In an assessment center, students answer standardized questions and are rated by multiple evaluators on a common standard.

Now I cannot think of any student at MIT who would pass such an exam. It was tried during the early 70s, some form of getting in touch with yourself. Now we promote faculty based on performance and not on getting in touch with themselves. No Psychologist could have a conversation with a student interested in applying. There is no point of connection. Imagine some brilliant math or computer science applicant sitting in front of some at best average Psychologist. One has to be a bit awry to even contemplate this.

Also the cost of such a screening would in extraordinary. Yet all too often writers of pieces like this do not seem to recognize this.

Frankly of all the suggestions I have heard over decades this is by far the most absurd in my opinion. But I suspect that they will never stop.

Labels: Academy

WEDNESDAY, OCTOBER 1, 2014

PROSTATE CANCER UPDATES

We continue to see a back and forth on measuring the aggressiveness of PCa. The range is from determining a specific gene aberration to panels of multiple genes. We briefly examine two recent presentations which highlight the continuing issue of cause and prognostic tests. The discussion herein is an extension of what we have discussed previously[22][1].

In a recent paper the authors at Oncogene describe why the TMPRSS2:ERG translocation results in AR PCa[23][2].

The biological outcome of TMPRSS2:ERG chromosomal translocations in prostate cancer (PC) remains poorly understood. To address this, we compared the transcriptional effects of TMPRSS2:ERG expression in a transgenic mouse model with those of ERG knockdown in a TMPRSS2:ERG-positive PC cell line. This reveals that ERG represses the expression of a previously unreported set of androgen receptor (AR)—independent neuronal genes that are indicative of neuroendocrine (NE) cell differentiation—in addition to previously reported AR-regulated luminal genes. Cell sorting and proliferation assays performed after sustained ERG knockdown indicate that ERG drives proliferation and blocks the differentiation of prostate cells to both NE and luminal cell types.

Inhibition of ERG expression in TMPRSS2:ERG-positive PC cells through blockade of AR signaling is tracked with increased NE gene expression. We also provide evidence that these NE cells are resistant to pharmacological AR inhibition and can revert to the phenotype of parental cells upon restoration of AR/ERG signaling. Our findings highlight an ERG-regulated mechanism capable of repopulating the parent tumor through the transient generation of an anti-androgen therapy-resistant cell population, suggesting that ERG may have a direct role in preventing resistance to anti-androgen therapy.

Now as we have already stated[24][3]:

ERG produces a protein which is a transcriptional regulator in the nucleus. ERG is also known for its movement from its base location 21q.22.3 and binds to TMPRSS2 at 21q22.3 . This is effect a gene fusion and is frequently found in Androgen Resistant PCa. We demonstrate this

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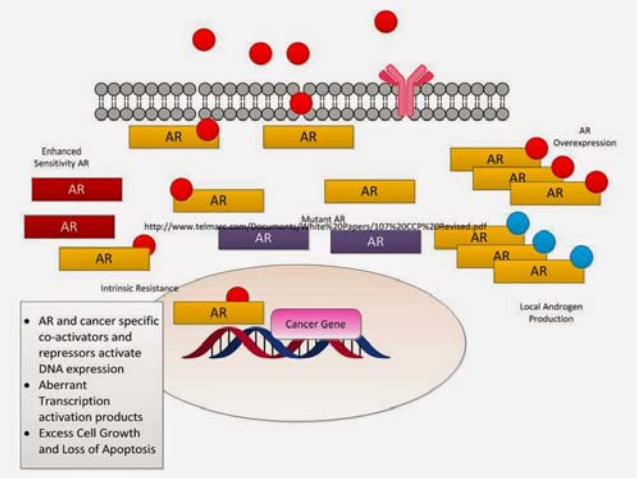
[22][1] http://www.telmarc.com/Documents/White%20Papers/110%20ERG%20and%20PCa.pdf, and http://www.telmarc.com/Documents/White%20Papers/107%20CCP%20Revised.pdf

[23][2] See, Mounir, Z., et al, TMPRSS2:ERG blocks neuroendocrine and luminal cell differentiation to maintain prostate cancer proliferation, Oncogene , (29 September 2014) | doi:10.1038/onc.2014.308, http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2014308a.html

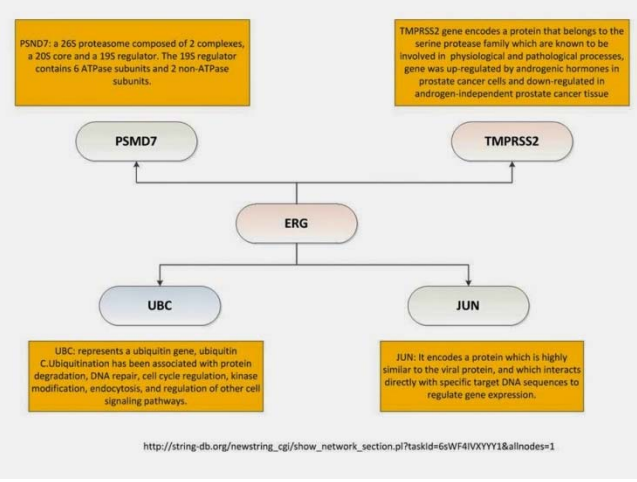
[24][3] http://www.telmarc.com/Documents/White%20Papers/110%20ERG%20and%20PCa.pdf

change below, by showing the exons of TPMRSS2 and ERG and how they get fused producing a new gene with deleted exons but producing an oncogene product. In essence TMPRSS2 is androgen activated and the ERG gene becomes a promoter more fully activated via the TMPRSS2 association. In a sense it is not a true translocation, namely the genes have not been moved from the original chromosome like that in CML but a section is removed and they are joined.

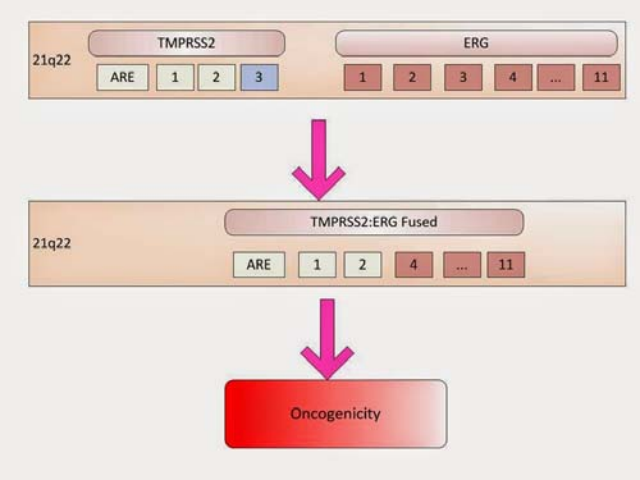
But it is the recognition that ERG represses AR that is a significant factor. This paper opens another door in explaining why the ERG fusion can be so serious a factor in PCa. Specifically as we show below the AR loss of control results in aggressive PCa.



Now we have also previously shown the relationship of ERG to other pathway elements as shown below.



Finally the ERG fusion can be viewed as below.



Now in contrast to the attention to a specific gene and a specific function we have the other extreme of mapping multiple genes onto a metric for assessing aggressive PCa. In a recent ESMO conference we have the report as seen on Businesswire[25][4]:

... multiple studies across different cancer types demonstrating how its genomic test Oncotype DX has led to a greater understanding of cancer at the molecular level, enabling more personalised treatment decisions.

"The results of this study confirm that the information provided by the Oncotype DX prostate cancer test can help physicians and patients choose the most appropriate treatment approach, based on an individualized risk assessment."

Data from the additional prostate cancer clinical validation study confirm that the Genomic Prostate Score (GPS) provided by the Oncotype DX prostate cancer test is a significant predictor of disease aggressiveness at the time of diagnosis based on assessment of biopsies from the tumour and provides information beyond currently available risk factors. In particular, this new study confirms Oncotype DX as a predictor of adverse pathology from the biopsy, as previously demonstrated in a published validation study, and demonstrates the test's ability to predict the risk of recurrence after surgery....

The Oncotype DX prostate cancer test measures the level of expression of 17 genes across four biological pathways to predict prostate cancer aggressiveness. The test results are reported as a Genomic Prostate Score (GPS) that ranges from 0 to 100 and is combined with other clinical factors to further clarify a man's risk prior to treatment intervention. This first-of-its-kind, multi-gene test has been validated to guide treatment decisions using the prostate needle biopsy sample taken before the prostate is removed − thereby providing the opportunity for low-risk patients to avoid invasive treatments such as radical prostatectomy or radiation.

What is unfortunate are the following:

[25][4] See, http://www.businesswire.com/news/home/20140929005110/en/Oncotype-DX%C2%AE-Test-Precision-Oncology-Data-Presented#.VCqe11etZrs , http://www.esmo.org/Conferences/ESMO-2014-Congress/Abstracts

1. Methylation effects as well as miRNA effects have not been incorporated in many of these studies. A gene may not be expressed due to the methylation of the promoter or some similar controlling region. Also we may have histone methylation again turning on or off any transcription. Translation may also be blocked by miRNAs and there are now dozens of possible candidates.

2. Which cell or cells should we test? Selecting prostate cells for testing may become a significant demand on the analysis of the grade of PCa. At one extreme we may want to find a stem cell and at the other extreme we may need to profile the tumor across all cells. Generally no one cancer cell is genomically expressive as all others. There is variability. We have examined techniques that would allow for such analysis but they are still in the R&D state. Yet having this ability to genomically profile the entire tumor mass will become mandatory. There will then be a profile of the mass. This profile must also include any transcriptional and translational influences from methylation and miRNAs.


Labels: Cancer

MOOCS, HEIDEGGER AND DIFFICULTY

In a recent piece in the Harvard Crimson a student was bemoaning the issue of difficulty. The author states:

This past summer, Harvard announced that it would remove difficulty scores from the Q-Guide. ...said that "these changes reflect the decisions of the Faculty Council that were intended to make the Q a more accurate, sophisticated, and helpful mechanism for learning about and choosing courses." Much of students' outrage centers upon the idea that we have the right to know this information and to choose classes as we please. I have a question ...: How do we, as Harvard students and faculty members, define difficulty? This question may seem overly simplistic, but in my mind, it is actually quite nuanced. When the Q asks us whether or not a class is difficult, is it asking us how hard it is to get an A? Or how easy it is to get a B? Is it how difficult the day-to-day work is, or how hard the final assignments are? I am sure that when many students answer on the Q, they have one or all of these definitions in mind. Difficulty could mean something more thought provoking though. It could be how much a class forces us to think about our own values and preconceived ideas and either change them or inspire us to believe them more deeply. Similarly, it could be how challenging the test material is, instead of how harshly the professor grades those tests. Or, maybe, something being difficult means that it forces us think about the big questions of life that frequently make us uncomfortable.

I have never been a fan of student reports of this type, they all too often reflect the weakness of the students rather than the quality of the course. But that is only part of the issue.

But how does one get Heidegger into this fray? In the NY Review of Books is a review of

Heidegger's Black Books. His notes during his Nazi involvement. It is an excellent review and does bring to bear the Nazi past of Heidegger, the oft praised philosopher whose observations led to the Existential movement, based somewhat on the question of; what is life if there is no God? Thus we have Sartre and de Beauvoir and the post WWII "thinkers" in and around Paris.

As the reviewer so well states:

In his early masterpiece, Being and Time, first published in 1927, Heidegger set forth a bold challenge to the conventional picture of the human being that, in his view, had held sway in philosophy at least since Descartes if not long before. According to this picture, the human being confronts the external world as a disengaged thinker or res cogitans. Knowledge of the world is therefore a matter of correct representation, and truth is essentially a correspondence between an external state of affairs and one's representation of that state of affairs within the confines of one's own consciousness. Heidegger objected to this picture not only because he felt it was bad epistemology but, more importantly, because he felt it was bad metaphysics. It splits reality in two, placing the mind on one side and the world on the other, and then makes representation do the work of bridging the divide. Heidegger proposed instead that philosophy should take as its cue our everyday commerce with worldly things. When I wield a hammer, my knowledge of that hammer is not primarily a matter of how it is represented or conceived; it is an implicit know-how that animates my action and embraces its elements all at once: the weight of the tool, the heft of the wood, my care in the work, and so forth. This everyday kind of purposeful involvement motivates a general picture of the human being as already immersed in its world. To emphasize the this-worldly character of such immersion Heidegger uses the term Dasein (which is simply the German word for existence). Dasein is not consciousness but rather "being-in-the-world." It is an ongoing event that is thrown into time and can only come upon itself as it presses forward into its own possibilities.

Thus for Heidegger it is the Dasein, the "being in the world", the throwness, the breakdown, etc that is the core of his epistemology. Namely we learn by doing, we learn by our mistakes, and we learn by being in the process of learning. The classic statement that "if one wants to get on the bus and go somewhere, then one must be at the bus stop to start" is all too true. Sometimes it may be the wrong bus but we should then learn from that mistake.

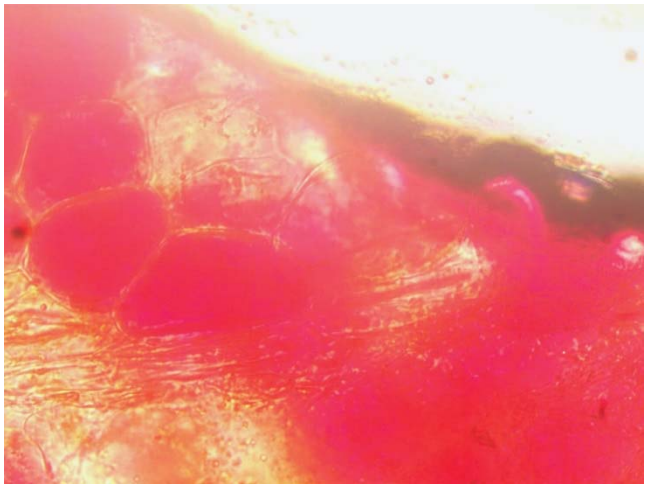
How does this relate to MOOCs? Simply, as the Harvard student recognizes, the Quality of a course or its complexity is really the result of the interaction between the student and the instructor. Lander and Biology is an almost religious experience. Many others are painful reminders of childhood rote education. But is an exciting professor the useful source of wisdom? Or is the professor just an entertainment akin to a weekend at Las Vegas. Did we learn something that has value and which is extensible and enriches our lives and others? Tough question. Yet it should be examined. Lander and his class wins on all fronts.

Yet many other MOOC instructors are treating this like some Freshman High School Algebra course, they give the rules, and then they demand a recitation of examples.

Perhaps the Dasein of Heidegger and the Q issue at Harvard could be a melding of issues to assist MOOC instructors to seek out what education could and should be.

Labels: Academy

MODERN DAY BOTANISTS



Thousands of students come out with PhDs in the Life Sciences, and especially in genetics and often come pouring into the world of Pharma. They focus on cancer and its genetic factors so that one can now look for over 100 genes related to almost any cancer. The number of genes is all too often a result not of importance but to the overflow of researchers seeking to publish.

In contrast in the field of Botany paralleling this effort, with thousands of species, if not millions, we have a dramatic paucity of such researchers. In a crowd of folks looking at genomic issues oftentimes the botanist feels like the one left out. After all who thinks about plants? At least until one look beyond the humans and sees what is out there.

The Scientist has a compelling piece on this issue. As they state:

The unsustainable rate of PhDs awarded per year in the biomedical sciences does not extrapolate to the rate of PhDs in other life sciences, however, especially the agricultural sciences, where the rate of PhDs per year has remained flat for decades. Since 1982, we have consistently trained only about 1,000 PhDs in applied agricultural and related sciences each year. And over the last decade, the U.S. has annually produced only 800 or so plant scientists working in applied agricultural science and only 100 with the skills for basic plant research. (See "Plant science stagnates.") Given the global agricultural challenges we now face, this is a problem.

Oftentimes the student feels inferior if they study plants, after all the hot areas all relate to humans. In reality we can learn a great deal from plants. They are really not that different from us humans. Yet their differences are oftentimes enlightening. Again all too often one thinks of Botany in the context of plant classification or agriculture. In reality plants are a wonderful vehicle to study complex mechanism. I have examined tessellation effects based on complex gene interactions which in turn apply to many cancer pathways.

Perhaps a solution is not to separate Botany and plants from animals and humans. The real problem is the paucity of voices in this area.

Labels: Academy, Science

SATURDAY, SEPTEMBER 27, 2014

HIGHER EDUCATION COSTS

Somehow both the left and the right miss the issue on Higher Education costs. Recently from one of the Libertarian web sites, Cafe Hayek, they state:

This graph shows changes, in the United States from the early 1960s, in the average annual monetary-income return to each year of college education. For this time period, these returns reached a low in the mid-1970s – looks like a mere two years before I started college in 1976 – and began rising impressively starting in 1981. These returns have leveled out (with some year-to-year variability, of course) since about 2000. When an asset – in this case, human capital – becomes more productive, it's neither a surprise nor a 'market failure' for the cost of acquiring that asset to rise.

Let's briefly look at some facts, an oftentimes brutal exercise for some Academics:

1. In 1965 the costs of MIT per year for tuition was about $1,500 and room and board was about the same. This ration was somewhat constant for the next 25 years. Now tuition is 3 time room and board.

2. In 1965 that $1,500 annual tuition resulted in a starting salary of $9,000. That was a 6:1 ratio in salary to tuition. Now tuition is about $60,000 and starting salary on a good day can be as high as $90,000. That is a 1.5:1 ratio. Is that good?

3. Universities have more buildings than ever and at costs per sq ft that are extraordinary. Then the care and upkeep is even worse.

4. Universities now also have massive explosions in Administrative staff. These are usually Government mandated positions that serve some obscure and quite limited purpose, and do not produce any academic value.

So is the argument above with merit. Doubtful. Yet it does justify the exorbitant salaries paid to Faculties, possibly a bit self serving.

Labels: Academy

THURSDAY, SEPTEMBER 25, 2014

RATIONING: NHS AND THE ACA

Perhaps a closer examination of the NHS is worth the effort. As the Guardian reports:

Intolerably long waiting times to see a GP have become a national disgrace that could endanger people's health, the leader of Britain's family doctors has warned. Increasingly unacceptable waits for an appointment risk illnesses not being spotted quickly enough and chances to prevent them being missed, said Dr Maureen Baker. The chair of the Royal College of GPs spoke out as NHS figures showed that one in six patients have to wait at least a week before they see a GP or practice nurse. A total of 58.9 million patients in England are set to have waited for a consultation for a week or more by the end of 2014, up almost 50% from the 40m who waited that long during 2012, according to a new RCGP analysis of data from NHS England's six-monthly GP patient survey. "These devastating statistics show that waiting times are now a national disgrace and that the situation is set to get even worse over the year ahead," Baker said.

This should be a warning for the effective rationing we will see in the next two years.

Labels: Health Care

INTERESTING DELIVERY MECHANISM

One of the challenges that face teams finding ways to deliver a specific protein into a cell is the delivery mechanism. Namely how does one get the protein into the cell to do what is required; activate or block a pathway. In a recent paper in ChemBioChem the authors propose using a controlled anthrax mechanism. They state:

Antibody mimics have significant scientific and therapeutic utility for the disruption of protein–protein interactions inside cells; however, their delivery to the cell cytosol remains a major challenge. Here we show that protective antigen (PA), a component of anthrax toxin, efficiently transports commonly used antibody mimics to the cytosol of mammalian cells when conjugated to the N-terminal domain of LF (LFN). In contrast, a cell-penetrating peptide (CPP) was not able to deliver any of these antibody mimics into the cell cytosol. The refolding and binding of a transported tandem monobody to Bcr-Abl (its protein target) in chronic myeloid leukemia cells were confirmed by co-immunoprecipitation. We also observed inhibition of Bcr-Abl kinase activity and induction of apoptosis caused by the monobody. In a separate case, we show disruption of key interactions in the MAPK signaling pathway after PA-mediated delivery of an affibody binder that targets hRaf-1. We show for the first time that PA can deliver bioactive antibody mimics to disrupt intracellular protein–protein interactions. This technology adds a useful tool to expand the applications of these modern agents to the intracellular milieu.

In the MIT News release they state:

"Crossing the cell membrane is really challenging," he says. "One of the major bottlenecks in

biotechnology is that there really doesn't exist a universal technology to deliver antibodies into cells." For inspiration to solve this problem, Pentelute and his colleagues turned to nature. Scientists have been working for decades to understand how anthrax toxins get into cells; recently researchers have started exploring the possibility of mimicking this system to deliver small protein molecules as vaccines. The anthrax toxin has three major components. One is a protein called protective antigen (PA), which binds to receptors called TEM8 and CMG2 that are found on most mammalian cells. Once PA attaches to the cell, it forms a docking site for two anthrax proteins called lethal factor (LF) and edema factor (EF). These proteins are pumped into the cell through a narrow pore and disrupt cellular processes, often resulting in the cell's death. However, this system can be made harmless by removing the sections of the LF and EF proteins that are responsible for their toxic activities, leaving behind the sections that allow the proteins to penetrate cells. The MIT team then replaced the toxic regions with antibody mimics, allowing these cargo proteins to catch a ride into cells through the PA channel.

This technique may have substantial merit and worth investigating for a multiplicity of therapeutic applications.

Labels: Cancer

THURSDAY, SEPTEMBER 25, 2014

USPTF AND PROSTATE CANCER

A while back the USPTF, despite the lack of clear evidence one way or the other, dictated as one would expect of an Government formed entity that PSA testing should be abandoned. Now in a JAMA Internal Medicine report they find little if any compliance. As is reported in Medscape:

The team analyzed data from the 2012 Behavioral Risk Factor Surveillance System, which is a joint initiative of the Centers for Disease Control and Prevention and the US states. They focused on data collected between January 2012 and February 2013, and identified male respondents aged 50 or more without a history of prostate cancer or prostate problem who reported undergoing prostate-specific antigen (PSA) testing within the preceding year. The researchers found that overall, 37.1% had been tested. But there was far more testing in older men compared with younger men. Nearly half of the older men in the survey had undergone PSA testing — 48.5% of men aged 70 to 74 years and 48.4% of men aged 65 to 69.

Now in a NEJM article this past March the authors concluded:

Extended follow-up confirmed a substantial reduction in mortality after radical prostatectomy; the number needed to treat to prevent one death continued to decrease when the treatment was modified according to age at diagnosis and tumor risk. A large proportion of long-term survivors in the watchful-waiting group have not required any palliative treatment.

Thus survival is a true benefit and physicians are acting rationally as are patients. Yet the USPTF persists in its rationing and in my opinion unrealistic stance on this test. This is but one of the "benefits" I have previously discussed about the ACA.


Labels: Cancer, Health Care

WEDNESDAY, SEPTEMBER 24, 2014

GETTING INTO TROUBLE IN MARYLAND

In an article in Tech Dirt they observe the following:

But his new argument takes it even further, arguing not just that they were unethical, but flat out illegal, based on his reading of the Common Rule and a particular Maryland law that effectively extends the Common Rule. The Common Rule basically says that if you're doing "research involving human subjects" with federal funds, you need "informed consent" and further approval from an institutional review board (IRB), which basically all research universities have in place, who have to approve all research. The idea is to avoid seriously harmful or dangerous experiments. The Maryland law takes the Common Rule and says it applies not just to federally funded research but "all research conducted in Maryland."

Now this is in response to the Facebook user test for what makes someone happy. Facebook allegedly manipulated what users saw based upon some criterion and then published the results.

Now if the above theory holds, then any market research, for example, in Maryland, without both an IRB and signed consent is criminal. Perhaps that is the case. Maryland is a strange place, I live there for a few years and it is an amalgam of many strange interests.

But if this is correct, then if I were to approach someone to ask their opinion, say at a party, and my day job was as a pollster then I may be committing a crime if I were in Maryland.

This is a classic example, if true, of the collection of laws that were half baked and that can be used to silence anyone.

In fact, one may consider the extreme, if for example you walk down the street and say, "How are you?", perhaps that could be considered research and without a written consent one is guilty of a crime. In many ways this is a classic example of Legislators and the Executive going a bit too far. Thank God for EZPass, I cannot be tempted to be friendly to any Maryland toll taker.


Labels: Internet, Law

TUESDAY, SEPTEMBER 23, 2014

ARENDT, HEIDEGGER AND EICHMANN

In a recent book on the Eichmann papers, by Stangneth (*Eichmann Before Jerusalem: The Unexamined Life of a Mass Murderer*)[26[1]], the author presents a superbly researched and

[26[1]] Stangneth, B., Eichmann Before Jerusalem: The Unexamined Life of a Mass Murderer, Knopf (New York) 2014.

prepared documentation on Eichmann and his thought as well as his putative strategy when dealing with the Israeli Courts at his Trial. This book also peripherally reflects on the Arendt book of over a half a century ago at the time of the Trial which caused such uproar. In the Trial, Arendt had asked to be sent and record what transpired. This was in the early sixties and at the time she was in New York. Her reporting became an amalgam of her German scholarship, of which Heidegger was central, and in an almost equal way her place in the then New York intellectual circles. Both influences became filters for what she saw and how she then reported the events at the Trial.

Benhabib in the NY Times has written a critique of the book and she states[27][2]:

The Emory University historian Deborah E. Lipstadt told The Times this month that Stangneth "shatters" Arendt's portrait of Eichmann. In The Jewish Review of Books, the intellectual historian Richard Wolin writes: "Arendt had her own intellectual agenda, and perhaps out of her misplaced loyalty to her former mentor and lover, Martin Heidegger, insisted on applying the Freiburg philosopher's concept of 'thoughtlessness' (Gedankenlosigkeit) to Eichmann. In doing so, she drastically underestimated the fanatical conviction that infused his actions."

The fact is that Arendt had an affair with Heidegger when she was his student, as one gathers he had affairs with other students at the same period, all the while he was married. Arendt continued a somewhat close relationship with Heidegger up to her death despite the fact that Heidegger was a member of the Nazi party and had personally expelled Jews from his Faculty. Heidegger had a long history of extreme National Socialist tendencies and his joining the Nazi Party was but a step in that process[28][3].

This was a complex relationship as exhibited by the book by Ettinger which recounts the letters exchanged between Heidegger and Arendt. Ettinger's work allows insight into the complex and continuing relationship between Arendt and Heidegger, a relationship built in many ways by the basics of German philosophy, from Kant onwards. She remains almost devoted to him to the end, despite the continual exposure of his actions during the War and before. Heidegger in a manner that we see in Eichmann tries to reconstruct a new portrayal of his actions, trying to show that he was not a real Nazi and that his actions were just in line with what was expected of him at the time. It is this situational ethics that somehow Arendt dismisses and she renews and expands the friendship despite the involvement that Heidegger had.

Benhabib continues:

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[27][2] http://opinionator.blogs.nytimes.com/2014/09/21/whos-on-trial-eichmann-or-anrendt/?module=Search&mabReward=relbias%3Ar

[28][3] One could examine the Farias book, Heidegger and Nazism, Temple Univ Press, 1989, to get what may be a critical but detailed overview, limited somewhat by the time of its writing because of the still closed access to closed East German archives. A subsequent book by Ott, Martin Heidegger, A political Life, Basic (New York) 1993, which provides a similar but less polemic a presentation of Heidegger and the Nazis.

This sort of dismissal of Arendt's work — essentially a rejection of the "banality of evil" argument — is by no means new, but it does not hold up when one truly understands the meaning of her phrase. Couldn't Eichmann have been a fanatical Nazi and banal? What precisely did Arendt mean then when she wrote that Eichmann "was not stupid. It was sheer thoughtlessness — something by no means identical with stupidity — that predisposed him to become one of the greatest criminals of that period."? Arendt certainly did not think that ordinary human beings were all potential Eichmanns; nor did she diminish the crime Eichmann committed against the Jewish people. In fact, she accused him of "crimes against humanity," and approved his death sentence, with which many, including the Jewish philosopher Martin Buber, disagreed.

The problem with this argument is that Arendt examined Eichmann by what he said at Trial, and she did not examine the record of Eichmann as one would have done either as a Historian or as the Prosecutor. Eichmann, the defendant, had prepared himself for the very role of Defendant. His writings as presented by Stangneth clearly demonstrate the mind of a Nazi, clever, plotting, planning and executing with precision. His defense at Trial was a planned and rehearsed presentation of what he wanted people to believe. Arendt it appears fell into the trap. The four walls of her understanding of Eichmann were delimited by the well prepared presentation he made at Trial. In contrast, in Stangneth, we see the drafts of Eichmann's own words and what is revealed is the truth of what Eichmann truly was, a classic Nazi.

Thus the Benhabib defense of Arendt is somewhat weak. Arendt, it appears, went to the Trial to absorb from the Eichmann testimony a measure of the man. Yet as was shown in his writings and with an additional half century of discovery the man was quite complex and had anticipated such an event as the Trial. Thus he took it upon himself to present a stage persona at the Trial as a means of presenting his message.

To better understand the mindset of Arendt at the time of the Trial one need read Elizabetta Ettinger work on the correspondence between Heidegger and Arendt[29][4]. Ettinger had access to the papers, via allegedly Mary McCarthy, a close friend of Arendt, and a fellow traveler in the circle of the then New York intellectual elite. As Wistrich stated in Commentary on the review of Ettinger[30][5]:

Among the story's more troubling aspects is the extent of Arendt's submissiveness to Heidegger. Both as a student and later as a friend and equal she displayed an extraordinary readiness to put herself at his beck and call, to place him on a pedestal, and to subject herself to his arrogance. Ettinger, whose analysis eschews crude psychological reductionism, accounts for Arendt's actions in broad sociological and historical terms:

[29][4] Ettinger, E., Hannah Arendt Martin Heidegger, Yale Press (New Haven) 1995.

[30][5] http://www.commentarymagazine.com/article/hannah-arendtmartin-heidegger-by-elzbieta-ettinger/

[Arendt] shared the insecurity of many assimilated Jews who were still uncertain about their place, still harboring deep doubts about themselves. By choosing her as his beloved, Heidegger fulfilled for Hannah the dream of generations of German Jews, going back to such pioneers of assimilation as Rahel Varnhagen.

The irony here is that Arendt's own book-length study of Rahel Varnhagen, a German Jewess prominent in early-19th-century literary circles, displays keen insight into the delusions and self-deceptions which are entailed in the Varnhagen "model" of assimilation, but which in her relationship with Heidegger she appeared unable to resist.

The assimilation construct was one of trying to shed the long held anti-Semitism on the part of the non-Jewish population. Arendt it appears tried to shed that both with her relationship with Heidegger and possibly by her later claim of certain German Jews facilitating the work of the Nazis, a claim rejected by many.

Benhabib further states:

It is this strange mixture of bravado and cruelty, of patriotic idealism and the shallowness of racialist thinking that Arendt sensed because she was so well attuned to Eichmann's misuse of the German language and to his idiosyncratic deployment of concepts like the Categorical Imperative. As Stangneth puts it, "Hannah Arendt, whose linguistic and conceptual sensibilities had been honed on classical German literature, wrote that Eichmann's language was a roller coaster of thoughtless horror, cynicism, whining self-pity, unintentional comedy and incredible human wretchedness." Eichmann's self-immunizing mixture of anti-Semitic clichés, his antiquated idiom of German patriotism and the craving for the warrior's honor and dignity, led Arendt to conclude that Eichmann could not "think" — not because he was incapable of rational intelligence but because he could not think for himself beyond clichés. He was banal precisely because he was a fanatical anti-Semite, not despite it.

Eichmann had studied Jewish culture and thought, almost as a way to perfect his job. Thus he knew his adversary, his prey, oftentimes using that knowledge to effect his task. Arendt in many ways was critiquing Eichmann for his lack of acumen, lack of education, and then and again Eichmann had spent years developing this very persona as a means to present his tale, and most likely Arendt fell into the well laid trap. One could truly question the use of the phrase "banal" for Eichmann, for he was a shrewd manipulator of not only the facts but oftentimes of the audience listening to them.

In contrast in a review in the NY Times by Schuessler the author states[31][6]:

Listening to Eichmann in Jerusalem, Arendt saw an "inability to think." Listening to Eichmann before Jerusalem, Ms. Stangneth sees a master manipulator skilled at turning reason, that weapon of the enemy, against itself.

[31][6] http://www.nytimes.com/2014/09/03/books/book-portrays-eichmann-as-evil-but-not-banal.html?module=Search&mabReward=relbias%3Ar

That assessment is true but it appears to be only part of the overall truth. On the one hand Arendt did not due her due diligence; she did not independently investigate Eichmann. On the other had she let her Heideggerian training overtake the cunning rationality of Eichmann, she failed to see him as an actor in a play reading lines he had rehearsed again and again. One could say she let her German arrogance get in the way of what was in front of her, true evil. She was still a student of Heidegger, she was not able to become a common Police detective and see a criminal for what he was.

As Honan stated in the NY Times in a review of Ettinger in 1995[32][7]:

Heidegger, then the newly appointed rector of Albert-Ludwigs-University in Freiburg, had just joined the Nazi party and had delivered the infamous rector's address in which he declared his allegiance to Hitler. With heavy sarcasm, he denied Arendt's accusations. The truth is, as Professor Ettinger points out. His anti-Semitism had been well-established four years previously when he wrote to warn a high official in the Ministry of Education against the "growing Judiaization" of Germany's "spiritual life." Among his more abominable acts while rector in Freiburg, Heidegger banned from the campus all Jewish professors including his mentor, the aging Edmund Husserl —an act that is believed to have contributed to Husserl's death.

In a sense, as Arendt accused many German Jews of complicity with the Nazis out of some form of self-deception, perhaps she also could be criticized for missing the point of Eichmann by a form of self-interpretation. Eichmann may very well have used his well-planned defense as a means of leaving a trail of confusion to all but those who would eventually become privy to his writings.

To understand the conflicts of Arendt one may look for the inherent conflicts in Heidegger; his philosophy and his life. To do so it is worth examining the book by Winograd and Flores written in the 1980s[33][8]. Winograd was well known and highly respected at MIT at the time as a brilliant engineer in the Artificial Intelligence community. His career has subsequently secured that reputation. Flores was a politician in exile from Chile, a former member of the prior Communist Government overthrown by Pinochet, studying Philosophy at Berkeley. The combination of these two individuals had created a book, which now some 26 years later, is truly timeless.

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[32][7] Honan, NY Times, Nov 5, 1996, p 25.

[33][8] Winograd, T., F. Flores, Understanding Computers and Cognition, Addison Wesley (Reading MA), 1987. My old copy, I have a second, is marked page by page recording each time I went through it. As a result I went and taught the first course at MIT on Multimedia Communications (Fall 1989), influenced by this short treatise. The question I was trying to address at the time was: how would people communicate as we moved into a distributed multimedia environment? The semiotics of communicating was at that time becoming the challenge. In a sense Winograd and Flores saw that through the lens of Heidegger.

The book fundamentally is a fusion of philosophy with technology and it does so through the eyes and minds of philosophers, especially Heidegger. By doing so, the authors demonstrate what technology, media, can do to not only elucidate knowledge but to frame and reposition what we seem to feel is "immutable truth". Truth then becomes what we may perceive through the eyes of the medium, the signs placed before us so to speak. Thus, as we see so many "Apps" being developed on so many platforms in today's world we seem not to stop and ask the question of how these Apps may be changing what we hold as knowledge, as truth, and how they reflect on the meaning of our existence. The authors have used this work to address these issues in the context of Heidegger and his view of being. Thus one can use this interpretation of Heidegger as a lens to focus on the relationship between the view of Arendt of Eichmann's world. In a sense, Eichmann used the medium of the Trial as a way to recast Truth, and it was incumbent upon Arendt, having been trained by Heidegger, to recognize this. She did not.

The authors use the ideas of such opaque philosophers as Heidegger to establish a basis for their exposition. As ***Scrunton*** has noted Heidegger is obtuse, he is a quintessential German, creating a plethora of neologisms in German, which get half translated to English[34][9]. Heidegger deals with existence, ontology, and how we as humans are created as individuals by our interactions. The example of a man using a hammer to insert a nail becomes the amalgam of the hammer, human and nails as a process, and it is that at hand process that the human understands and becomes one with hammering. In a sense that is what we do when we create programs; we try to engage the human user with the process and its externalities to become one concerted effort.

Chapter 3 is seminal, for it is a wonderful summation of Heidegger and Gadamer, or what they would have said had they tried to do it in a few pages. The rationalist versus the idealist, the subject and object, the observed and the observer are all explored, The introduction of Heidegger's *Dasein* is made in such a manner that the reader just flows with its insertion as being-in-the-world, and that one comes away with a highly readable and understandable grasp of what Heidegger meant to say[35][10].

They end with, *"Heidegger insists that it is meaningless to talk about the existence of objects and their properties in the absence of concernful activity, with its potential for breaking down"*. The interaction between the individual and the medium presenting facts then is essential to understanding. It is akin to the McLuhan statement regarding any medium used for transmitting knowledge, that is the medium will define what is truth or knowledge, not the "facts" or objects which the one conveying them wishes to transfer. This understanding or interaction of message and messenger, the hermeneutic view, and object and understanding, were what the authors saw as critical in developing "software".

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[34][9] Scrunton, R., A Short History of Modern Philosophy, Routledge (New York) 2002. pp 270-280. In fact Scrunton states: "*It is impossible to summarize Heidegger's work, which no one has claimed to understand completely*."

[35][10] See on p 31

Now here we again come to Eichmann. Eichmann was in a sense both the messenger and the message. He viscerally understood that and had prepared for the confrontation that was his Trial. Heidegger understood that, it was Dasein confronting the world. The one wonders why Arendt of all people would not have had the openness to both understand that as well as the ability to translate it properly.

Breakdown can be a noun or a verb. As a noun it is failure, as a verb it is "taking apart". [36][11] For Heidegger it was the noun that was operative. It was a failure of something. In essence we "learn by our mistakes". Ironically Heidegger did not achieve this and Arendt was a front row observer of that process. As Koschmann et al state:

Heidegger, Leont'ev, and Dewey held surprisingly similar views on the role of ***breakdown or failure*** *as a means of* ***revealing the nature of the world around us****. For Heidegger, the resources by which we conduct our day-to-day activities do not usually require our conscious awareness. If our ongoing activity is blocked, however, this "transparency of equipment" is dispelled, forcing a more deliberate mode of action. Leont'ev's development of breakdown hinges on the analytic distinction he made among Activities, Actions, and Operations. When the necessary conditions for an Operation are absent, the chain of Operations becomes transformed ("unfolded") back into a sequence of independent Actions. Dewey's notion of breakdown is related to his views on sensory excitation, stimulus and response, and the habit-formation function in the lives of complex organisms. Implications of these three models for learning and instruction are developed.*

Thus we often learn more by our mistakes rather than by rote. We learn by reassembling that which we erred in. In a similar vein being-in-the world is also a noun a verb. On the one hand it may mean an individual, or being, modified by "in-the-world" or it may be the action of being, the gerund of to be, "in-the-world". Ironically reading and interpreting Heidegger is itself filed with such noun type breakdowns and needs to reassemble them. Perhaps it is the German mannerism. Heidegger, even in his later years, after having been exposed to the evils of the Nazis, did not learn by breakdown, in fact he continued to try to justify his actions. In a similar manner Eichmann tried not to correct the past evils but to reconstruct them to his own ends. Arendt, thus trained by Heidegger in the world of Dasein, breakdown, semiotics, seems to have missed the very drama before her in Jerusalem. Thus the value of Stangneth's work is the opening up of the process, deconstructing the text, and laying bare the players.

Labels: Books, Commentary

[36][11] Timothy Koschmann, Kari Kuutti & Larry Hickman, The Concept of Breakdown in Heidegger, Leont'ev, and Dewey and Its Implications for Education, Mind, Culture, and Activity, Volume 5, Issue 1, 1998 pages 25-41

MONDAY, SEPTEMBER 22, 2014

MIT STUDENTS AND NEW JERSEY COURTS

Wired has an interesting piece on the New Jersey AG attempting to intimidate a set of MIT students for some software they developed in prototype form which the AG seems to believe on some yet to be defined basis as in violation of New Jersey law even thought the software has never been sold and resides in the Commonwealth of Massachusetts. The article states:

Four MIT students behind an award-winning Bitcoin mining tool will face off against New Jersey state authorities in court today when they attempt to fight back against a subpoena demanding their source code. The Electronic Frontier Foundation is representing 19-year-old MIT student Jeremy Rubin and three classmates in a remarkable case that stands out for the measure of aggression the state is using to obtain the code and identify anyone who might have tested the mining tool.

Now perhaps this is one way to get some talent back to New Jersey but seems a bit heavy handed. The article continues:

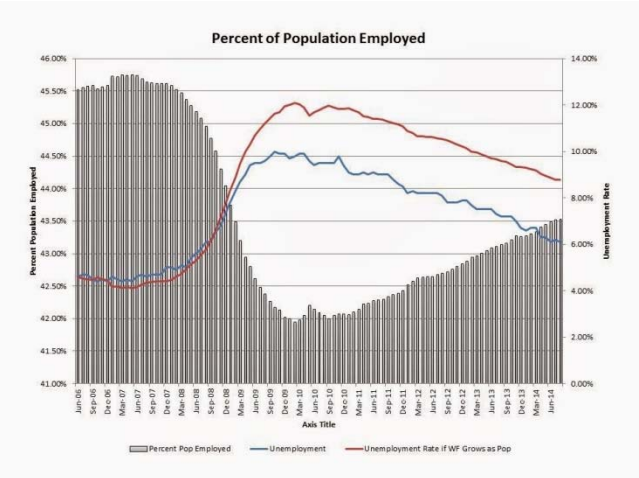
"It's a very broad subpoena that hints at criminal liability and civil liability," he says. "For a bunch of college kids who put something together for a hackathon—they didn't make any money, the project never got off the ground and now is completely disbanded—there are some very serious implications."

There is always the mens rea part of criminality which seems to be missing here as well as the act of doing something covered by and withing the State of New Jersey. Perhaps the Sopranos managed to survive because they did nothing with computers!

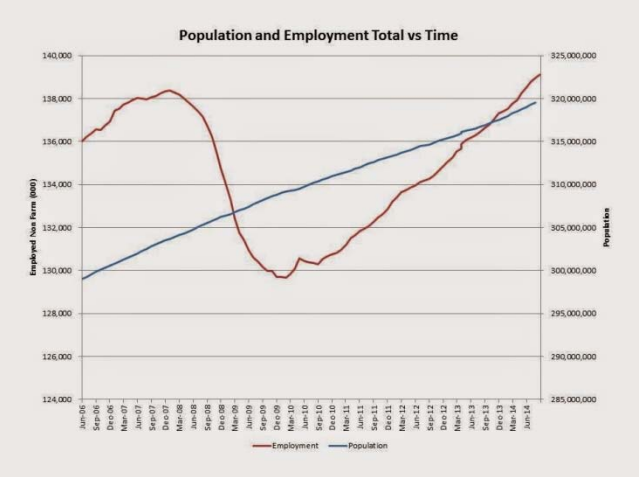
Labels: Law

FRIDAY, SEPTEMBER 5, 2014

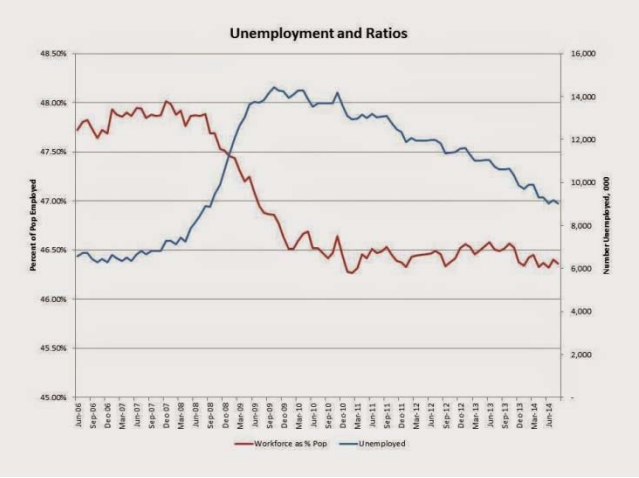
EMPLOYMENT STATS



Employment is still quite sluggish especially at the top line. The 6.1% number is not what we should look at, it is the participation rate which is still very low relative to before this Recession.



This past month as shown below we saw another dip, which is not a good sign for August.



The above is a key chart which shows a reduction in unemployed but against a steady and poor participation rate.

It is not anticipated that the Economy will rebound until the next Administration.

Labels: Economy

WEDNESDAY, SEPTEMBER 3, 2014

COMMON SENSE: NOT THOMAS PAINE

In the NY Times there is some erstwhile entrepreneur who is in my opinion bemoaning the process of raising money,

She bemoans the following:

The problem is, refusing to do any work until a term sheet is signed sounds great but is hard to do. When you first meet, you are excited and the investor promises that the process will take only a few weeks. You can afford to invest a few weeks. Even as time drags on, everything appears to be proceeding, and you are certain the deal will close. As time drags on, costs pile up and cash reserves dwindle. You realize that, with so much time invested, you cannot afford to start the process again. I will never get stuck in this situation again. I will never let an investor seduce me into believing that a term sheet is around the corner while I put time and money into meetings and answering thousands of questions. I will ensure that a term sheet is agreed upon up front and then start the due diligence process. If the V.C.s find something they do not like during due diligence, they can always back out of the deal, but at least I will have established that there is a deal to be done. Even though I know their firm is big and my company is small, I will do this because I know that time and energy are my biggest assets.

Now I was involved in my first VC backed start up in 1969. Most likely one of the very early ones. The lesson is that you always have to be ready with the due diligence packages. It is standard, it is expected, and you better get your act together as part of any business, you will be doing it again and again.

I had it down to an art. You know what is expected and what is asked for is what any business should have ready at hand. Dealing with investors takes time, so expect it.

This write up in the Times is a display of the generational changes we have seen. These folks seem to expect everyone to see how great they are and when one asks for some form of proof, they seem affronted. They believe they are perfect and should be taken at face value, whatever that may be.

Raising money is like any other sales effort, but not the "buyer" is dealing with money, theirs and their investors. The entrepreneur must understand that and demonstrate that they will take care of that responsibility.

The term "seduce" is foolish in my opinion, for to me it demonstrates a level of arrogance and entitlement that one sees in young inexperienced start up players whose understanding of business is limited.

As for a term sheet, it can be drawn but it still has outs, namely the due diligence outs for whatever reason the investor so chooses.

So folks like this had better get used to having due diligence packages ready at hand, on line, sent with the push of a button! In fact one can even send it via this new service called the "Internet". cool thing this new technology!

Labels: Commentary

UNDAY, AUGUST 31, 2014

RED WINE AND CVD

Eureka reports on an interesting finding by a Czech researcher. Wine protects only those who also exercise from CVD.

They state:

Evidence suggesting that mild to moderate consumption of wine protects against cardiovascular disease has been accumulating since the early 1990s. In particular, retrospective studies have found that wine increases levels of HDL, the "good" cholesterol. But until now there has been no long-term, prospective, randomised study comparing the effects of red and white wine on HDL cholesterol and other markers of atherosclerosis. The IVV study is the first long-term, prospective randomised trial comparing the effect of red and white wine on markers of atherosclerosis. The study included 146 people with mild to moderate risk of cardiovascular disease according to the HeartScore . Participants were randomised to one year of moderate consumption of red wine (Pinot Noir) or white wine (Chardonnay-Pinot) from the same year and wine region of the Czech Republic....
He added: "The only positive and continuous result was in the subgroup of patients who took more exercise, which means regular exercise at least twice a week, plus the wine consumption. In this group HDL cholesterol increased and LDL and total cholesterol decreased in the red and white wine groups. There may be some synergy between the low dose of ethyl alcohol in wine and exercise which is protective against CVD."

Now this is interesting since having lived in Prague for a while I found the Czechs drink beer and the Slovaks drink wine, usually white. Also there is often a genetic tendency for very low HDL and at the same time low cholesterol, with very low risk of CVD.

Just what this all means I do not know but since it is the middle of Labor Day weekend I thought it would be worth a comment!

Labels: Health Care

SATURDAY, AUGUST 30, 2014

EVEN THE BRITS HATE THE CATV COMPANIES

The Guardian has a post regarding Comcast and its attempts to block any competition.

They state:

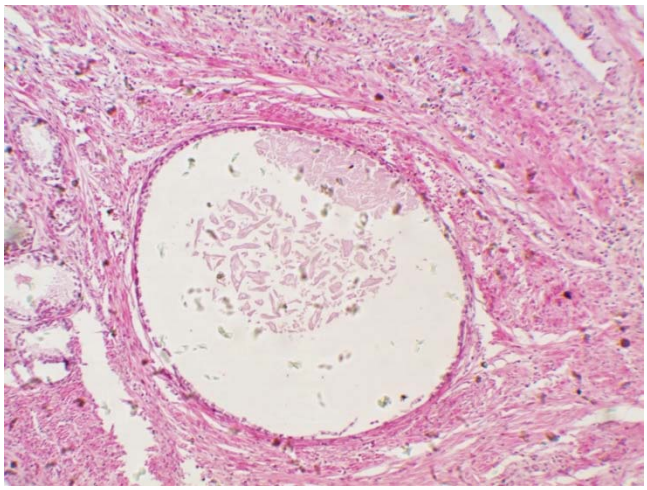
The US cable industry called on the Federal Communications Commission on Friday to block two cities' plans to expand high-speed internet services to their residents. USTelecom, which represents cable giants Comcast, Time Warner and others, wants the FCC to block expansion of two popular municipally owned high speed internet networks, one in Chattanooga, Tennessee, and the other in Wilson, North Carolina. "The success of public broadband is a mixed record, with numerous examples of failures," USTelecom said in a blog post. "With state taxpayers on the financial hook when a municipal broadband network goes under, it is entirely reasonable for state legislatures to be cautious in limiting or even prohibiting that activity." Chattanooga has the largest high-speed internet service in the US, offering customers access to speeds of 1 gigabit per second – about 50 times faster than the US average. The service, provided by municipally owned EPB, has sparked a tech boom in the city and attracted international attention. EPB is now petitioning the FCC to expand its territory. Comcast and others have previously sued unsuccessfully to stop EPB's fibre optic roll out.

One of my more referenced papers from 2002 on Municipal Broadband detailed what was to happen. No surprises. But what is shocking is that the current Administration appears in my opinion to be in collusion with these characters to further hinder any competition. Pity. But again no surprises.

Labels: CATV

FRIDAY, AUGUST 29, 2014

PSA: BEYOND LOGIC



In a recent Medscape article on the PSA debate the author states:

Cost is another issue. It is estimated that to prevent a single cancer death through screening and treatment costs more than $5 million. Could those dollars be better used to have a greater impact on society? Because although we may prevent a man from dying from prostate cancer, in many cases that doesn't mean that he is going to live a whole lot longer than he would have lived anyway. We have a net dilemma in trying to resolve these controversies. They are not going to be resolved tomorrow. Ultimately, we can hope that 2 things occur. One, going forward, it would be great if the gene tests that are in development turn out to be able to tell us which men need to be diagnosed and treated and which men can be spared. Two, we need to ensure that a similar fiasco does not occur. By that, I mean another screening test for early cancer that is not specific for that cancer being developed, without the right studies being done before it is used. We must avoid approving tests when we don't know for certain that they will be associated with more benefit than harm.

Let me now address each of these assertions:

1. Cost: This calculations makes a set of assumptions which in my opinion as discussed before herein are incorrect. We know the mortality rate of PCa and the costs associated with it. We also know that PSA velocity and % Free are excellent when combined with PSA. What we do not know is when we see a Gleason 6+ cancer whether it is aggressive or indolent. That is a genetic problem. Thus lacking such knowledge it is impossible to make a financial assertion of this type.

2. Genetic Tests: BRCA is a reasonable test for Breast cancer. The problem is that many PCa are not BRCA like, they may be methylation like and thus one needs to sample the actual cancer cells, not just one but many, and many individually to seek a stem cell as well. Not a simple problem.

3. Many tests lack great sp0ecificity. Welcome to testing. We cannot only use tests that are perfect, medicine is never really like that. We never can give an answer to a patient who says

"Doc, how long do I have?". No one patient is the same to all others.

Thus when we see statements like this we should take them with a grain of salt. We use the tools at hand and learn, many of the tools are poor, but they do work, somewhat. Perfection we leave to zealots.

Labels: Cancer

THURSDAY, AUGUST 28, 2014

CATV AND MONOPOLIES

I read a piece in Ars Technical alleging that Comcast is taking measures to delimit competition.

The article states:

CenturyLink has accused Comcast of trying to prevent competition in cities and towns by making it difficult for the company to obtain reasonable franchise agreements from local authorities. CenturyLink made the claim yesterday in a filing that asks the Federal Communications Commission to block Comcast's proposed acquisition of Time Warner Cable (TWC) or impose conditions that prevent Comcast from using its market power to harm competitors. Comcast has a different view on the matter, saying that CenturyLink shouldn't be able to enter Comcast cities unless CenturyLink promises to build out its network to all residents. Without such conditions, poor people might not be offered service, Comcast argues.

Now that was the same game we saw when we tried to build Hanover, NH. The incumbent had been Adelphia then bought by Comcast. Then things started, the town demanded almost 100% coverage and more. We wrote a paper discussing this at the time.

It was this added cost that made any entry prohibitive. As we saw it the town just did not comprehend the economics. All we had asked for was a equal and level playing field, the town apparently at the CATV's insistence demanded complete coverage. Frankly no CATV system does that, there are always dead zones due to reasonable economics.

As we have noted before, the merger, politically correct with the current administration, is unacceptable from any reasonable antitrust position in my opinion.

Labels: CATV

NOT A NICE APPLICATION OF COASE

As I had written yesterday, the poor bemoaning writer from the Times tried to apply Coase to seats on a plane.

Let us use a simple and well used example of Coase.

1. A railroad has a right of way across farm land. Let us assume that as a train goes across the land it sends off sparks.

2. The farmer has given a right of way to allow the tracks to be built but the right of way has no other conditions other then for say $1, and the railroad can then build the tracks and use them.

3. Now the farmer grows acres of corn and wheat. It is harvest time and the crops are dry but well developed and ready to be harvested.

4. A train comes along the tracks spitting out sparks. It sets the fields afire and the farmer looses all his crops.

How can this problem be dealt with.

For Coase there are two options:

1. The State, whatever that is could pass a law mandating how this is to be treated in all cases. The EPA and OSHA are examples of such agencies.

2. Assuming zero litigation costs, whenever such an occurrence happens the parties go to Court and litigate. Let the Courts decide. This is the Common Law approach.

Coase alleges that the second way is always cheaper. That is assuming zero litigation costs.

Now there is a third way in which one could have dealt with this; namely contractual. In the easement or right of way agreement there should be some negotiated and agreed to remedy for direct and indirect harms. A good attorney would have crafted such.

Now in the airline seat case there are, as I had indicated, two levels of rights; "property" right to a seat and a legal right not to be assaulted, which is a criminal issue not a civil one.

Now Mankiw appears to applaud their application to property rights but fails to understand, apparently, the right not to be physically harmed. This I find is common amongst Economists, a certain tunnel vision of self justifying assertions. The real issue here is not a property right, even in the Coasian sense, but the right not to be harmed, assaulted, by another party.

Now let me go back to Coase and the Farmer. Let us assume that the train set off sparks, the corn went afire but this time the farmer was in the field. He get burned to death, a criminal act perhaps, reckless indifference. Here we have two distinct effects. One is a simple Coase quid pro quo. Sparks and burnt corn. If that were the case then the Farmer could have bought an insurance policy and factored the cost into the right of way. The no matter what both parties would be happy. That is a nice application of Coase. A fried Farmer now is a different story. That now requires, no demands, State intervention.

Let us then return to the airline seat. Yes, I could pay the inconsiderate character in front of me not to swing his seat back, if one were to agree to such an unencumbered property right. Yet there is a second set of issues here, my separated patella, the pain and resulting disability. I could then enter into an agreement with this character in the front seat not to file criminal charges. That is a second Coasian transaction. You see, there are two distinct actions and thus two distinct transactions.

Unfortunately that would not apply in the fried Farmer case, we hope.

Labels: Economics

WEDNESDAY, AUGUST 27, 2014

WHOSE RIGHTS

I just read a NY Times piece by some individual who apparently in my opinion believes that his right to smash someone's body and thus inflicting pain and harm for his personal comfort is a property right!

Let me pose the issue:

1. Assume that a passenger who is 6'3" is assigned to a seat in which his knees abut against the seat in front of him. Namely the passenger is tall, not obese, and the passenger consumes all of the space allotted to him. Specifically this passenger is using to the fullest his space. No more.

2. Assume we have in front of him a passenger who may or may not fills the space. Yet assume

that this passenger desires to recline his seat to the fullest.

3. Now it is a physical impossibility to recline the seat without assaulting the passenger in the seat behind the front passenger. Yet he insists on his property right.

4. If we believe that each has a property right then the assault by the front passenger denies not only the back passenger property right but also inflicts harm. Namely deliberate bodily assault. Let us assume the rear passenger does not employ any means other than his body to inhibit the exercise of the assumed front passenger property right.

5. Then the rear passenger should have a right to file a criminal complaint against the front passenger for deliberate bodily harm, namely depressing the patella and inflicting pain.

Now the Times author in my opinion misrepresents the Coase Theorem. He states:

.... airline seats are an excellent case study for the Coase Theorem. This is an economic theory holding that it doesn't matter very much who is initially given a property right; so long as you clearly define it and transaction costs are low, people will trade the right so that it ends up in the hands of whoever values it most. That is, I own the right to recline, and if my reclining bothers you, you can pay me to stop. We could (but don't) have an alternative system in which the passenger sitting behind me owns the reclining rights. In that circumstance, if I really care about being allowed to recline, I could pay him to let me.

That would apply if and only if bodily harm were not inflicted. The act of so inflicting harm may very likely may possibly be criminal and this negates any Coasian solution.

However this piece in my opinion does clearly demonstrate the ego of those people who believe the world owes them and to hell with anyone else. It also perhaps represents the paper in which it was printed!

In fact in the old Salic law there are remedies for this type of assault. On the other hand perhaps we should be glad we no longer apply that law.

Labels: Commentary

WEDNESDAY, AUGUST 27, 2014

THE CBO REPORT

The CBO issued its update on the economy report. What was of most interest was their projections on renormalization of interest rates while keeping inflation at arm's length. Worth a read.

Labels: Economy

MONDAY, AUGUST 25, 2014

CAUSES OF OBESITY

In almost all cases the cause of obesity is over eating. Simple. Now the over eating can be driven by many factors. Family situations are often a driver but that is complex. There are obese family members in the same household as those of normal weight. There is the phenomenon of ethnic groups who have lived for many generations on low caloric diets suddenly being exposed to "regular" diets and becoming obese. Two cases are of merit.

One is the Native American tribes in the Southwest. High obesity and high Type 2 Diabetes. There seems to be a lowered set point in metabolism that when presented with "normal" diets they seem to horde calories. The second is an interesting example, say the Irish after the famine and they come to the US and face a "normal" diet and thus have the same effect, obesity and in turn Type 2 Diabetes.

Now along comes another reason, somewhat suspicious. Namely racial and ethnic subtypes. In Eureka they state:

Many Americans need extraordinary willpower to avoid becoming obese – or to slim down if they already weigh too much. For members of minority groups, maintaining a healthy weight can be that much harder according to new research led by Luis Rivera, an experimental social psychologist at Rutgers University-Newark. Rivera says it is common for minorities in the United States to endure negative stereotypes, pervasive messages that suggest those groups are inferior, and that these attitudes can prevent people from doing what is needed to care for their health. "When you are exposed to negative stereotypes, you may gravitate more toward unhealthy foods as opposed to healthy foods," explains Rivera, whose study appears in this summer's edition of the Journal of Social Issues. "You may have a less positive attitude toward watching your carbs or cutting back on fast food, and toward working out and exercising."

This seems to be based upon shaky ground. The same effects as seen in Native Americans and Irish Famine immigrants seem to be a better explanation. Immigrants from Hispanic lands in Central and South America come from low caloric diets and heavy manual labor. When the come here they face higher caloric intakes socially. Thus like the other cases one can see a set point difference, one lasting a few generations.

One may ask if this is akin to the methylation arguments seen in the Dutch Famine cases. It most likely is not attitude but a new set point.

Labels: Health Care

SUNDAY, AUGUST 24, 2014

DE TOCQUEVILLE AND DRIVING SCHOOLS

I read in the NY Times today and interesting piece about the excess regulation in France. They state:

Partly because they are young business school graduates and partly because getting a driver's license here is so difficult and expensive that it has inspired books on the subject, Mr. Chartier and Mr. Gaignault have become minor celebrities. Various experts say their struggle highlights how the myriad rules governing driving schools — and 36 other highly regulated professions — stifle competition and inflate prices in France.

One need read no farther than de Tocqueville's "Ancient Regime" to see that this is not only new but as he notes was a primary cause of the French Revolution. Paris controlled everything, from the size of milk bottles to the size of sewer caps. People just got fed up.

I suggest that anyone who wants to understand where we seem to be going in the US today read just one page of The Ancien Régime and the French Revolution and then think how it applies to what we are seeing today with the heavy hand of a centralized Government. Then look at France and see how absurd it can become!

Labels: Commentary

THURSDAY, AUGUST 14, 2014

JUST A REMINDER

Today is the 69th anniversary of VJ Day. It was on this day in 1944 that Japan formally agreed to a surrender.

Labels: Commentary

DELAY IS THE DEADLIEST FORM OF DENIAL

In a Guardian piece they recount the fact that due to delays in the NHS approach to dealing with cancer patients that the mortality is excessively higher in some areas than others.

They state:

Thousands of people are dying early of cancer every year because of an "inexcusable postcode lottery" in how quickly the NHS diagnoses and treats the disease, a leading charity warns. Delays mean that cancer patients in some areas of England have up to a 61% higher risk of dying within a year of their diagnosis than those in other places, simply because of where they live. While one in four (24%) of newly diagnosed cancer sufferers in north-east Hampshire and Farnham in Surrey die within a year, 38% of those in the London borough of Barking and Dagenham do so, according to a new Macmillan analysis of data from the Office for National Statistics. The same proportion (38%) of patients also die within a year in five other places – Crawley, Sussex; Newham, east London; Swale, Kent; Vale Royal, Cheshire; and Thanet, Kent.

As we look at the massive complexity under the ACA one expects that we will be seeing the same effects here in the US.

It is not that the care is better or worse it is that there is an overwhelming number of patients and too few physicians.

Labels: Health Care

LAYOFFS IN CHINA

In a recent piece by China Daily they report on the layoffs amongst high tech companies. They state:

Labor unrest is expected to spread following massive layoffs at several IT giants, with experts calling on multinationals to take the issue seriously. Cisco Systems has announced a plan for global job cuts, while thousands of Microsoft employees in China are trying to negotiate a deal for better compensation following layoffs. "Labor disputes involving overseas information technology companies are set to grow for the next two years at least as the Chinese economy slows," Zhang Zhiru, a labor rights expert at Shenzhen Chunfeng Labor Disputes Services Center, said on Thursday.

Thus China is starting to see the contraction that can occurs as salaries rise and labor can be outsourced elsewhere.

Labels: China

THURSDAY, AUGUST 14, 2014

OBESITY, DIABETES AND HEALTHCARE COSTS

In a recent CDC study they predict a 40% incidence of Type 2 Diabetes in men as BMI continues to increase and as we continue to "treat" the disease instead of eliminating it.

In the Lancet study they state:

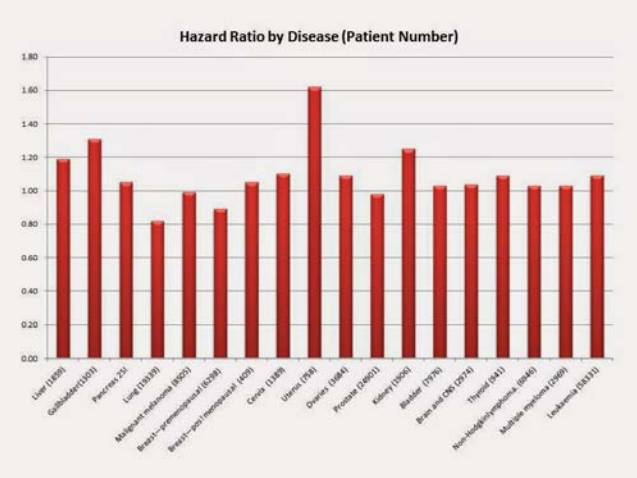
On the basis of 2000—11 data, lifetime risk of diagnosed diabetes from age 20 years was 40·2% for men and 39·6% for women, representing increases of 20 percentage points and 13 percentage points, respectively, since 1985—89. The highest lifetime risks were in Hispanic men and women, and non-Hispanic black women, for whom lifetime risk now exceeds 50%. The number of life-years lost to diabetes when diagnosed at age 40 years decreased from 7·7 years in 1990—99 to 5·8 years in 2000—11 in men, and from 8·7 years to 6·8 years in women over the same period. Because of the increasing diabetes prevalence, the average number of years lost due to diabetes for the population as a whole increased by 46% in men and 44% in women. Years spent with diabetes increased by 156% in men and 70% in women.

In a WebMD article they state:

The ongoing diabetes and obesity epidemics have combined with ever-increasing human lifespans to increase lifetime risk of type 2 diabetes to about 40 percent for both men and women,

said lead study author Edward Gregg, chief of the epidemiology and statistics branch in the division of diabetes translation at the U.S. Centers for Disease Control and Prevention (CDC). "We weren't necessarily surprised that it increased, but we didn't expect it to increase this much," Gregg said. "Forty percent is a humbling number." The odds are even worse for certain minority groups. Half of black women and Hispanic men and women are predicted to develop type 2 diabetes during their lifetime, the researchers reported.

In another Lancet study they comprised data on BMI and cancers. We summarize the Hazard Ratios below:



Thus BMI has such a broad impact that it is becoming the number one health hazard with no way to stop it.

Labels: Health Care

SATURDAY, AUGUST 9, 2014

THE START OF THE END

From the notes of the men of the DD 649 USS Albert W Grant, on August 9th 1945:

On the 6th of August, 1945, Ensign Hartung reported to me that he had heard a news broadcast over the wardroom short wave radio saying that a new powerful bomb had been exploded over the Japanese city of Hiroshima and that President Truman had issued an ultimatum to the Japanese to surrender or experience "a rain of destruction such as the world has never known." Ensign Hartung literally lived by the wardroom radio during the next few days and kept me advised of the bombing of Nagasaki and the Japanese surrender. On the day of the surrender I ordered that two cans of beer per man be served in the mess hall and opened a bottle of medicinal whiskey in the wardroom to drink a toast to victory. Normally the beer was kept under lock and key and taken ashore for picnics on atolls. Drinking on board ship was forbidden by Navy regulations, but I felt that the occasion warranted bending the rules.

Then a personal note regarding my Father and his best fried:

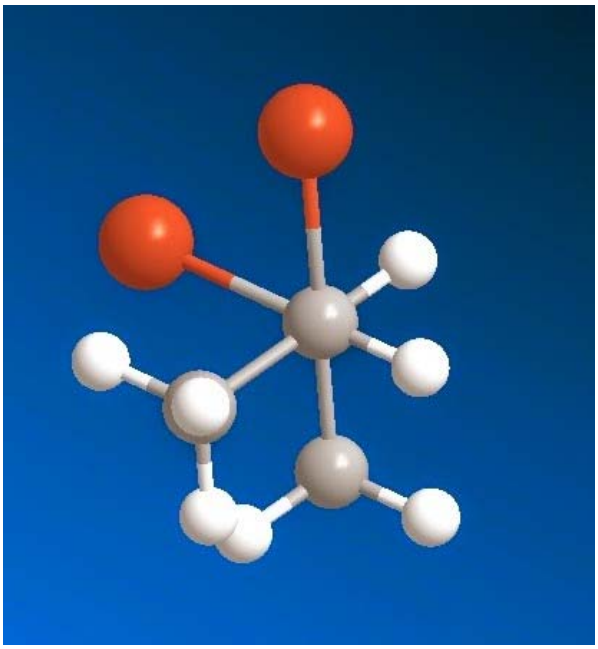
From the crew perspective the end was a bit more enthusiastically received. Carlson recalls:"THE WAR WAS OVER! Terry McGarty, a fire control man and myself were sitting together on deck when we heard the news and both of us cried like babies. So what, we, before long, would be with our loved ones. We had been planning to invade the islands of the Japanese because we had now became a part of the 12th Fleet.

More than likely the second bomb saved his and many other lives. One always looks back in history and tries to understand how best to handle the slaughter of the innocents in today's world.

Labels: Commentary

THURSDAY, AUGUST 7, 2014

THIS MAKES ORGANIC MORE LOGICAL



Organic Chemistry synthesis was always a bear. Frankly you just memorized what you needed and forgot it later. You needed the concepts but the details were alchemy to most. I realize that authors try to make it logical but it often falls on deaf ears especially for those of us who are never going to be chemists. Pathways, epigenetics, reaction rates, even phys chem, they all make sense, but synthesis?

I recall asking years ago if one could use a computer to do synthesis and of course the Organic Chemist looked at me as if I was asking to talk with God.

But Nature has a nice piece that seems to she light on this area. They state:

But a growing band of chemists is now trying to free the field from its artisanal roots by creating a device with the ability to fabricate any organic molecule automatically. "I would consider it entirely feasible to build a synthesis machine which could make any one of a billion defined small molecules on demand," declares Richard Whitby, a chemist at the University of Southampton, UK. True, even a menu of one billion compounds would encompass just an infinitesimal fraction of the estimated 10^{60} moderately sized carbon-based molecules that could possibly exist. But it would still be at least ten times the number of organic molecules that have ever been synthesized by humans. Such a device could thus offer an astonishing diversity of compounds for investigation by researchers developing drugs, agrochemicals or materials.

Seems logical, given what we do with genes why not! Good luck to these folks!

Labels: Chemistry

TUESDAY, AUGUST 5, 2014

CRISPR AND GENE CORRECTION

There is a report in Genome Research of CRISPR being used to correct β-Thalessemia. They state:

β-thalassemia, one of the most common genetic diseases worldwide, is caused by mutations in the human hemoglobin beta (HBB) gene. Creation of human induced pluripotent stem cells (iPSCs) from β-thalassemia patients could offer an approach to cure this disease. Correction of the disease-causing mutations in iPSCs could restore normal function and provide a rich source of cells for transplantation. In this study, we used the latest gene-editing tool, CRISPR/Cas9 technology, combined with the piggyBac transposon to efficiently correct the HBB mutations in patient-derived iPSCs without leaving any residual footprint. No off-target effects were detected in the corrected iPSCs, and the cells retain full pluripotency and exhibit normal karyotypes. When differentiated into erythroblasts using a monolayer culture, gene-corrected iPSCs restored expression of HBB compared to the parental iPSCs line. Our study provides an effective approach to correct HBB mutations without leaving any genetic footprint in patient-derived iPSCs, thereby demonstrating a critical step toward the future application of stem cell-based gene therapy to monogenic diseases.

This is a real major breakthrough. Wait for more!

Labels: CRISPR

MONDAY, AUGUST 4, 2014

THE HEALTHCARE WEB SITE

The GAO issued a scathing report on the HHS development of the web site which was in the news last Fall. They state:

CMS did not develop a required acquisition strategy to identify risks and document mitigation strategies and did not use available information, such as quality assurance plans, to monitor performance and inform oversight. CMS incurred significant cost increases, schedule slips, and delayed system functionality for the FFM and data hub systems due primarily to changing requirements that were exacerbated by oversight gaps. From September 2011 to February 2014, FFM obligations increased from $56 million to more than $209 million. Similarly, data hub obligations increased from $30 million to nearly $85 million. Because of unclear guidance and inconsistent oversight, there was confusion about who had the authority to approve contractor requests to expend funds for additional work. New requirements and changing CMS decisions also led to delays and wasted contractor efforts. Moreover, CMS delayed key governance reviews, moving an assessment of FFM readiness from March to September 2013—just weeks before the launch—and did not receive required approvals. As a result, CMS launched Healthcare.gov without verification that it met performance requirements.

Anyone thinking that the Government can do a better job ought review this Report. Always

remember that morbidly obese GS 9 with an attitude sitting there denying you and your family coverage from some life threatening problem. They already exist in the VA.

Labels: Health Care

SATURDAY, AUGUST 2, 2014

CIVIL DISCOURSE

In a recent link, Mankiw noted an excellent piece in Forbes regarding Civil Discourse. The Forbes article comments on the loss of civil discourse amongst Economists, and also amongst many others, when it comes to opining on the Internet.

The author states:

But what I'm writing about is not Paul Ryan. I'm writing about the level of national discourse. No one, and I mean no one, deserves to be called stupid. It's a nasty, demeaning, and incredibly elitist term. Paul, you should know better than to use your very special position to insult people. But this is a longstanding pattern with you. You go after people personally and in so doing you go after yourself. Paul, as someone who knows you, respects you, shares your values, and appreciates your marvelous academic work, knock it off. Stop calling people names. You will feel better about yourself and get people like me to take your views much more seriously.

Indeed there are many Economists at prestige institutions who act rather childishly when it comes to commenting on their foes, foes in ideas, not in fundamentals or facts. Indeed Economists are all too often at odds and thus one really questions their advice. It is an opinion and not clarity into economic reality. Keynes understood that but many of the current band do not.

Perhaps listening to mother could help. After all, one never saw Einstein rant at his colleagues calling them dumb. But one guesses that few if any were.

And oh by the way, just read one of the snarkiest yet. QED.

Labels: Economics

FRIDAY, AUGUST 1, 2014

PROSTATE CANCER, METHYLATION, AND PROGNOSTICS

There seems to be a continuous flow of genes, miRNAs, epigenetic factors including methylation, SNPs and the like all both diagnostic and prognostic for various cancers. A decade ago one looked for a gene, some gene that somehow got broken, changed, deleted, or the like. The paradigm was the Philadelphia chromosome of a cut and paste example. With the understanding we now have of methylation we see the same occur here, and methylation can be acquired and/or genetically inherited (see imprinting examples). However methylation is still

somewhat poorly understood; what causes it, why does it work positively in some cases and negatively in others?

Methylation is but one of the many facets of what we now see as causes of Cancer. We depict a short summary below.

We examine the work of Wojno et al which has received recent interest. They examine the impacts of methylation upon 3 genes and see their presence as prognostic of potential aggressive prostate cancer. Specifically they conclude:

The diagnosis of prostate cancer is dependent on histologic confirmation in biopsy core tissues. The biopsy procedure is invasive, puts the patient at risk for complications, and is subject to significant sampling errors.

An epigenetic test that uses methylation-specific polymerase chain reaction to determine the epigenetic status of the prostate cancer–associated genes GSTP1, APC, and RASSF1 has been clinically validated and is used in clinical practice to increase the negative predictive value in men with no history of prostate cancer compared with standard histopathology. Such information can help to avoid unnecessary repeat biopsies.

The repeat biopsy rate may provide preliminary clinical utility evidence in relation to this assay's potential impact on the number of unnecessary repeat prostate biopsies performed in US urology practices.

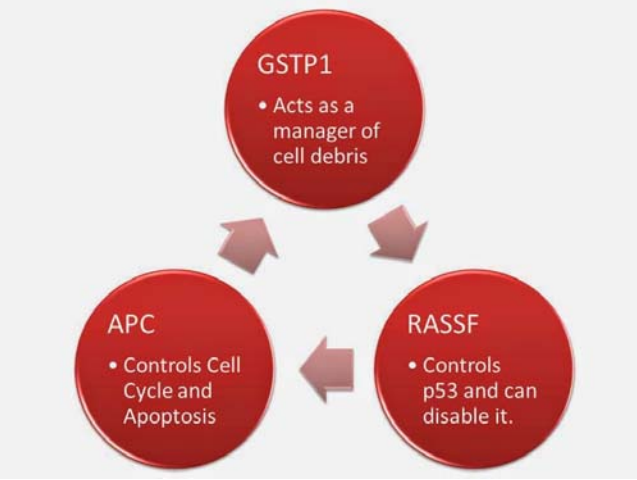
DNA methylation normally can result in the silencing of genes by interrupting the normal process of promoters. CpG islands are often hypermethylated and thus the gene which may regulate cell proliferation is silenced. This may result in uncontrolled cell growth. For example genes controlling MYC are not produced and MYC may then result in excess cell cycle proliferation. Methylation is hypermethylated in the regions of intergenic regions and in repetitive elements and this hypermethylation silences these regions and facilitates normal cell DNA transcription of the gene. Disruption of DNA, namely hypomethylation, in the intergenic

and repetitive regions may result in possible loss of imprinting. This hypomethylation is also related to the production of lncRNAs which may in turn interfere with normal gene transcription.

Decitabine is a DNMT inhibitor. Namely, it inhibits the DNA methyltrasferases that facilitate methylation (such as DNMT3 which are de novo and DNMT1 which is maintenance). Decitabine thus has then tendency on the specific hematologic cell lines in MDS to remove methylations which have caused the aberrant cell line proliferations and allow for the return of homeostasis. MDS is a quasi-malignant condition originating in the bone marrow which may in many cases result in Acute Myelogenous Leukemia. With the use of decitabine or a similar DNMTI azacitidine, demethylation of these rapidly reproducing cells may be achieved and possible a normal state of homeostasis achieved.

The use of pharmaceuticals that alter the methylation patterns of DNA can have lasting effects because those patterns may last through subsequent mitotic changes. On the one hand that may be beneficial as is the case with MDS but such broad demethylation may also alter other segments of the DNA altering essential control elements and pathways. In cell development there are two sensitive periods; germ cell development and early embryonic development. It is during these periods that methylation is cleared and reset and that a drug-like a DNMTI would pose a serious risk to the proper resetting of the marks and could result in substantial DNA expression damage.

In summary we will examine the three gene methylation proposition with this test. We summarize this below:



Let us examine what the study presents in a bit more detail. Basically it does the following:

1. It examines three gene products; *GSTP1, APC, and RASSF1*

2. It determines if the genes are methylated so that the gene products are suppressed.

3. If that is the case after a first biopsy which is deemed normal, then a second biopsy is mandated due to the high incidence of a positive result on the second biopsy for PCa.

Specifically from the paper by Partin et al on the same topic the authors' state:

The DOCUMENT multicenter trial in the United States validated the performance of an epigenetic test as an independent predictor of prostate cancer risk to guide decision making for repeat biopsy. Confirming an increased negative predictive value could help avoid unnecessary repeat biopsies. We evaluated the archived, cancer negative prostate biopsy core tissue samples of 350 subjects from a total of 5 urological centers in the United States. All subjects underwent repeat biopsy within 24 months with a negative (controls) or positive (cases) histopathological result. Centralized blinded pathology evaluation of the 2 biopsy series was performed in all available subjects from each site.

Biopsies were epigenetically profiled for GSTP1, APC and RASSF1 relative to the ACTB reference gene using quantitative methylation specific polymerase chain reaction. Predetermined analytical marker cutoffs were used to determine assay performance. Multivariate logistic regression was used to evaluate all risk factors.

The epigenetic assay resulted in a negative predictive value of 88% (95% CI 85-91). In multivariate models correcting for age, prostate specific antigen, digital rectal examination, first biopsy histopathological characteristics and race the test proved to be the most significant independent predictor of patient outcome.

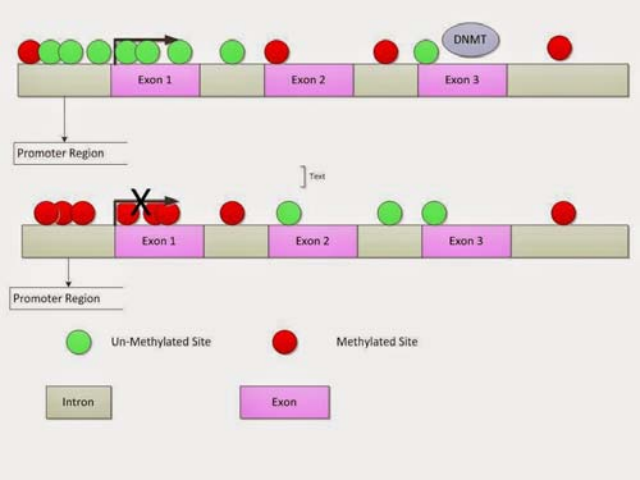
The DOCUMENT study validated that the epigenetic assay was a significant, independent predictor of prostate cancer detection in a repeat biopsy collected an average of 13 months after an initial negative result. Due to its 88% negative predictive value adding this epigenetic assay to other known risk factors may help decrease unnecessary repeat prostate biopsies.

Recall that the *negative predictive value* or NPV is defined as:

Thus an NPV of 88% for the sample size used implies that it is fairly high in predicting True Negatives a priori but may still miss a percentage. There of course is the issue of the pathologist missing the PCa as well. This could be done by a sampling deficiency or confusion on a reading. It is not clear if for example a HGPIN is read.

Thus focusing on methylated genes, specifically just 3 of them, GSTP1, APC and RASSF1, they were able in a small sample to ascertain that there would be no need of a second biopsy if they were found to be unmethylated in the first.

Recall the effects of methylation as we show below:



From an article in Medical Express[37][1] as well as from an article in Eureka[38][2] as well as from an article in Science Codex[39][3] we have the following summary:

More than one million prostate biopsies are performed each year in the U.S. alone, including many repeat biopsies for fear of cancer missed. Therefore there is a need to develop diagnostic tests that will help avoid unnecessary repeat biopsies. Two independent trials have now validated the performance of an epigenetic test that could provide physicians with a better tool to help eliminate unnecessary repeat prostate biopsies, report investigators in The Journal of Urology.

In the previously reported independent MATLOC (Methylation Analysis To Locate Occult Cancer) trial, a multiplex epigenetic assay (ConfirmMDx for Prostate Cancer) profiling the APC, GSTP1 and RASSF1 genes demonstrated a negative predictive value of 90%. GSTP1 methylation is a specific biomarker for (prostate) cancer and this gene is methylated in up to 90% of prostate cancer cases. Additionally, APC and RASSF1 are important field effect markers and increase the diagnostic sensitivity of the assay.

A second multicenter study, DOCUMENT (Detection Of Cancer Using Methylated Events in Negative Tissue), has validated the performance of the epigenetic assay used in the MATLOC trial as an independent predictor of prostate cancer risk to guide decision making for repeat biopsy. In the DOCUMENT study patients with a negative biopsy were evaluated to identify

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37[1] http://medicalxpress.com/news/2014-07-accurate-epigenetic-unnecessary-biopsies-prostate.html

38[2] http://www.eurekalert.org/pub_releases/2014-07/ehs-nae072114.php

39[3] http://www.sciencecodex.com/new_accurate_epigenetic_test_could_eliminate_unnecessary_repeat_biopsies_for_prostate_cancer-137932

those at low risk for harboring cancer missed, through biopsy sampling error, who could forego an unnecessary repeat biopsy. The validation study resulted in a negative predictive value of 88%.

"This epigenetic assay is a significant, independent predictor and has been shown to be the most valuable diagnostic aid of all evaluated risk factors in two independent trials," comments Alan W. Partin, MD, PhD, of the James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland. "Negative findings of this assay could be used to reduce concern over unsampled cancer and effectively avoid unnecessary repeat biopsies."

A total of 350 patients were enrolled in the DOCUMENT trial from five geographically dispersed medical centers: Cleveland Clinic, Eastern Virginia Medical School, Lahey Hospital & Medical Center, Johns Hopkins University, and University of California Los Angeles. Patients were grouped into those with two consecutive negative biopsies (controls) and those with a negative biopsy followed by a positive biopsy within 24 months. The initial archived, negative for cancer, prostate biopsy core tissue samples were evaluated. All of the men underwent a repeat biopsy on average one year after the initial biopsy.

Only biopsies with a minimum of eight cores per biopsy, collected no earlier than 2007, were included in the study, while initial biopsies with atypical cells suspicious for cancer, i.e. atypical small acinar proliferation by the sites' pathologists, were excluded, since this would have triggered a repeat biopsy based upon histopathology alone.

After correcting for age, prostate specific antigen (PSA), digital rectal exam, histopathological characteristics of the first biopsy, and race, this epigenetic test proved to be the most significant, independent, and strongest predictor of patient outcome with an odds ratio of 2.69 as well as the most valuable diagnostic aid of all evaluated risk factors. The slightly decreased sensitivity of the DOCUMENT trial compared to the MATLOC trial is most likely associated with a higher PSA screening prevalence in the DOCUMENT cohort.

It is important to note the following:

1. The genes selected have been studied for over two decades and especially as regards to their hypermethylation status.

2. The test is an early prognostic test which when combined with prostate biopsy data, especially a benign reading on the prostate biopsy.

3. The test has reasonable statistics given its small sample size but as we shall see there is substantial variability in these tests.

Methylation is but one of the very many changes we see in cancers. Whether they are cause or effect is yet to be determined. We know, for example, that methylation is causal in MDS, myelo-dysplasia syndrome, a precursor often of ALL. However, the cause of this methylation is still

problematic. Drugs like DNMT inhibitors, azacitidine and decitabine are methylation inhibitors that seem to work for a while in this disorder. However what they do to other cells is uncertain.

In this study which we examine, there is a multiplicity of questions.

1. What causes the methylation?

There is still a lack of clear process as to how methylation occurs. As we will note shortly there are hypothesis that it is a result from inflammatory states and others that there may be secondary effects of autoimmune conditions. The elements of the process are understood to some degree but no true full causal chain is established.

2. Why are these gene sites methylated?

Why specific CpG islands at specific genes are methylated is still unknown. Are these initial locations or are the related to other as yet to be determined sites. Are certain CpG site more susceptible? Is there some histone issue wherein the histones are demethylated opening the DNA and thus allowing CpG methylation?

3. Why not try the DNMT inhibitors if these methylations are causal for PCa?

DNMT inhibitors are used for MDS with some short term success. Can they be used here as a step towards reversal? The problem is that we do not know what DNMTI sequellae are. The unintended consequences could be significant. Can we develop cell specific DNMTIs or are they even too potent?

4. Are many cancers caused by methylation or demethylation? If so which ones and why?

We have examined several different cancers and there is a large putative collection of genes, translocations, miRNAs, SNPs, methylations, and the like. Almost weekly and perhaps soon daily we will be seeing alleged markers for every element of a cancer development. Two decades ago we saw just gene issues. Today we have a problem of ascertaining the chicken or the egg. This is both a challenge and an opportunity. The problem, however, is that each time one of these has been developed, we see a Press release frenzy as it be a sine qua non.

5. Are the observations made by the researchers causal or coincidental?

This is always a critical question. Is this specific methylation of genes the cause of ultimate PCa or the coincidental effect of some other factor?

6. Are the methylation observations drivers or therapeutic approaches?

This question is a follow on to our question regarding DNMTIs.

7. Should we be examining more cancers from an epigenetic point of view rather than a genetic mutation perspective?

We have examined a few cancers for methylation as drivers for malignancy and metastatic behavior.

8. If as we have seen anecdotally, patients determined to have widespread HGPIN on a first 24 core biopsy and then none on a second 24 core biopsy, is this possibly a demethylation result, a stem cell result, or some other factor.

We have examined HGPIN in previous analyses. Although not considered a true PCa it has been considered as a natural pre-cursor. Namely many assume that HGPIN will always turn into PCa. However we have anecdotally seen patients where the HGPIN actually regresses, to the level of being unidentifiable at on a high density core biopsy. Thus we have asked if the first biopsy actually precipitated the remission, if so how and why, or was there some other factor. Unfortunately there is inadequate data for this study.

9. What of the stem cell factor in PCa?

PCa stem cells are always a concern. We have discussed them at length and basically research continues into these cells in PCa. Yet it does beg the question; what cells need be methylated and are certain cells more likely than others? Furthermore we can ask; how do we segregate prostate cells so as to ascertain the severity of methylation?

10. PTEN mutations have been proposed as a major causal effect of PCa. How does this relate to epigenetic factors?

We have shown that PTEN is controlled in the process of p53 and in turn the MDM2 and its RAS precursor control. Thus the focus on RAS derivatives is consistent with the PTEN argument.

11. Are epigenetic factors the results of inflammatory states? Namely in a patient with for example Type 2 Diabetes and elevated inflammatory status, does this become an initiating factor for methylation?

Hartnett and Egan have recently written:

Recently, epigenetic alterations, in particular alterations in DNA methylation, have been observed during inflammation and inflammation-associated carcinogenesis. The mediators of this, the significance of these changes in DNA methylation and the effect this has on gene expression and the malignant transformation of the epithelial cells during IBD and CAC are discussed in this review. The recent advances in technologies to study genomewide DNA methylation and the therapeutic potential of understanding these molecular mechanisms are also highlighted.

Dayeh et al focus on these types of methylation induced by Type 2 Diabetes in a recent paper as well.

Also it is worth examining the summary by Kundu and Surh on inflammation and cancer. They state:

DNA methylation, the covalent addition of a methyl group to the 5-position of cytosine base in the DNA, represents a critical epigenetic control of gene expression. The perturbation of methylation patterns as either aberrant loss of cytosine methylation in transforming genes or inappropriate gain of cytosine methylation in tumor suppressor genes has been involved in various human malignancies.

The most predominant aberrant DNA methylation is hypermethylation that typically occurs at the CpG islands located in the promoter regions of tumor suppressor genes. Promoter hypermethylation of tumor suppressor genes, such as p16, von-Hippel Lindau (VHL), adenomatous polyposis coli (APC), breast cancer susceptibility gene (BRCA1), retinoblastoma (Rb), E-cadherin (CDH1), p73, p53, and p57, results in transcriptional silencing . By analyzing the methylation status of 11 candidate cancer-related genes in cutaneous squamous cell carcinomas, Murao et al. have demonstrated that the promoter hypermethylation of CDH1, p16, Rb1 and p14 results in the loss of respective protein production.

Therefore, the epigenetic silencing of tumor suppressor genes by promoter CpG island hypermethylation perturbs cell cycle control, apoptosis, DNA repair and cell adhesion, and is recognized as an important mechanism in the tumorigenesis. However, global hypomethylation of certain genes, e.g., insulin-like growth factor-2 (IGF-2), can also result in genomic instability, accelerating malignant transformation.

As Donkena et al state:

"Oxidative stress" is the state of a cell, which is characterized by excess production of reactive oxygen species (ROS) and/or a reduction in antioxidant defenses responsible for metabolism. ROS are formed as a natural byproduct of the normal metabolism of oxygen. Under normal circumstances, the cell is able to maintain an adequate homeostasis between the formation of ROS and its removal through enzymatic pathways or via antioxidants. If, however, this balance is disturbed, then oxidative stress occurs.

This generates an imbalance of production/removal of ROS, which is either directly or indirectly involved in initiation, promotion, and progression phases of carcinogenesis. Oxygen radicals may cause damage to DNA and chromosomes, induce epigenetic alterations, interact with oncogenes or tumor suppressor genes, and impart changes in immunological mechanisms.

The extent of ROS induced oxidative damage can be exacerbated by a decreased efficiency of antioxidant defense mechanisms. .... Hypermethylation of a combination of genes including APC, RASSF1A, PTGS2, PDLIM4, and MDR1 could distinguish cancer from benign prostate tissues with sensitivities of 97.3%–100% and specificities of 92%– 100%. The increase in methylation of these genes with cancer progression indicates that they could be used for biomarkers for both diagnosis and risk assessment

Furthermore, we showed significant differences in the frequency of methylation at individual CpG sites of PITX2, PDLIM4, KCNMA1, GSTP1, FLNC, EFS, and ECRG4 in recurrent and nonrecurrent subtypes of prostate tumors. Indeed, hypermethylation of a CpG island in PITX2 portended an increased risk of prostate cancer recurrence and was a predictor of distant disease recurrence in tamoxifen-treated, node-negative breast cancer patients.

12. HGPIN has always been an issue of concern. In some cases it appears to revert to fully benign states and in others it progresses to PCa. The question is: How useful would such a test be in HGPIN conditions?

The concern always is the HGPIN cells are confined to the glandular portions of luminal and basal cells. Is it necessary to get HGPIN cells to test or can the test be performed on other cells? Specifically how large a sample is necessary to get adequate sensitivity and specificity?

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Labels: Cancer

PROSTATE CANCER AND THE USPTF

There is an ongoing debate about the use of PSA testing for Prostate Cancer. The USPTF continues to rate it as a D and that is essentially a useless procedure. Specifically they state:

The harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and overdiagnosis. Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are

being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

It is recognized that certain PCas are highly aggressive and result in short term mortality. However it is still problematic as to how best to determine them although multiple genetic tests seem to hold out significant promise. Notwithstanding this progress the USPTF offhandedly rejects the PSA for all because for some it may be uncomfortable. This Rawlsian approach to social interaction is typical of the left and their desired management of society. One wonders what the incompetently managed VA does with the tests.

As recently stated by a Urologist in Medscape:

My own feeling is that screening via PSA testing should continue to be an informed decision between doctor and patient. Patients should not have a PSA test without first being consulted and informed of the risks and benefits, and of some of the uncertainty. When a man is diagnosed with prostate cancer, even if he has a low-risk cancer, he must be prepared to have psychological difficulty accepting active surveillance.

Patient survival and patient choice should trump a few patients who select the procedure and are left feeling poorly.

Labels: Cancer

WEDNESDAY, JULY 30, 2014

MOOC PHILOSOPHY?

In a recent New York Review of Books piece the author writes about the film Ivory Tower, a work commenting on contemporary higher education. At one point he makes the observation:

At the heart of the MOOC model is the idea that education is a mediated but unsocial activity. This is as strange as the idea—shared by ecstatic communities of faith—that the discovery of truth is a social but unmediated activity.

This is a truly powerful observation. It is McLuhan in insight. It is the essence of the "peer review" process.

Do Instructor have value, besides the "stars". My classic example is Lander and Biology, he has no equal. But what of those others whose influence made us what we are today. I recall two, both in my secondary school, both sort of Mr Chips, at two extremes. Brother Edward set my mathematics career aflight, and Mr Brown made me think. Mr Brown made us work in Middle English, do Chaucer, see the future through past. Brother Edward taught how mathematics really was, discovering cause and effect.

Would a Lander on video have replaced them? No. They were essential. Without Mr Brown taking us for drinks before my final French exam, I would never have become fluent in French, and as for Brother Edward, he created the ability to "see" the answer.

The group, the mass, the consensus of opinion, it is useless, it is the insight of the individual into something new. The person willing to use their intellect to see the world in a different manner is the person who creates a difference. Truth is all too often destroyed by the social and unmediated activity. The individual is destroyed, the individual is silenced by the opinions of those without knowledge. Worse those without knowledge are empowered to apply their ignorance as truth. That is the evil in "peer reviews" by those without knowledge. Just a thought for the end of July.

Labels: Academy, MOOCs

MONDAY, JULY 28, 2014

MOOC STYLE PREFERENCE

MIT just posted a note as to what "styles" were working best for EdX. They argue:

In a paper published this spring, the CSAIL team outlined some key findings on what online learners want from videos. These include:

- *Brevity (viewers generally tune out after six minutes)*
- *Informality, with professors seated at a desk, not standing behind a podium*
- *Lively visuals rather than static PowerPoint slides*
- *Fast talkers (professors seen as the most engaging spoke at 254 words per minute)*
- *More pauses, so viewers can soak in complex diagrams*
- *Web-friendly lessons (existing videos broken into shorter chunks are less effective than ones crafted for online audiences)*

Now this should be really segmented by the market demographics. Any credible market research effort segments the demographics by enough dimensions to make it work and then seeks what is most desirable for each segment of the demographic. Usually a sophisticated task. Yet this report just assumed that everyone was the same. The results are generally interesting but a good demographic and psychographic set of dimensions would make it useful.

In my experience, I will leave my demographic and psychographic to the reader, I want:

1. A short lecture and six minutes is good.

2. A Lander approach with the Prof in front of a class, makes you feel it is real and you are pert of the process. Also it paces the instructor. It appears that Lander was the only one I used that did this.

3. I really liked the white board approach. I had the notes and could then annotate them as the lecture proceeded.

4. The rate at which a person speaks is not as critical and the rate which the transfer information. Again Lander is sine qua non, he had one to three points to get across and he did it simply.

5. Pauses, if the lecture is in front of a class they take control.

6. "Web friendly", again Lander was spot on, you did something with genes, you learned by your mistakes, my dyslexia came to the fore so I had to do a work around. This did Python program to read and translate the gene structures.

It would really be worthwhile to do real market research on these courses and not just a computer science approach. Yet that means you have to know your "students".

Labels: MOOCs

SUNDAY, JULY 27, 2014

I REMEMBER THE ELECTRIC CAR

There are times when I read some comments by Academics that I am very glad that I wandered astray and did something real.

First, I remember the Electric Car, it was a Department of Energy project dating back to the 1960s, yes the 1960s. There was always a group of folks who tinkered with electric motors and batteries and tried to stuff them in cars.

Second, there was and is the Air Traffic Control System. In the early 1970s I spent time developing a new digitized system. Any change, not really, we still use WW II systems to track aircraft.

Third, then there is GPS. I remember GPS well, I taught the first course on GPS at GWU in the mid 70s as it was being developed. Yes the mid 70s. What made GPS a consumer product, Trimble, the Gulf War and mothers who sent their sons low cost GPS units so they did not get lost! What held GPS back, well I argued at Sen Kennedy's staff in the mid 70s since they saw it as a strategic threat at the time. I saw it as a commercial opportunity.

Thus what does the above tell you? Government is not really good at commercializing anything!

Now comes the Guardian and some Brit Academic which states:

Mazzucato points out the state played a role in financing nearly every key technology in an iPhone, from GPS to the touch screen. She says that, even now, the lion's share of funding for climate change technologies comes from state investment banks and public utilities, with just 6% coming from private capital. The problem is, the modern state sees this as accidental and residual. It avoids major projects, and their associated risks, seeing its role as mainly to act where the market "fails" – as with the near evaporation of venture capital funding for technology startups in the UK. Mazzucato, in a paper with LSE professor Carlota Perez, points out the danger of leaving tech to the private sector. In an economy bloated with printed money and cheap credit, if capital can't find real-world, high-growth, high-profit opportunities to invest in, it will pool into the finance system, creating one bubble after another.

You have to be kidding us! The opposite is true, leaving anything to the Government will stifle the economy! GPS would never have prospered had it been left to the Government, and as for the authors claim on the iPhone, perhaps they are looking at a different universe!

Labels: Commentary

CLIMATE: POLICY, TECHNOLOGY AND REALITY

I just read a piece in CFR by a Former Banking and Government official bemoaning what we do not know about Climate Change. What surprised me is that he says the following:

*What we already know is frightening, but what we don't know is more frightening still. For example, we know that melting polar ice sheets will cause sea levels to rise, but we don't know how **negative feedback** loops will accelerate the process. As polar ice melts, the oceans absorb more heat, which causes more ice to melt. And the polar ice sheets have already started to melt.*

But negative feedback often stabilizes systems, depending on where the poles of the system may lie. Yet he appears to be describing positive feedback which may often tend to destabilize a system.

If one forgot remeber:

Negative Feedback:

Out=GainForward*In- GainReverse*Out
or
Out=[GainForward/(1+GainReverse)]In

Note that Negative Feedback reduces output variation.

Positive Feedback:

Out=GainForward*In+ GainReverse*Out

or
Out=[GainForward/(1-GainReverse)]In

Note that Positive Feedback increases output variation.

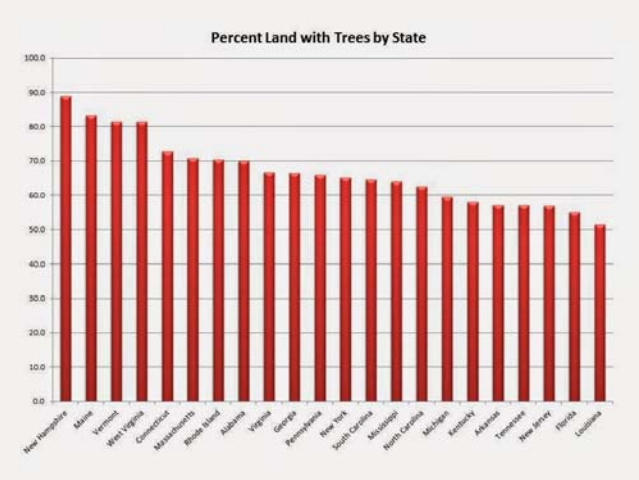
Now this may be a nit but it does tend to demonstrate the problem we have with "Policy Types" who take words without meanings. Moreover the technical people all too often throw the words about as if they have both meaning and understanding.

This is a cooler summer than usual, but that is weather and not climate. Climate seems to be warming, but is that good or bad, depends one guesses where one is. But it would help if the Policy Types would get their words right or abstain from pretending they know whence they speak.

Labels: Climate Issues

FRIDAY, JULY 25, 2014

WHO WOULD HAVE GUESSED?



The USDA just issued a report that listed the land mass per state covered by trees. Above is the set of states where it exceeds 50% of the land mass. There are seven at 70% ore more and New Jersey has almost 60%! That is 60% for the most populated state per square mile! California is half that number!

It is interesting to examine the report and consider the data. New Hampshire is almost 90%. A century ago it we near total deforestation due to rampant cutting. Maine is at 85% and lumber is one its main industries!

One wonders how the current Bishop of Rome seems to worry that we Americans have deforested our lands. As VoA stated:

In an address at the University of Molise, an agricultural and industrial region in southern Italy,

Francis said the Earth should be allowed to give her fruits without being exploited. "This is one of the greatest challenges of our time: to convert ourselves to a type of development that knows how to respect creation," he told students, struggling farmers and laid-off workers in a university hall. "When I look at America, also my own homeland [South America], so many forests, all cut, that have become land... that can longer give life. This is our sin, exploiting the Earth and not allowing her to give us what she has within her," the Argentine pope said in unprepared remarks.

With this data one really questions that assertion. Perhaps on his proposed trip to Philly he could cross the Delaware and see the trees! The facts can be so disconcerting.

Labels: Commentary

VIVE LA FRANCE, OU EST LA FRANCE?

Le Monde observed that the LA Times showed a map of three air crashes but in the process eliminated France, exactement! As they state:

Sauf que le journal californien y dévoile une audacieuse image du monde... où la France a purement et simplement disparu, noyée sous les eaux :

I guess out there in California Europe begins with Germany. Or we now have some new scheme in Geography, we can just imagine what it looks like.

Labels: Commentary

THURSDAY, JULY 24, 2014

DOES THIS MAKE ANY SENSE?

The City of LA has issued an RFI for a fiber build for the city. The intents are:

1. *Ensure that every home and every business in Los Angeles can be served by an advanced communications network that will provide a high-speed, high quality broadband connection to the Internet.*
2. *Ensure that areas of the City that are currently underserved are promptly served.*
3. *Ensure that the City is served by an open network, so no one is prevented or blocked from taking full advantage of the Internet's capabilities; and*
4. *Ensure that every Angeleno can enjoy the benefits of broadband, regardless of income or the area in which they reside.*

Now this is projected to cost well in excess of several billions, to be controlled by the city, at no cost to the city, and to provide free service to those who cannot afford it. This has the signs of a total disaster.

First, there are two strong players there already; cable and telco.

Second, wireless is a clear winner in LA, it is flat for the most part.

Third, the costs are extraordinary and the revenue is problematic.

Fourth, litigation will just explode for a variety of reasons.

Fifth, well its LA.

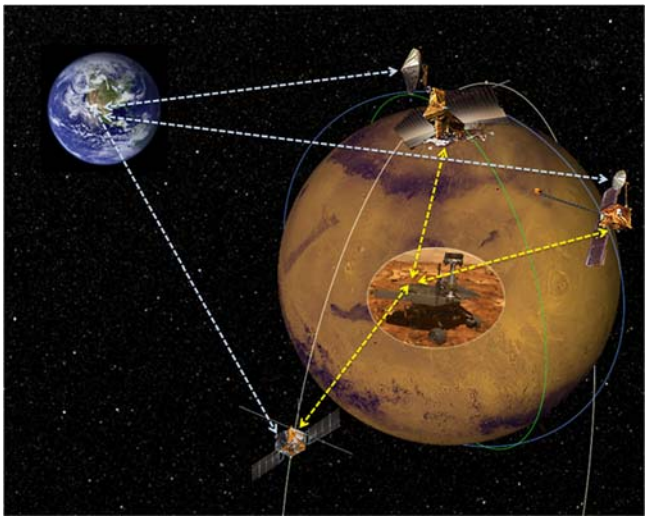
And we thought Washington had the hold on most dumb ideas!

Labels: Broadband

WEDNESDAY, JULY 23, 2014

TDRSS FOR MARS

TDRSS was and is the satellite relay system for collecting and communicating satellite data. NASA has announced an RFI for a TDRSS like system for Mars.



The above from NASA is a conception of such a system. The objective is overall Mars coverage and its ability to transmit back and forth to the earth. It is intended for controlling Martian robots and is considered as a joint commercial venture. The commercial side is interesting.

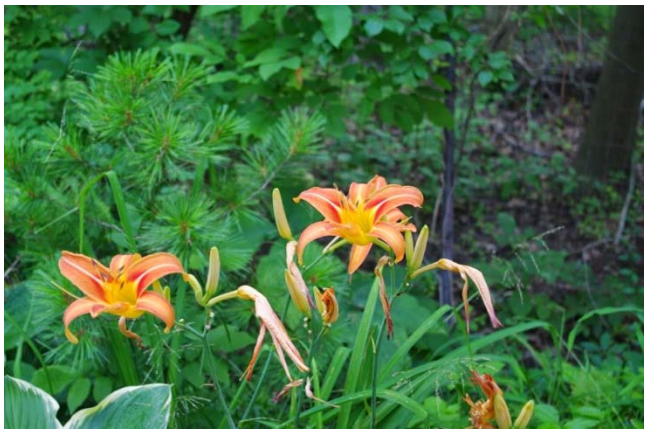
Worth following.....

Labels: NASA

MONDAY, JULY 21, 2014

FULVABLASTOMA MULTIFORME

The plant H fulva has a subspecies which is a triploid and is sterile. It is the common orange daylily and as one looks around each year this time and see them everywhere in the world one should remember that they are all the same plant! Yes, the one very same plant since they propagate only vegetatively.



Now they seem to attack weak hybrids. Let me explain.

Here is the root structure of what was at one time an attractive fertile hybrid. It is not totally invaded by H fulva, which managed to kill off the hybrid, I suspect it took 2 years to do that, and then sent out its runners to an adjacent hybrid.

These are some runners left behind. Even a little piece of this is capable of total regeneration. It is like glioblastoma multiforme or an ovarian cancer. Just one cell spreads out everywhere.

Now washing the roots one see the pathognomonic orange colored root and runner structures. One can see the attack on the former plant. The H fulvas seem to focus on certain hybrids. I have lost about a dozen so far to this attack. Species seem to be immune at least as of now.

Here is a closer look and the poor old hybrid, just gone! How did it die? Starved or consumed. It the plant a herbivore? That could be a first.

Its behavior seems directed and its method of attack seem quite effective.

Here is an array of the above plant after it has been separated.

There are some interesting questions here. I now know the what and how, I am still trying to figure out the why!

Specifically:

1. Why do the H fulvas target existing hybrids. The runners are almost directed to clusters of a hybrid which they then attach to, devour, and spread from there.

2. Is it a chemical attractant or random. My analysis seems to indicate it is targeted. I have now seen it on three dozen hybrids. However there are some on which there is nothing.

3. How can it be prevented? Good question since I believe just one H fulva cell, yes one cell, is enough to regenerate.

Interesting problem.

Labels: Commentary, Daylilies

OBESITY, TYPE 2 DIABETES AND SOME RECENT WRITINGS

I was interested in two recent papers on Type 2 Diabetes and Obesity. The first paper really startled me. The paper by Rolls starts out by saying:

Systematic studies have shown that providing individuals with larger portions of foods and beverages leads to substantial increases in energy intake. The effect is sustained over weeks, supporting the possibility that large portions have a role in the development of obesity. The challenge is to find strategies to effectively manage the effects of portion size. One approach involves teaching people to select appropriate portions and to use tools that facilitate portion control….A more effective strategy may be to encourage people to increase the proportion of foods low in energy density in their diets while limiting portions of high-energy-dense foods. If people lower the energy density of their diet, they can eat satisfying portions while managing their body weight.

In reality this is common knowledge. I am reminded of the day I brought one of my Czech partners and his family out to lunch in Boston. The portions arrived and they were aghast. The plate was about 18" across in an oval and it was piled high with food. I explained that they were not expected to finish the meal. Then I turned around and saw the Americans devouring the plates and then ordering deserts, all of them obese or morbidly obese. In Prague our lunch was on a small plate and like almost all Czechs they had a 6 oz glass of beer. Portion size is both cultural and personal. Just because it is placed in front of you there is no need to eat all of it. Thus in my opinion the Rolls paper is typical of many, an attempt to shift the blame.

Rolls concludes:

In an obesogenic environment where large portions of energy-dense foods are pervasive and viewed as appropriate, it is challenging to find effective strategies to help people consume portions that match their energy requirements. Although there are a number of tools to teach people to recognize appropriate portions, it is not clear that these tools produce sustained changes in eating behavior that facilitate weight management.

There is a simple tool, the scale. Weigh yourself. The problem is that we all too often shift the blame to some third party. The solution lies within themselves, self-control.

Now to the second article by Suh et al. As VoA remarks[40][1]:

Scientists have known about the protein, called FGF1, for several decades. But researchers discovered the potential of the molecule, which is part of a family of so-called growth factors, when they injected it into mice that were engineered to have Type 2 - or adult-onset - diabetes. The blood sugar levels of the experimental animals were restored to a healthy range for more than two days after a single injection.

[40][1] http://www.voanews.com/content/researchers-discover-protein-that-regulates-diabetics-blood-sugar/1959155.html

Now Suh and the authors state:

Fibroblast growth factor 1 (FGF1) is an autocrine/paracrine regulator whose binding to heparan sulphate proteoglycans effectively precludes its circulation. Although FGF1 is known as a mitogenic factor, FGF1 knockout mice develop insulin resistance when stressed by a high-fat diet, suggesting a potential role in nutrient homeostasis. Here we show that parenteral delivery of a single dose of recombinant FGF1 (rFGF1) results in potent, insulin-dependent lowering of glucose levels in diabetic mice that is dose-dependent but does not lead to hypoglycaemia. Chronic pharmacological treatment with rFGF1 increases insulin-dependent glucose uptake in skeletal muscle and suppresses the hepatic production of glucose to achieve whole-body insulin sensitization. The sustained glucose lowering and insulin sensitization attributed to rFGF1 are not accompanied by the side effects of weight gain, liver steatosis and bone loss associated with current insulin-sensitizing therapies. We also show that the glucose-lowering activity of FGF1 can be dissociated from its mitogenic activity and is mediated predominantly via FGF receptor 1 signalling. Thus we have uncovered an unexpected, neomorphic insulin-sensitizing action for exogenous non-mitogenic human FGF1 with therapeutic potential for the treatment of insulin resistance and type 2 diabetes.

The problem is that many of the insulin stimulating drugs for Type 2 Diabetes do not solve the underlying problem of chronic inflammation. That seems only solvable by a restricted dies and weight loss. Thus FGF1 is an interesting approach it still may not solve the underlying set of issues found in obesity. The problem is first obesity and then its sequella, increased blood sugar.

References:

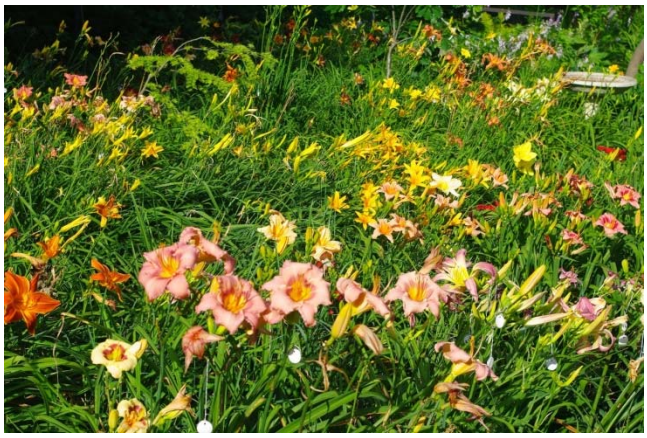
Rolls, B., What is the role of portion control in weight management? International Journal of Obesity (2014) 38, S1–S8. http://www.nature.com/ijo/journal/v38/n1s/full/ijo201482a.html

Suh, J., et al, Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer, Nature, July 2014. http://www.nature.com/nature/journal/vaop/ncurrent/full/nature13540.html

Labels: Diabetes

SUNDAY, JULY 20, 2014

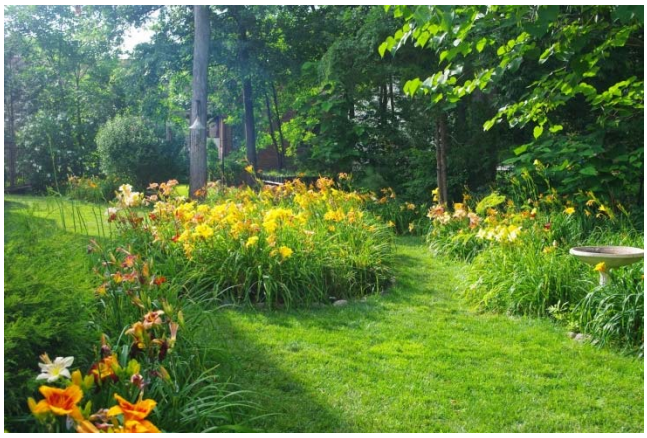
JULY DAYS



I have a few thousands of these in bloom and each day I have to record what has bloomed and then proceed to select several dozen possible crosses. To select a cross one looks for a good paternal pollen contributor and then wanders about thinking of the maternal recipient. One considers the possible offspring but like humans there is always a great deal of luck.

Thus across a wide field one wanders thinking of great parents for great offspring knowing that at best it would be two years hence and most likely four years before one sees anything.

Hybridizing requires patience and commitment. It is real genes in action, not that lab stuff with little mice but nature at its wildest.



Then there is always the battle with nature. The triploid H fulvas are like cancerous tumors, targeting weaker hybrids, surrounding them, killing off their nutrients and taking over. One must be vigilant, seeing them and then performing surgery. First the removal from the ground, then identification of the malignant cells, carefully separating them from the hybrid and destroying them, and then setting them aside for growth till the fall. In many ways it is akin to being a cancer surgeon, knowing what to cut and what to keep and then bringing the patient back.

Nature is the same everywhere, just in different forms.

Labels: Daylilies

SATURDAY, JULY 19, 2014

"ETHICAL" MANIPULATION

I was an early user of Facebook thanks to the prodding of my Grad students and I soon became an early ex-user. It had zero value as far as I was concerned and moreover had negative value relating to the postings of people who I somehow had befriended. These friends were bemoaning their personal and/or love lives and frankly that was not at my level of interest. So Farewell Facebook.

Now the manipulation of Facebook participants without their knowledge has caused a bit of a flurry. If this were say a clinical trial in medicine then I would be very concerned. It would clearly violate a bunch of standards. But alas it is beyond my kin of expertise in the wild world of Social Sciences.

Yet some person from a New York Hospital alleges that we are all wrong in our assessments, in fact she is right and we appear to be just ignorant naysayers. In Nature she states:

Let us be clear. If critics think that the manipulation of emotional content in this research is sufficiently concerning to merit regulation or charges of unethical behaviour, then the same concern must apply to Facebook's standard practice — and many similar practices by companies, non-profit organizations and governments. But if it is ethically permissible for Facebook to offer a service that carries unknown emotional risks, and to alter that service to improve user experience, then it should be allowed — and encouraged — to try to quantify those

risks and publish the results. ***Much has been made of the issue of informed consent,*** *which the researchers did not obtain. Here, there is some disagreement even among the six of us. Some think that the procedures were consistent with users' reasonable expectations of Facebook and that no explicit consent was required. Others argue that the research imposed little or no incremental risk and that informed consent might have biased the results; in those circumstances, ethical guidelines, such as the US regulations for research involving humans, permits researchers to forgo or at least substantially alter the elements of informed consent. Although approval by an institutional review board was not legally required for this study, it would have been better for everyone involved had the researchers sought ethics review and debriefed participants afterwards. The Facebook experiment was controversial, but it was not an egregious breach of either ethics or law. Rigorous science helps to generate information that we need to understand our world, how it affects us and how our activities affect others. Permitting Facebook and other companies to mine our data and study our behaviour for personal profit, but penalizing it for making its data available for others to see and to learn from makes no one better off.*

Now the tone, "Let us be clear" is a bit off putting. She is not lecturing to some collection of inmates at Sing Sing, this is in Nature. As to the Review Board, perhaps someone should have given a thought. Is this mind-manipulating? I see no reason why it is not. Yes, "much has been made of informed consent" . They disagree amongst each other. If so then there should have been some addressing the issue, any disagreement indicates a concern.

In my opinion this write-up is near callous and appears to reflect in my opinion a level of arrogance that one should be seriously concerned with. Should on-line sites who have very manipulable audiences try out the manipulation. They apparently do so with Ads but with the News we may be seeing for example what may be going on in Russia as we speak. Is that a good idea? Hardly.

Labels: Commentary, Internet

WEDNESDAY, JULY 16, 2014

JE PENSE FRANCAIS

The NY Times has a piece about learning French. Now being a rainy Wednesday in July I thought why not comment. Languages are a bit complex. I agree, but as a kid growing up in a mixed New York neighborhood I was exposed to Italian (really Sicilian but I did not know that until I tried it in Florence), Spanish (my father's first job was as a Spanish-English translator for a shipper in New York, and my friends were Puerto Rican so my accent is a Brooklyn-Spanish), and of course like any good Catholic School Boy in the 1950s a great wealth of Latin, all before High School. In fact I was great at Latailian, that mix of Latin and Italian we spoke at Mass.

Now in Secondary School we had French, after all it was the French Christian Brothers, Latin, it was Catholic, and Greek, it was a Prep School.

In Grad School for some reason I chose Russian for my language, the last person perhaps at MIT having to take a language exam. By then you could bring anything you wanted and the

translation was some electronics paper and all you had to do was kind of get close. Actually I learned some Russian from a fellow Life Guard in New York, one Jimmy Bula, a Ukrainian, who taught me pronunciation and the vernacular. Little did I know but half the words were Polish.

So when I went off to Europe and Asia for my companies I had been exposed to Homeric Greek, Latin, Sicilian Italian, Puerto Rican Spanish, Ukrainian Russian, and some semblance of American English. I tried my Homeric Greek in the Marriott in Athens, and well, the waitress was from Astoria Queens working for her uncle for the summer so we went to English and I decided I would come up to speed. You see Greek is real easy, if you had medical and scientific training you were halfway there.

The solution, 3X5 index cards, 20 words a day, and trying to get around Athens by Taxi. You are surrounded by Greek, signs, people, papers, and after a week it starts to be absorbed. You get the first 100 words, here, there, this, that, where, how much, thank you, please, etc. The most important is "where is the bathroom?". For my wife it was "How much is it?" She knows that in 22 languages, and that is all.

But the language steps are simple:

1. Go to where it is spoken.

2. Lern the first 100 words

3. Learn the present, past, future of to be and to have

4. Get 20 verbs in present past and future.

5. Get 25 adverbs

6. Every day write and memorize 20 new words. Look fr them

7. Try your skill on the locals. They will enjoy it and at first you will not.

8. Repeat the steps again and again.

9. Watch television, except in France. Somehow French TV is too intellectual. Spanish TV is great!

10 Realize that for some reason you will learn some languages and others will be impossible. I am good at Russian but Czech and Polish are impossible. Too old to wonder why.

Now the Times piece state:

Last year researchers at the Chinese University of Hong Kong and Northwestern University in Illinois hypothesized that language study should prove beneficial for older adults, noting that the

cognitive tasks involved — including working memory, inductive reasoning, sound discrimination and task switching — map closely to the areas of the brain that are most associated with declines due to aging. In other words, the things that make second-language acquisition so maddening for grown-ups are the very things that may make the effort so beneficial. The quest for a mental fountain of youth, pursued by baby boomers who fear that their bodies will outlive their brains, and who have deeper pockets than Juan Ponce de León, has created a billion-dollar industry. There is some evidence that brain exercise programs like Lumosity and Nintendo's Brain Age can be beneficial, but if my admittedly unscientific experience is any indication, you might be better off studying a language instead. Not only is that a far more useful and enjoyable activity than an abstract brain game, but as a reward for your efforts, you can treat yourself to a trip abroad. Which is why I plan to spend the next year not learning Italian.

Frankly it seems that the author has missed all the steps. You want to learn French, go live in France, and work at it. You want to learn Spanish, ride the NY Subways, do garden work in the summer, or watch soccer.

Labels: Commentary

TUESDAY, JULY 15, 2014

NET NEUTRALITY AND THE FCC

It appears that the FCC may be entering a state of chaos. Internet Neutrality is a simple concept. The local carrier, CATV or Telco, provides an interconnection service. It enters into an agreement with a customer to provide them access to what is termed a "meet point" with some other entity afar. The local customer then pays for the use of the facility between their location and the meet point. Simple. Like a bus taking you to the airport. The bus company does not want to charge you based on what city you are flying to but only the fact that you got from your home to the airport.

We have written extensively on Internet Neutrality over the years. We conclude that the local carrier for the purposes of interconnecting a customer to a meet point is a common carrier. There should be no doubt.

Now the FCC is trying to square the circle. As the Hill states:

An avalanche of net neutrality comments have been dumped on the Federal Communications Commission, highlighting the passions stirred over whether Internet service providers like Comcast should be allowed to charge companies more money for quicker delivery of their movies and television shows....FCC Chairman Tom Wheeler said the agency is "mining through" the submissions from lawmakers, content providers, public interest groups and citizens who have seen fit to tell the FCC what is on their mind.....In a blog post Monday, prefacing comments to be filed with the FCC on Tuesday, the National Cable and Telecommunications Association representing cable companies such as Comcast, Time Warner and Cox Communications doubted the need for new rules at all.
"We remain skeptical that new rules are necessary to achieve that result, but if new rules are

considered, we feel strongly that they should be built within a framework that encourages continued investment and innovation in broadband networks," the group said. The group also pushed back on calls for reclassification, which would "be misguided from a policy perspective" and "likely fail to survive judicial scrutiny." Tech companies — through their trade group, the Internet Association — are asking for broader new rules. The group includes Google, Netflix, Amazon and Facebook.
They want new net neutrality protections preserving access to the Internet to be extended to cellphone networks. The rules also should protect websites when they fight with Internet providers over traffic, the group said.

Now in my experience of dealing with the FCC it is clear that they already have decided and some lobbyist has already written the rules. The whole ruse of asking for public comment is a front. One further suspects that the CATV folks will prevail since they control the news channels. Further in my experience Comcast is not the nicest entity to compete with.

The result will be a loss of a voice for the American people and a step closer to a rather ugly end.

Labels: FCC

MONDAY, JULY 14, 2014

BACTERIAL IMMUNE SYSTEM

Each time one finds a new and innovative biological mechanism one finds another twist and turn. CRISPRs have been explored for a short while but they were understood to be an immune system for bacteria against viral phages. But now there is evidence that they are also used against antibiotics.

Eureka states:

The CRISPR system has attracted considerable attention for its potential uses in genetic engineering and biotechnology, but its roles in bacterial gene regulation are still surprising scientists. It was discovered by dairy industry researchers seeking to prevent phages, viruses that infect bacteria, from ruining the cultures used to make cheese and yogurt. Bacteria incorporate small bits of DNA from phages into their CRISPR region and use that information to fight off the phages by chewing up their DNA. Cas9, an essential part of the CRISPR system, is a DNA-chewing enzyme that has been customized for use in biotechnology.

The interesting question is that CRISPRs must have developed this capability in bacteria over the past fifty years or so. If so this adds a dynamic to CRISPs that is quite startling.

Labels: Epigenetics

HAPPY BASTILLE DAY

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

But remember the consequences.

Labels: Commentary

MONDAY, JULY 14, 2014

BLOOD TESTS AND CANCER DIAGNOSIS

There are a multiplicity of tests for cancer diagnosis, mostly genetic in nature, but a recent example details the use of the immune system.

In a recent paper in The Scientist they report:

Researchers from Arizona State University in Tempe have created an inexpensive blood test that can detect several common cancers based on the immune responses they evoke. They used arrays of randomly generated peptides to bind antibodies from human blood samples belonging either to healthy controls or to people with one of five different cancers. Based on the binding patterns—or immunosignatures—the researchers were able to distinguish between all five cancer types. The team also used another array of randomly generated peptides to differentiate among a broader range of cancers and other diseases.

However there were some doubts expressed:

But Vlahou and Mischak argued that such a general cancer screen has limited clinical relevance, as doctors tend to test specific at-risk populations rather than the general population. Vlahou said that doctors would be more interested in validating biomarkers to differentiate between bladder cancer and benign bladder conditions, for instance, rather than administering a catch-all cancer test. "I don't think finding a multi-cancer test is going to make a clinical impact," she said.

There is such a proliferation of tests that one wonders what the clinical significance is.

Labels: Cancer

CANCER AND SINGLE PAYER SYSTEMS

Cancer Research UK presents a troubling report of the dramatically higher moralities to cancer in the UK as compared to the rest of the OECD.

They conclude:

Delay in Diagnosis:

You are more likely to survive cancer if it's spotted early. But the ICBP studies showed that for lung cancer and, to a lesser extent, bowel cancer, UK patients are often diagnosed at later stages compared to other similar countries. This could help explain the lower survival we see for those cancers.

Lower Access to Treatment:

But early diagnosis alone does not explain the UK's lower survival; access to the best treatment has increasingly been shown to be a problem. And this is particularly true of treatment rates in older people. Both the EUROCARE and ICBP studies have shown the survival for older patients in the UK is lower than in comparable countries.

It appears as if the problem is a poorly organized and over-controlled centralized system rationing health care. Sounds like the VA or perhaps the ACA.

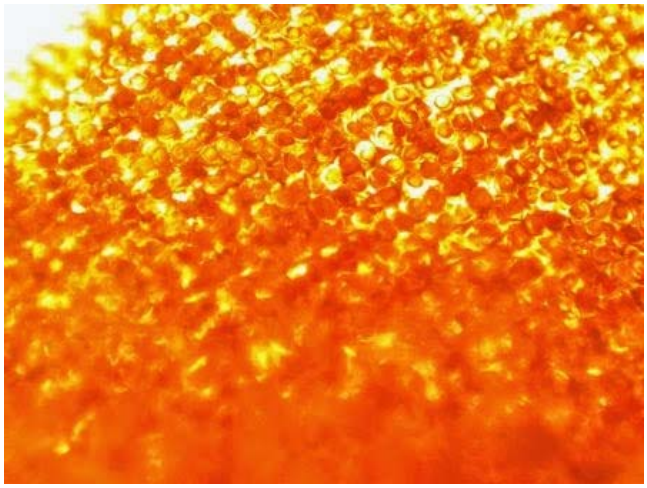
Labels: Cancer

TUESDAY, JULY 8, 2014

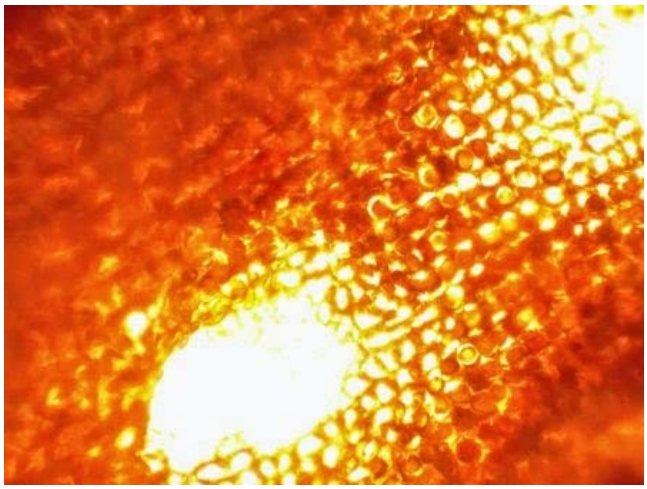
GUEST BLOGGER

I (See Bella's Big Blog) looked at flower cells with my grandfather today. It was cool to see the chamber like organisms. You could see the nucleus in some pictures. We also looked at cells in a fish scale. They actually look like cells in a prison cause of their shape. We also crossed some flowers and looked at parts under a microscope. The female part is the one with the hair parts and the male part has the pollen. In the morning we took pictures of some flowers and used my grandfather's book to make a log about some.

This is a flower that we took a picture of. Isn't it pretty?

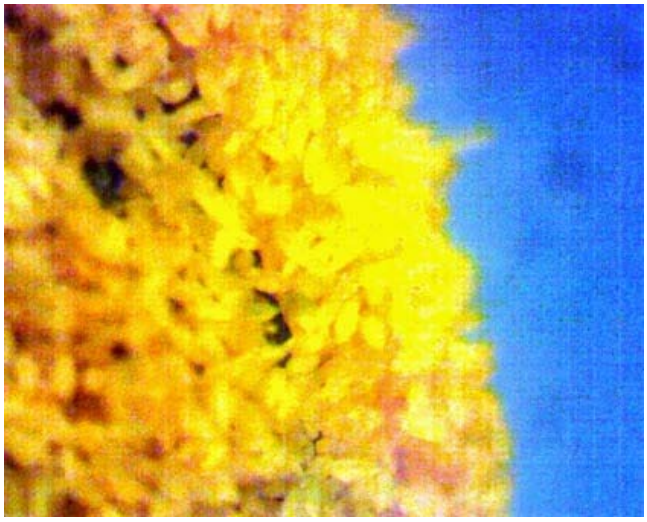


You can see cells in this picture at the top part but you can't see that many nuclei.



In this picture you still can't see a lot of cells but you can see a one very nice nucleus.

This is the male part of the flower it's got the pollen on it.



This is a closer picture of the pollen. It looks a little like rice.

This is the female part of the flower. It has the hair like parts on it. I think it's a little longer than the male part.

Labels: Commentary

FRIDAY, JULY 4, 2014

THERE ARE TIMES WHEN THIS IS REALITY

We Must Believe In Magic (Crystal Gayle)

Mad is the captain of Alpha Centauri
We must be out of our minds
Still we are shipmates bound for tomorrow
And everyone here's flying blind
Oh, we must believe in magic
We must believe in the guiding hand
If you believe in magic
You'll have the universe at your command

Mad is the crew bound for Alpha Centauri
Dreamers and poets and clowns
Bold is the ship bound for Alpha Centauri
Nothing can turn it around
Oh, we must believe in magic
We must believe in the guiding hand
If you believe in magic
You'll have the universe at your command

In many ways this seems to be the way we are drifting. Happy 4th.

Labels: Commentary

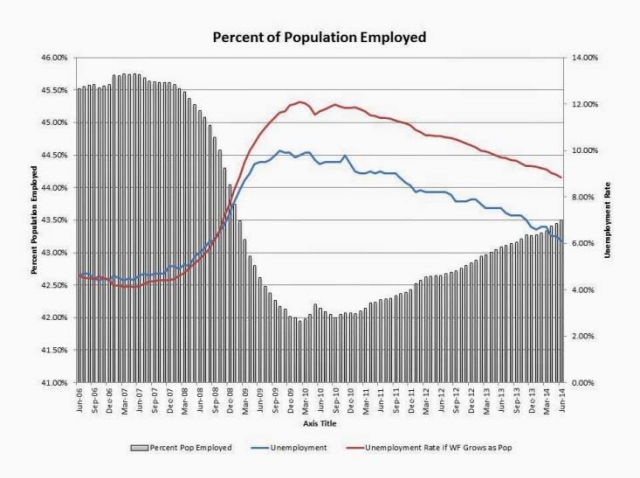
HAPPY 4TH!

Above is Washington's home at Mount Vernon.

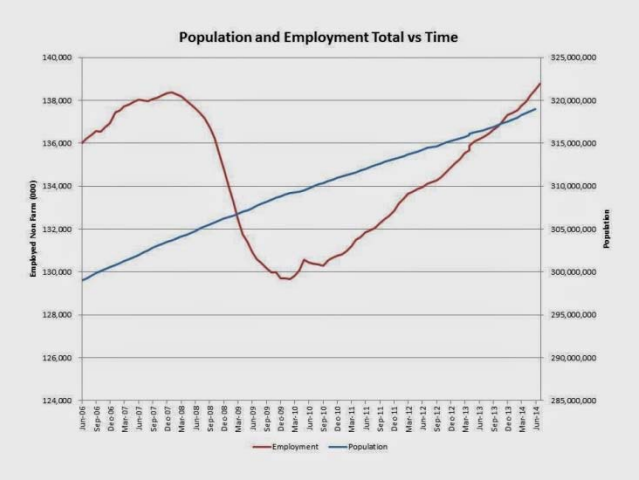
Labels: Commentary

THURSDAY, JULY 3, 2014

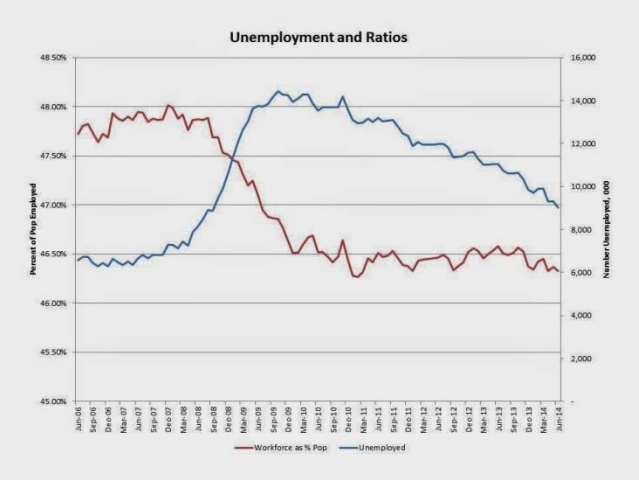
EMPLOYMENT JULY 2014



The above is the totality numbers. Reported unemployment is 6.1% but we are still at 9% if we use the 2006 base numbers. The reported numbers are getting lower faster than the pegged numbers because people are just plain leaving the workforce and living on the dole.



This is the chart which shows that we now have the same number employed as we did before the recent Recession. Big deal! We now also have over 10 million more employable people. We also have more employees now than we did in 1835 but who cares! The Administration likes to spin but there is little to truly spin here.



The above is a summary showing that as a percent we have a permanent loss of 1.5% of the employables or a 3% drop from before the Recession.

Labels: Economy

THURSDAY, JULY 3, 2014

MEDIUM, MESSAGE AND EDUCATION

In considering McLuhan and his observations of the medium of presentation actually redefining what is knowledge and thus what we see as truth, one can look at the on-line educational attempts in a similar vein. Namely, if we were to develop education methods using not only the Internet but the Internet community approach with such elements that we see in the Social Media areas then how would that change not only education but the very way we think and create. That

is, does the social context in which one "lives" "on-line" directly influence what we consider as scientific truth? Do the ways in which we see a generation interacting on the Internet, when transported to an educational process, change that educational result for the better or worse?

Over the last few years I have examined a dozen or so on-line courses. I do so having begun my teaching career in 1963 and having had Faculty positions at such institutions as MIT, GWU, Columbia and NYU/Poly. Over more than fifty years I have had thousands of students and thus have a modicum of experience, albeit not in the new on-line context. Thus I bring perhaps some bias of the old school to my opinion and my perspective.

To examine this I will consider a few applications. One of the methods the on-line educational systems use for grading their “students” is the process of what they term “peer review”. Based upon my limited but to some degree in depth analysis, it consists of the following:

1. Students are asked to answer certain questions in a prose like manner which means paragraphs and not bulleted sentences. The first problem here is the very definition of prose. To those of use with some educational background prose is merely the absence of poetry. Poetry however may lack structure of rhyme and rhythm such as free verse and thus defining something by what it is not when what it is not cannot be defined leaves one in a conundrum. However when one has half the students coming from non-English speaking backgrounds this leaves them cold, as apparently it does the instructors. Thus for the sake of simplicity we would then define “prose” as complete sentences collected together in a paragraph.

2. Now as to the “peer” nature of the students we have a problem. The students may range from PhD/MDs to High School drop-outs. They may have no initial knowledge of the subject, they may have some education in the area, or they may be professionals with publications. Thus the students are often a true broad based spectrum of individuals. Yet for the sake of this peer review process they are all considered equal. In a sense it becomes the ultimate Millennial world view that everyone’s opinion has equal merit. The discovery of any scientific fact is non-existent. Furthermore there is also a massive culture clash. In certain countries and in the highest ranking schools one is judged by one’s ability to seek out facts from the observations. In contrast, in certain countries, one is judged by one’s ability to memorize exactly what is taught and to return what is memorized flawlessly. As I will later note both approaches place the student at risk.

3. Instructors often add to the confusion by contributing their own personal views on how grades should be determined. The instructor often seems to believe that by performing this peer review process that the students will learn. The major problem is that the students who grade others bring to the table many personal and cultural biases and prejudices. For example, the students are actually instructed to see if the answer is literally “word for word” as the instructor may have indicated. If not, then the grade will be lowered in some totally random manner. If the student responding to the question manages to phrase the result in their own terms then they will be marked down. In the Discussion sections one see the instructor and their alleged assistants reinforcing this bizarre approach! Namely the answer must match what the instructor wrote “word for word”, yet as we shall also see that would have been plagiarism or fortune telling!

In addition, if the student wants to improve their own overall ranking, then they grade everyone lower. If the student does not understand the material, then whatever they give as a grade is meaningless. Thus we have cultural, ethical, and intellectual challenges that impact the process and are reflected in the student's grade. In reality the grade all too often a reflection of the biases of the grader and the instructor and does not reflect the students comprehension. This is in no way a true real peer grading system function. In such a system, there are true peers, persons with professional credentials chose by an arbiter Editor for example, and a process of due process to rebut any claims.

4. The issue of plagiarism is also introduced as an element to be considered by the students in their process of evaluation. The issue of plagiarism is highly complex. To claim one plagiarized is to accuse one of what may, in certain countries, be considered a crime. It is a fraud, a theft, an act which can have significant consequences. Thus it should not be treated lightly. To do so there must be three elements; (i) proof that what is delivered as being expressly represented as the student's, (ii) a clear demonstration by objective evidence that what is presented has been purloined from a second source, (iii) a due process offering whereby the student can have a hearing to remedy the claim. Accusation without those elements may very well be *per se* defamation. It is actionable. Furthermore if the instructor inserts themselves in the process in any manner, say by altering the existing definitions, then the instructor becomes a party to the defamatory act.

This somewhat characterizes a peer review process. The problem, simple, with thousands of students all having different ethical standards and almost all never having graded a test in their lives and having confused directions from the woman instructor, this led to chaos. If one did not answer word for word as the instructor demanded after the fact the grades were reduced, and plagiarism was alleged a multiple of times without basis, in my opinion, due to the interference of the naive instructor.

The solution is simple, avoid these "peer" reviews at all costs. First there are no "peers" in this process. Second, remove the commentary by both the instructors and the alleged "Community TAs" who especially seem to be grossly unqualified. I have seen one who alleges to be an out of work teach-at-home parent with no experience in the real world! They somehow seem to feel that their world view should be everyone's. Third, Instructors should let the Honor Codes speak for themselves. Once they get into the fray they tend to add their own ideas which frankly for almost all Instructors go well beyond their core expertise. That is what they have lawyers for; Instructors should teach and not practice law.

Now in Science and Engineering one should be able to avoid "peer" review of written materials. Yet the worse example of this practice going awry is in the Science area. The excuse of the Instructor is that it gives the student a feel for real peer review. The problem is that real peer review is real peer review, and it has the chance to remedy complaints. It has the ability to have a due process. On-lines do not.

The net result is that on-lines have so many failings that one wonders if they are converging on something that works or diverging into chaos. One awaits the lawsuits. They may very well come.

Now there is another element in on-lines which is a potential concern; the Discussion sections. Here we have the alleged “student” using this to voice their own opinions and views as to the material. This can be a potential mine field, especially one of generational warfare. Again in the context of the Millennial mindset is that each opinion has equal value. There is no basis of facts, not ability to judge based upon analysis and prior art, no true scientific method. This is merely a mechanism for the “students” to voice their world views, and one must be careful if one’s views, even if based upon facts, are at odds with some of the participants.

A second dimension is the Discussion boards. I had for two years looked but kept quiet. They seem to be filled with big ego Millennial who seem to want to give an opinion of tell the world of their perfect grades. I had an experience where I decided to post a technical comment along with a technical basis to support the observation. Then out of nowhere some, in my opinion, rather bizarre character emerges who begins to lecture me on what I said with no basis in fact. Bizarre is an understatement for the way the interaction went.

The only remedy is to remove the observation and let the responses speak for themselves. Such an interaction was unseen at MIT and frankly would most likely not be tolerated. However with the “Facebook” like Discussions it becomes a Wild West of opinion. That in my opinion is not productive and is destructive. But these Discussion boards seem to foster such an attitude. There is no use of facts, no logic, no specifics, just gross and oftentimes arrogant anonymous attacks. Pity humanity if these folks take over, they just most likely will not be tolerated long. The core problem of on-lines is the inability to have any adult supervision.

Now what makes an on-line work, if anything? I have tried to give some thought to this process.

The on-line concept has been around now for a couple of years. I have followed several of them in some detail. I have taken a few courses both to experience the process and to learn what they are presenting. To be honest, in all cases I have had the material before and in many cases even have written on the topics, some but not all. Thus, unlike many students who approach it fresh I had seen much of what was presented. On the other hand I spent no more than 3 hours per week on a course that required twelve. Thus, I did not “study” for exams. Instead I used the exams as a learning experience rather than a valuation metric. That works well especially if one’s intent is to learn the material. In fact the issue of grades is itself specious. There is no value to the grade, there is no validation that you learned anything and moreover even if there was such an acceptable validation the courses themselves are all too often limited in scope.

Let me now present some observations on what works and what does not in several key areas:

1. Lecture Style

There are two elements of a good lecture style: First, having a live class makes a world of difference. You see others and you feel part of the process. Second, the classic MIT approach as demonstrated by Lander which is to develop and explain two or three topics or ideas at each lecture so that the student gains critical insight. It is NOT to read through a collection of power point slides or to ramble on with dozens of facts without any attempt to connect them. Power

point presentations do not work very well. They foster too rapid a presentation. Poor video quality does not work at all. Assuming students are Juniors at a Public High School does not work. Interjecting one's political views do not work. Using local colloquialisms do not work. Also there is the general problem of accents, and that is always a problem. Unfortunately there is no way to remedy that.

2. Exams

Lander's exams are perfect. They make you understand the issues including the details. No one else seems to do this. The multiple choice exams are the lazy way to deal with the subject. Having others student's grade is worse than lazy.

3. Grading

Here I have a conundrum. Some students want to score perfectly and then let everyone else know their alleged performance. The grades may or may not reflect a gain in knowledge. In Lander's course the feedback often lets you know that you were sloppy, you guessed too quickly. Grading should be interactive, reflective of new knowledge, fair, balanced. Frankly, grades are just a mechanism to let you know what you did wrong. The problem is that many foreign students seem to think they have completed an MIT or Harvard course. The issue of ambiguity of expectations is a major problem.

4. Peer Grading

There is no advantage conceivable. Peer grading is an abomination. There are several reasons:

a. There are no real peers. It appears that there is an amalgam of various egos that want to be self-assured of their own value and will do anything to get it.

b. Peers generally know next to nothing. Thus, especially if the English and American systems are different for them, they then interject their own values. That often leads to massive misunderstandings.

5. Discussion Groups

I guess in the younger set it enables the communicating that they are used to. The intent of the discussions groups is valid, namely to discuss the topics, but they all too often turn into a "Facebook" type dialog. There is all too often a rambling of personal issues and the overly sympathetic colloquialisms that detract from the intent from the course. I have yet to see the type of dialog one would have at a truly first class graduate school no less a competitive Secondary School. The overhead of watching what is said is not worth the cost. I see no real benefit. There are those complaining that they got a bad grade, those puffing up about a good grade, those making politically useless remarks about something that has nothing to do with the course material. On the other hand, Discussions have great potential, especially if managed by Teaching Assistants who are educated and trained in the art of managing them. Having TAs who are unqualified just reinforces the chaos.

6. Material

I have generally managed many without a text. A few demand a text just to be able to do the required manipulation. Some courses had what may be considered notes but they were few and far between. Lack of a text or class notes can be a disadvantage for many students. Faculty Capability is also a key factor. Lander is the *sine qua non*. He knows the topic, he presents it well, he engages the students, and thus the listener. It appears that some educational institutions get an instructor who simply has the time and wants to do this. That approach shows immediately.

7. Expectations

The courses are NOT true University courses. They are abbreviated at best. Lander's course is close, and in fact as close as one gets. The others are long Seminars. Thus one should expect to learn something but not to be as accomplished as an MIT or Harvard student. There is a balance which must be met. The MIT Electronics course found some student in Mongolia who allegedly scored 100%. I gather they then tried to get the student into MIT. Yet that is one in 100,000 or more. The dropout rate is 95% or greater. In fact of the courses I took, I dropped more than half. The reason was quality of the Instructor or the lack of quality in the teaching materials on line.

Thus on-line courses face challenges. There are massive ambiguities of expectations. The cultural variances are quite large. These factors must be examined and considered. If all the courses were like Lander's Biology course it would be a perfect world. However it is not that way. But improvement is essential and this can be a powerful tool if well done. It can be a waste of time if not.

Labels: Academy

WEDNESDAY, JULY 2, 2014

WALLOPS ISLAND LAUNCHES

NASA has a hidden gem in the Wallops Island launch site. I was there last Fall for a moon launch but for anyone interested it is a great place!

Labels: NASA

ENDOSOMES AND MELANOMA

As is well known, melanoma is a highly aggressive form of cancer and is tends to metastasize very rapidly. The analysis of various melanomas has demonstrated a wide variety of genetic alterations which have been alleged as cause for its initiation or factors in allowing for its aggressiveness. We have examined various elements from many internal pathway factors, extracellular factors, and epigenetic factors (including methylation and miRNA elements). In a recent paper by Alonso-Curbelo et al the authors examine endosomic elements, namely the interaction of RAB7 as a factor which brings in endosomes and apparently uses this process to add energy to the cell allowing it to enhance cell proliferation via Myc and other genes.

There is an almost continual determination of genes and their artifacts in the identification of specific cancer related presence. We have examined many of these before and each time there appears another target it is essential to ask; why this new target is chose and what does it do that results in a metastatic condition? The current analysis focuses on a small class of proteins which facilitate endocytosis, the bringing in of materials from the cell's surface.

In a recent paper the authors have identified the small 200 nucleotide protein Ras7 as a significant factor in the metastatic behavior of melanoma. We first examine that express consideration, then examine the details behind it and consider some observations.

As Alonso-Curbelo et al state:

Although common cancer hallmarks are well established, lineage-restricted oncogenes remain less understood.

Here, we report an inherent dependency of melanoma cells on the small GTPase RAB7, identified within a lysosomal gene cluster that distinguishes this malignancy from over 35 tumor types.

Analyses in human cells, clinical specimens, and mouse models demonstrated that RAB7 is an early-induced melanoma driver whose levels can be tuned to favor tumor invasion, ultimately defining metastatic risk.

Importantly, RAB7 levels and function were independent of MITF, the best-characterized melanocyte lineage-specific transcription factor.

Instead, we describe the neuroectodermal master modulator SOX10 and the oncogene MYC as RAB7 regulators. These results reveal a unique wiring of the lysosomal pathway that melanomas exploit to foster tumor progression.

The above observation contains an interesting connection between several elements:

1. Extracellular Matrix elements (ECM) which we have examined before as factors in driving melanoma metastasis.

2. Lysosome activity which is the counter to exosomes, which we have examined as markers for melanoma.

3. Cell surface receptors and ligands which reflect cell cycle activation and control.

4. Transcription factor management through MITF and MYC which result in loss of cell cycle homeostasis.

Thus to a degree in this paper we seem to be seeing a multifaceted response modulated by the RAB gene products. Thus it is worth a brief review of endosomes and RAB and then a re-examination of the transcription factors in the context of cell cycle control.

The authors especially note the following:

- *Melanoma-restricted lysosomal gene cluster uncovers tumor-type-specific roles of RAB7*: RAB7 is one of several RAB genes and it has a specific functionality which at face value does not relate directly to the management of transcription factors. Thus it is necessary to examine that in some detail.

- *RAB7-controlled pathways selectively modulate melanoma cell phenotypes:* One does not look at all the RAB7 pathways and what controls them. We often think of MITF, SOX10 and MYC as having other control elements.

- *RAB7 is an early-induced melanoma driver that defines patient prognosis:* RAB7 modification by some form of upregulation which in turn is driven by oncogenes is a significant factor in metastatic behavior. The details will be examined somewhat herein.

- *MYC and SOX10 regulate RAB7 in an oncogene- and lineage-dependent manner, respectively:* The issue is that it is MYC and SOX10 that modulate RAB7 upwards and thus use it as a means to bring more elements into the cell which are then broken down via a lysosome and use by the cell in its proliferation. The question which seems unanswered is; if MYC and COX10 are transcription factors and also oncogenes, then how do they regulate RAB7 and if they up-regulate RAB7 what does that result in since RAB7 drives endosomic activity?

Now there is a commentary which adds to what is presented above. It states[41[1]]:

[41[1]] http://www.news-medical.net/news/20140628/CNIO-researchers-identify-over-40-genes-that-predict-aggressiveness-of-melanoma.aspx

The results of the study could help to determine the development of metastasis in patients suffering from the disease….

What is the function of these genes? Strangely, the factors that are increased in melanoma share a common mechanism: the formation of vesicles called endosomes.

Endosomes are machinery that tumour cells, via a process called endocytosis, can use to incorporate components into their environment and obtain energy by degrading them via autodigestion or autophagy. Autophagy is also used for self-cleaning to eliminate other proteins as well as damaged or unneeded cellular components.

Thus at the heart of this theory is that RAB7 is activated and results in increased processing of endosomes taking proteins from the surface of the cell and breaking them down and allowing the cells to proliferate more aggressively. We will try to demonstrate some of this activity but many of the details are still wanting. They continue:

Among all the genes that control endocytosis, the authors of the study focused specifically on one, called RAB7; this gene is highly expressed in melanoma cells. After more than six years of research, the research team …showed that RAB7 acts as an orchestra director, determining the fate of melanoma cells: at high concentrations of RAB7, cellular autodigestion is very active, and this allows tumour cells to obtain energy, prevent the accumulation of toxic components and thus divide and proliferate; when RAB7 is reduced, cells use endosomes to recycle metastatic proteins, favouring their dispersal throughout the body.

To some degree this is a growth and proliferation issue. What specifically is driving RAB7 is open for debate and it does not appear to be any mutation in the gene or its product. The emphasis on RAB7 as the key factor may be begging the question in light of the many other factors known to take a role in melanoma development.

Defining "the key to the fate of the tumour cell", …is just one of many new aspects of melanoma uncovered by this study. "Finding which mechanisms determine why melanoma is so aggressive is very complex because more than 80,000 mutations have been described for this tumour", …

This study is also relevant for clinical work. One application is the prognosis of the melanoma: the authors show in tumour biopsies that the amount of RAB7 in a cutaneous tumour defines the risk of developing metastasis. "This study opens avenues for the potential use of proteins that control vesicles and regulate autophagy as novel markers of patient survival", …

Furthermore, these results help to understand the mechanism of action of a compound that, as the group discovered in 2009, is lethal in melanoma cells as well as in other tumour cells. This RNA-based nanoparticle compound kills the cells by acting on the formation of vesicles.

The above seems to imply that if one can stop the formation of such vesicles that one then possibly “starves” the specific cells. The issue is targeting just these vesicles and not all vesicles. This observations is noted as follows:

"We knew how our nanoparticles act inside tumour cells, but not how they selectively incorporate inside the cells", …The size of these molecules requires cells to form endosomes in order to be able to trap the compound. This study demonstrates that this endosome formation (via RAB7) is very active in tumour cells but not in normal cells. Normal cells, therefore, do not incorporate RNA nanoparticles, reducing the risk of toxic effects.

However RAB7 proteins do function in all cells, taking in items and participating in the "digestion" of many such items, many of which if left undigested could be harmful to the cell. Thus it could be problematic to try such a direct approach. To some degree it may be akin to DNMT interference drugs used to block hypermethylation.

The work … could lead to the development of novel drugs that selectively target the mechanism of cell autodigestion as a potential therapeutic strategy.

The target of a specific drug then must block either the generation of Rab7 or the Rab7 directly. The sequellae of such blockage may be significant.

We have previously discussed exosomes and cancer prognosis. Exosomes are what cells eject. Endosomes are what cells ingest and process. They do this in a complex manner and utilize lysosomes which have digestive capabilities which allow for the extraction of cell nutrients.

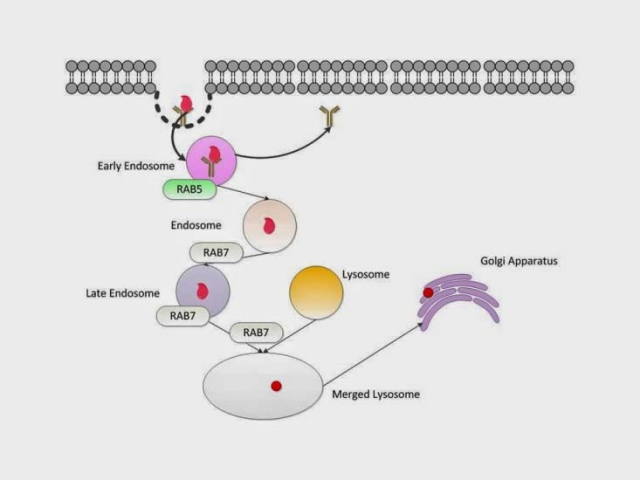
Endocytosis has several key functions for a cell[42][2]:

- It internalizes nutrients found outside the cell.
- It facilitates and regulates the expression of cell surface proteins so that cells can control the up-take of certain ligands.
- It facilitates the uptake of extracellular debris as well as other ECM items.
- Recovery of membrane structure.

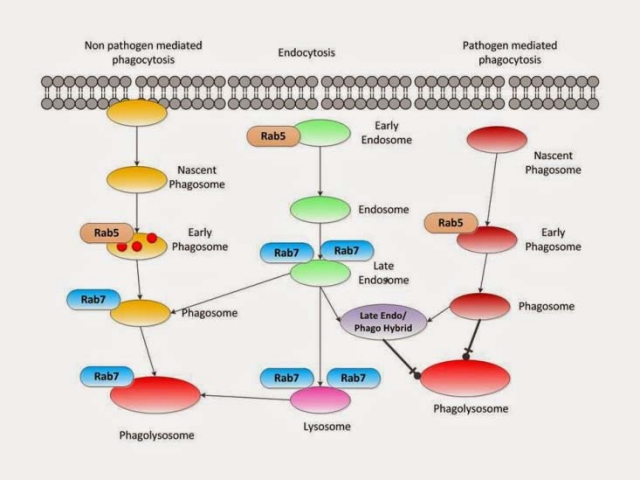
The endosomes are the transport vehicles and they function in concert with lysosomes which are enzymatically charged digestive vacuoles. Together they take in and process what is on the cell's surface and without the cell.

We depict this process generally below:

[42][2] See p 351 Cassimeris et al.



Now we can examine this process alongside several others as we show below.



Note above we show both Rab7 and Rab5 actions.

As Tabata et al note:

Endocytosis involves the intracellular transport of extracellular and plasma membrane substrates to endosomes/lysosomes and is involved in many physiological processes. Autophagy is also a process in which cytoplasmic constituents, including organelles, are transported within double- membraned autophagosomes to lysosomes for degradation.

Autophagy has divergent physiological roles in cancer, infection, immunity, and other processes. Many reports suggest there is a common element between the endosomal and autophagic pathways, but these commonalities have not been fully elucidated….

In this study, we described a novel RH protein domain that associates directly with Rab7. Rubicon and PLEKHM1 negatively regulate endosomal transport by binding to Rab7 via their RH domains.

Furthermore, this study provides novel insight into the function of PLEKHM1. These two RH domain–containing proteins also have several significant differences. Rubicon must bind to the Beclin 1–PI3-kinase complex in addition to Rab7 for its function, whereas PLEKHM1 only requires Rab7 binding. Rubicon, unlike PLEKHM1, is involved in autophagosome maturation. Both of these proteins localize to endosomes but do not show complete colocalization.

Therefore, these two RH domain proteins seem to function through different mechanisms. PLEKHM1 bound not only to wild-type Rab7 and the Rab7QL mutant but also to the Rab7TN mutant in a yeast two-hybrid assay and immunoprecipitation analyses in mammalian cells, suggesting that PLEKHM1 may bind to both the GTP-bound and GDP-bound forms of Rab7. However, the TN mutant is predicted to have reduced affinity for both GDP and GTP and may behave as a nucleotide-free Rab7 depending on the assay conditions.

Hence, in order to determine the precise nucleotide dependence, we performed an in vitro GST pulldown assay and found that recombinant PLEKHM1 strongly interacted with GTP

S-loaded Rab7 but only minimally interacted with GDP-loaded Rab7. The data convincingly confirm that PLEKHM1 preferentially binds to the GTP-bound form of Rab7, corroborating our hypothesis that PLEKHM1, like Rubicon, is a Rab7 effector.

The above analysis does reflect on a different binding domain and process from what was introduced earlier. We shall come back to this issue later.

We will now examine the RAB proteins in some detail. Vesicle targeting and fusion with acceptors on the membrane uses the collection of proteins at the vesicle membrane. These are managed by the Rab family of proteins which are small G proteins[43][3]. G proteins and Rab in particular are classified as amplifier, rectifier and organizing proteins. They can use GTP to act as a switch and these proteins are used by cells to make movement, transformations and activations. The Rab subclass of the Ras proteins plays a key role in the endocytosis and integration with lysosomes….

The following describes several of the Rab proteins and their functions[44][4]:

[43][3] See Marks pp 32-37. "small G" proteins are monomers about 200 amino acids in length. They are in the Ras superfamily and thus Rab is also in that family.

[44][4] See Marks et al, p 383.

RAB Type	*Function*
Rab1 and Rab2	Control vesicular traffic from the endoplastic reticulum to the Golgi apparatus.
Rab6	Controls inter Golgi traffic.
Rab8	Controls transport from the Golgi apparatus to the plasma membrane.
Rab4, Rab5, Rab9	Regulate endocytosis.
Rab7	Specialized for recycling of down-modulated membrane receptors.
RAB7A 3q21.3 RAB7B 1q32	Specific sub-types of Rab7

From NCBI we have[45][5]:

RAB family members are small, RAS-related GTP-binding proteins that are important regulators of vesicular transport. Each RAB protein targets multiple proteins that act in exocytic / endocytic pathways. This gene encodes a RAB family member that regulates vesicle traffic in the late endosomes and also from late endosomes to lysosomes. This encoded protein is also involved in the cellular vacuolation of the VacA cytotoxin of Helicobacter pylori. Mutations at highly conserved amino acid residues in this gene have caused some forms of Charcot-Marie-Tooth (CMT) type 2 neuropathies.

As we had discussed above the Rab 5 and 7 facilitate the endocytic paths for bringing in materials from without the cell. Thus they are simply transport facilitators. It is alleged that they can be easily targeted for suppression but then again they appear to be active elements in many cells and the blockage of them in a systemic manner may potentially have significant negative effects.

Let us go back to a statement made by the authors:

Importantly, RAB7 levels and function were independent of MITF, the best-characterized melanocyte lineage-specific transcription factor. Instead, we describe the neuroectodermal master modulator SOX10 and the oncogene MYC as RAB7 regulators. These results reveal a unique wiring of the lysosomal pathway that melanomas exploit to foster tumor progression.

MITF has been examined before in the case of melanoma. MYC and SOX10 are transcription factors and MYC is a well-known oncogene. How they then regulate RAB7 is a key question. Are they transcription factors that up-regulate the gene? If so, then what has activated MYC and is this the better target. Is RAB7 then just an artifact of such up-regulation. The same can be asked about SOX10.

[45][5] http://www.ncbi.nlm.nih.gov/gene/7879 and http://www.ncbi.nlm.nih.gov/gene/338382

As regards to cancers, Rab7 has been studied extensively. Zhang et al have presented results where they state:

Aberrant endocytosis and altered lysosomal function result in defective growth-factor transport and unbalanced levels of surface proteins, such as integrins and E-cadherin, leading to tumorigenesis and cancer metastasis. Rab GTPases, as master regulators in membrane traffic, are proved to be involved in cancer development. Rab25 is a well-established tumorigenesis associated Rab and is highly homologous to Rab11, and endogenously overexpressed in most ovarian and breast cancer samples in a constitutively active form, which is unique among Rab proteins. ...provided data indicating that overexpression of Rab25 promotes cell transformation, inhibits apoptosis and induces tumour progression, probably through the PI3K/AKT signalling pathway. Rab25 may also be related to other cancer such as OC/PPC (ovarian/primary peritoneal serous carcinoma) and prostate cancer.

Zhang et al continue as follows:

The results …showed that thyroid hormone production was regulated by Rab5a and Rab7. cAMP stimulation elevated the expression of Rab5a and Rab7 in adenomas, linking Rab7 to the formation of benign thyroid autonomous adenomas …also found Rab7 is overexpressed in DMPM (diffuse peritoneal malignant mesothelioma).

In addition, v-Src induces activation of Rab7, which may be related to epithelial-to-mesenchymal transition during tumour progression … indicate that Rab7 is involved in a cell survival pathway. Upon growth-factor depletion, Rab7 down-regulates surface nutrient transporters through endocytic degradation, preventing growth-factor-independent survival, but inhibition of Rab7 sustains surface nutrient transporters, thus promoting long-term cell survival, which is dependent on the AKT survival signalling pathway. Furthermore, … inhibition of Rab7 co-operated with the adenoviral E1A protein to promote transformation of p53−/− MEFs (mouse embryonic fibroblasts), thus Rab7 was proposed to act as a potential tumour suppressor.

however, there is insufficient evidence to conclude that Rab7 functions as a tumour suppressor. As mentioned above, Rab7 is actually overexpressed in some cancer cells or tissues, as described previously, and the transformation effects of dominant-negative Rab7 required the crucial help of the E1A protein and the absence of p53 … and these studies were carried out under nutrient starvation condition which may differ slightly from the environmental conditions for tumorigenesis that are usually rich in growth factors.

…another view on the function of Rab7 in apoptosis. Inhibiting the upstream regulator RabGGT prominently induces apoptosis of germ cells in Caenorhabditis elegans and mammalian cancer cells. … examined the effects of knockdown of Rab5, Rab7 and components of the HOPS complex by RNA interference in C. elegans, and found that knockdown of both Rab proteins promoted germ cells apoptosis…

Taken together, the underlying mechanism for cancer, cell survival and apoptosis regulated by Rab7 is still not yet understood. Rab7 is also emerging as a regulator for the autophagic

pathway, another mechanism for cell death and survival, which is related to many diseases, such as cancer and heart failure.

The autophagic process is initiated by engulfment of cytoplasmic materials into a unique membrane (phagophore) to form an autophagosome; the autophagosome then undergoes maturation through fusion with endosomal vesicles and lysosomes to form a lysoautophagosome, in which materials are degraded to provide nutrients and energy for cell survival under nutrient depletion.

It is thus fair to say that Rab7 functioning is still a work in progress.

Now it is worth a brief discussion of MITF which has been noted as an element in melanoma metastasis. As noted by Carreira et al[46[6]]:

It is widely held that cells with metastatic properties such as invasiveness and expression of matrix metalloproteinases arise through the stepwise accumulation of genetic lesions arising from genetic instability and "clonal evolution."

By contrast, we show here that in melanomas invasiveness can be regulated epigenetically by the microphthalmia-associated transcription factor, Mitf, via regulation of the DIAPH1 gene encoding the diaphanous-related formin Dia1 that promotes actin polymerization and coordinates the actin cytoskeleton and microtubule networks at the cell periphery.

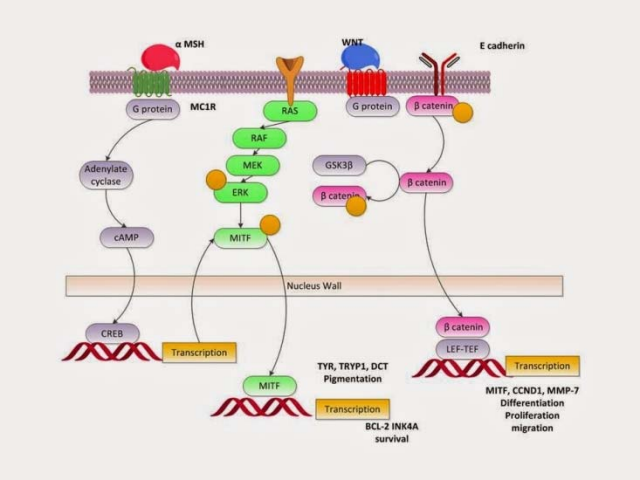
Low Mitf levels lead to down-regulation of Dia1, reorganization of the actin cytoskeleton, and increased ROCK-dependent invasiveness, whereas increased Mitf expression leads to decreased invasiveness.

Significantly the regulation of Dia1 by Mitf also controls $p27_{Kip1}$-degradation such that reduced Mitf levels lead to a $p27_{Kip1}$-dependent G1 arrest. Thus Mitf, via regulation of Dia1, can both inhibit invasiveness and promote proliferation.

The results imply variations in the repertoire of environmental cues that determine Mitf activity will dictate the differentiation, proliferative, and invasive/migratory potential of melanoma cells through a dynamic epigenetic mechanism.

Note that the discussion above shows that overexpression of MITF leads to less invasiveness. We show the details of the pathway dynamics below.

[46[6]] Carreira, S., et al, Mitf regulation of Dia1 controls melanoma proliferation and invasiveness, Genes Dev. 2006 20: 3426-3439.



Thus the MITF function, in their view, is critical. The recent work demonstrates that we can through an understanding of the pathways then target specific pathway control proteins by understanding their structure. We can already control B RAF in certain circumstances by targeting its specificity and that controlling the path but allowing MITF control in a broad sense may actually be much more powerful if the results hold for clinical applications.

The ability to find, characterize, and design binding site specific blocking agents is an essential step in a broader control of multiple cancers. From Eichoff we have:

In various cell types the MITF gene is transcribed from different promoters to generate cell type-specific isoforms. In the melanocytic-lineage, Wnt signaling is required for expression of the M-Mitf isoform essential for melanocyte development. M-Mitf has a role in the differentiation of neural crest cells to melanoblasts and melanocytes, as well as in their survival and maintenance, and is identified as the master regulator of melanocyte development . M-Mitf regulates the expression of melanocyte lineage-specific pigment-producing factors such as DCT and tyrosinase (TYR). Both the proliferation of melanocytes and M-Mitf expression and melanocyte proliferation is Wnt signal driven and inhibited by the Wnt signal inhibitor dickkopf-related protein 1 (Dkk1). Dkk1 antagonises Wnt signaling by binding to the Wnt receptor complex and inducing its internalisation. On palmoplantar skin, fibroblast release of Dkk1 is an important regulator of the hypopigmentation which is characteristic of these tissues.

The importance of Wnt signalling is also a critical factor here. We have examined this in detail elsewhere.

MYC is a well know transcription factor whose effects are often strongly seen in many cancers. It is an oncogene. As Nillson and Cleveland note regarding Myc:

At first glance, the selection for Myc activation in cancer seemed obvious. First, it was quickly established that enforced Myc expression was sufficient to provoke the entry and continuous, mitogen-independent, proliferation of cells and that it effectively blocked terminal cell differentiation.

Subsequently, Myc was shown to be necessary for traverse into S phase of the cell cycle, a finding recently underscored by the conditional knockout of c-Myc. Thus, not surprisingly, both c-Myc and N-Myc are essential for vertebrate development.

In addition, numerous studies showed that Myc activation was sufficient to provoke diverse cancers and, more recently, that Myc is continuously required to maintain the transformed state.

Finally, to round out the story was the revelation that c-Myc functioned as an angiogenic switch, and that its expression was in fact essential for proper and coordinate regulation of angiogenic and anti-angiogenic factors in cancer and development. This was satisfying – now we know why Myc activation was so pervasive in cancer.

As Yamamura et al state:

Rho GTPases are small G proteins that regulate various cellular processes, including cytoskeletal dynamics, migration, vesicle trafficking, cell proliferation, apoptosis and transcription. Rho GTPases, their regulators and their effectors have been suggested to control tumor formation and progression. RhoA has been found to control cancer metastasis and progression. Recently, the c-Myc–Skp2–Miz1 complex was shown to activate the RhoA gene.

The Ras superfamily incorporates the Ras, Rho, Rab Art and Ran families[47][7]. Now Rab7 is in the Rho GTPase class it may be considered controlled via Myc in a similar manner and mentioned above.

As stated in NCBI for Skp2[48][8]:

This gene encodes a member of the F-box protein family which is characterized by an approximately 40 amino acid motif, the F-box. The F-box proteins constitute one of the four subunits of ubiquitin protein ligase complex called SCFs (SKP1-cullin-F-box), which function in phosphorylation-dependent ubiquitination. The F-box proteins are divided into 3 classes: Fbws containing WD-40 domains, Fbls containing leucine-rich repeats, and Fbxs containing either different protein-protein interaction modules or no recognizable motifs. The protein encoded by this gene belongs to the Fbls class; in addition to an F-box, this protein contains 10 tandem leucine-rich repeats.

This protein is an essential element of the cyclin A-CDK2 S-phase kinase. It specifically recognizes phosphorylated cyclin-dependent kinase inhibitor 1B (CDKN1B, also referred to as p27 or KIP1) predominantly in S phase and interacts with S-phase kinase-associated protein 1 (SKP1 or p19).

[47][7] See Marks et al p 354.

[48][8] http://www.ncbi.nlm.nih.gov/gene/6502

In addition, this gene is established as a protooncogene causally involved in the pathogenesis of lymphomas. Alternative splicing of this gene generates three transcript variants encoding different isoforms.

And similarly for Miz1[49][9]:

This gene encodes a member of the protein inhibitor of activated STAT (PIAS) family. PIAS proteins function as SUMO E3 ligases and play important roles in many cellular processes by mediating the sumoylation of target proteins. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene.

Isoforms of the encoded protein enhance the sumoylation of specific target proteins including the p53 tumor suppressor protein, c-Jun, and the androgen receptor. A pseudogene of this gene is located on the short arm of chromosome 4. The symbol MIZ1 has also been associated with ZBTB17 which is a different gene located on chromosome 1.

Also note that Miz1 is also called PIAS2 protein inhibitor of activated STAT, 2.

As Qu et al state:

In addition to the PI3K/Akt pathway, c-Myc also plays a role during TGF-b-induced EMT. It has been demonstrated that high TGF-b levels are often associated with melanoma progression, and so does the Akt1, c-Myc, and SKP2 (S-phase kinase-associated protein 2) levels. However, it is not clear how these signals are interacted and integrated in melanoma metastasis.

The above observation specifically details c-Myc and Skp2 but also indicates the lack of specificity and clarity as to the roles of each, no less the specifics on the role of these in Rab7. Likewise Qu et al continue:

SKP2 is the substrate recognition subunit of SCF (SKP1- CUL1-F-box protein) ubiquitin ligase complex. Aberrant SKP2 expression plays an active role in tumorigenesis owing to its central role in degradation of a number of cyclin-dependent kinase inhibitors including p27kip1, p21cip1, and p57. SKP2 was overexpressed in melanoma and its levels were correlated with metastasis. SKP2 regulates c-Myc protein stability and activity at both transcriptional and post-translational levels. Whether and how SKP2 is regulated during TGF-b-induced EMT remains to be elucidated.

Again we have a lingering level of uncertainty.

SOX10 is a transcription factor and has been identified with melanoma by many authors[50][10]. They are characterized by the Sry-box binding site. Sry-box is a variant of the HMG domain.

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[49][9] http://www.ncbi.nlm.nih.gov/gene/9063

[50][10] See Wegner pp 71-80 in Hearing and Leong.

Sox10 has been identified with the performance of many functions. It is involved in maintaining pluripotency of neural crest cells, melanocytes are derived from neural crests, it remotes survival and proliferation, and in terminal differentiation. It requires other cell pathways to affect its results. In mice it has been shown that deletion of Sox10 results in the elimination of all melanocytes.

Sox10 also works directly with MITF and it is through this joint action that it supports proliferation and survival. Sox10 influences the M promoter as well as MITF.Sox10 expression precedes MITF expression.

From Eichoff we have:

In adult human skin, stem cells are found in the hair follicle where lineage-specific differentiation of neural crest cells to melanoblasts and melanocytes occurs in response to changes in signaling. Among the genes involved several are transcription factors that include the Wnt pathway target gene Microphthalmia-associated transcription factor (MITF), paired domain-and homeodomain-containing transcription factor 3 (PAX3), and Sry-related transcription factor 10 (SOX10).

Importantly, it has been shown that the loss of any of these factors results in the failure of melanoblasts to develop (White & Zon, 2008). The final fate determination for melanocytes occurs when migrating melanoblasts come into contact with epidermal keratinocytes, which regulate their rate of replication to establish a stable keratinocyte/melanocyte ratio (Fukunaga-Kalabis et al, 2006; Valyi-Nagy et al, 1993).

Differentiated human melanocytes remain strictly localized at the basement membrane and cannot survive within the upper epidermal layers unless transformed into nevi or melanoma cells.

The observations of melanocyte survival in the basement membrane are key. For example in melanoma in situ, as compared to superficial spreading melanoma, the melanocyte breaks loose from the basement membrane and wanders upward. The presence of melanocytes in the upper layers is often pathognomonic for MIS. However as we have discussed elsewhere the movement is also driven be E cadherin changes and β catenin expression.

From Shakhova et al we have:

Giant congenital naevi are pigmented childhood lesions that frequently lead to melanoma, the most aggressive skin cancer. The mechanisms underlying this malignancy are largely unknown, and there are no effective therapies. Here we describe a mouse model for giant congenital naevi and show that naevi and melanoma prominently express Sox10, a transcription factor crucial for the formation of melanocytes from the neural crest. Strikingly, Sox10 haploinsufficiency counteracts NrasQ61K-driven congenital naevus and melanoma formation without affecting the physiological functions of neural crest derivatives in the skin.

Moreover, Sox10 is also crucial for the maintenance of neoplastic cells in vivo. In human patients, virtually all congenital naevi and melanomas are SOX10 positive. Furthermore, SOX10 silencing in human melanoma cells suppresses neural crest stem cell properties, counteracts proliferation and cell survival, and completely abolishes in vivo tumour formation. Thus, SOX10 represents a promising target for the treatment of congenital naevi and melanoma in human patients.

The above observation regarding Sox10 for survival begs the question; why? Silencing Sox10 may silence the melanocyte.

As Hoek et al state:

Upregulation of SOX10 by Mitf-transfection is an interesting finding as SOX10 has long been held to be a regulator of MITF …indicating the possibility that these transcription factors regulate each other's expression. It may be that the myelinating cell genes mentioned here are detected because they are directly regulated by SOX10 … while its gene is being regulated by MITF, rather than being directly regulated by MITF itself. This, nevertheless, suggests that MITF may have a role alongside SOX10 in regulating the processes of myelination.

The role of MITF and SOX10 are known to be aligned, and one preceding the other. Yet the complete details of the interactions appears to be yet determined.

As Saskia et al state[51][11]:

The transcription factor SOX10 (SRY (sex determining region Y)-box 10) has a key role in the embryonic development of melanocytes. Recently, it has been suggested that SOX10 is highly relevant for melanoma development and survival. However, the distinct functions and downstream targets of SOX10 in melanoma remain widely unknown. In this study, we inhibited SOX10 via RNA interference in different human melanoma cell lines and found a significantly reduced invasion capacity in vitro and in the chick embryo model.

This recent paper still reflects the uncertainty for the downstream control of SOX10. Just what it does as regards to RAB7 is yet to be determined.

At later time points, SOX10 inhibition reduced proliferation and induced cell death. We identified melanoma inhibitory activity (MIA) as a direct target gene of SOX10, which is an essential protein for melanoma cell migration and invasion. Expression levels of SOX10 and MIA strictly correlated in melanoma cell lines, and SOX10 inhibition reduced MIA expression and promoter activity. Direct binding of SOX10 to the MIA promoter was demonstrated by electrophoretic mobility shift assay and chromatin immunoprecipitation.

Ectopic expression of MIA in SOX10-inhibited melanoma cells restored the invasion capacity, supporting the hypothesis that MIA is responsible for SOX10-mediated melanoma cell invasion.

[51][11] http://www.nature.com/jid/journal/vaop/ncurrent/full/jid2014128a.html

Our data provide evidence for a critical role of SOX10 in melanoma cell invasion through the regulation of MIA and highlight its role as a therapeutic target in melanoma.

The last observation was also present in the comments by Wegner. The interrelationship between SOX10 and MIT and MITF and MIA are somewhat understood. The details again need clarification.

This analysis of the Rab7 protein as a driver of melanoma metastatic dissemination appears to be predicated on the observation that endosomes can transport into the cell items which foster growth and proliferation. Further it is alleged that Sox10 and Myc are regulators of Rab7, and unlike their normal roles as oncogene transcription factors that in this case they appear to up-regulate Rab7 which in turn provides the cell with added nutrients that enable growth and proliferation. We have tried to piece together the details of this assertion and there appears to be multiple missing steps.

1. Pathway Control by Myc and Sox10: What are the pathway control elements related to the RAB7 controls? We have a general understanding but many details are yet to be fully elucidated.

2. Actions precipitated by Rab7 that promote Growth and Proliferation: What does RAB7 do to drive proliferation? Admittedly it can bring in nutrients but specifically what and why?

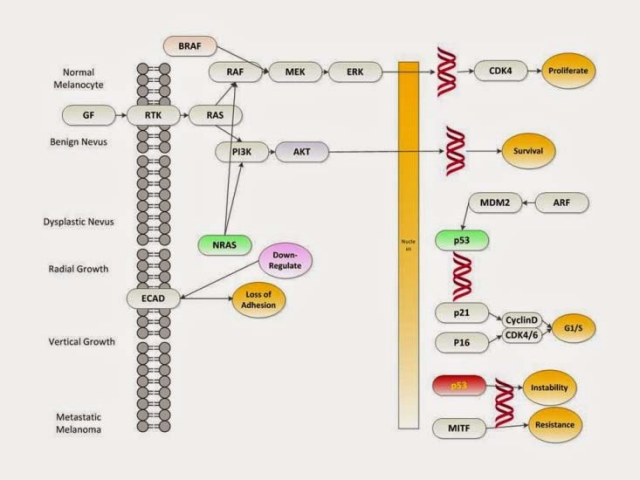
3. Mechanisms for the Control of Rab7: Just how do various sets of enzymes/proteins control RAB7? Is it just transcription control, or are there epigenetic factors as well?

4. Control of Myc and Sox10 versus Control of Rab7: What controls the two transcription factors which in turn activate RAB7?

5. It is known that there exists a melanoma stem cell. What is the relationship between the up-regulated RAB7 and the stem cell characteristics. In Girouard and Murphy we have an excellent overview of the melanoma stem cell. Thus if we accept the stem cell model is the RAB behavior an identifies of such a cell or is it a just an artifact?

Now from KEGG we have the following generic progression of melanoma and identified gene and pathway changes[52][12]:

[52][12] http://www.genome.jp/kegg-bin/show_pathway?hsa05218



Note that we do not see the targets discussed herein. In fact there are many alternative targets that have been discussed at length elsewhere.

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White Papers:

The following are various White Papers we have authored which are referred to herein.

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No. 114 NOTCH, miR-146a and Melanoma, June 2014
No. 112 Prostate Cancer: miR-34, p53, MET and Methylation, May 2014
No. 111 CRISPR and Cancer, April 2014
No. 110 ERG and Prostate Cancer, January 2014
No. 108 Cancer Cell Dynamics, January 2014.
No. 107 Prostate Cancer Genetic Metrics, January 2014
No. 106 Divergent Transcription, December 2013
No. 104 Prostate Cancer and Blood Borne Markers, December 2013
No. 103 Prostate Cancer Indolence, December 2013
No. 102 MDS and Methylation, August 2013
No. 101 Exosomes and Cancer, August 2013
No. 100 lncRNA and Prostate Cancer, August 2013
No. 99 SNPs and Cancer Prognostics, July 2013
No. 98 CCP and Prostate Cancer, July 2013
No. 97 ATF2 and Melanoma, July 2013
No. 96 PD-1 and Melanoma Therapeutics, June 2013)

No. 95 MER Tyrosine Kinase Receptors and Inhibition, June 2013
No. 94 Melanoma Therapeutics, May 2013
No. 93 Cancer Cell Dynamics April 2013
No. 91 Methylation and Cancer, March 2013
No. 90 Telomeres and Melanoma, February 2013
No. 89 miRNA and Melanoma, January 2013
No. 88 Extracellular Matrix vs. Intracellular Pathways
No. 87 Prostate Cancer Prognostic Markers
No. 86 Cancer Models for Understanding, Prediction, and Control
No. 85 Prostate Cancer Stem Cells
No. 84 Epistemology of Cancer Genomics
No. 83 Prostatic Intraepithelial Neoplasia
No 82 Prostate Cancer: Metastatic Pathway Identification
No 81 Backscatter Radiation and Cancer, November 2010
No 80 PSA Evaluation Methodologies, November 2010
No 79 The PSA Controversy, November 2010.

Labels: Cancer

TUESDAY, JULY 1, 2014

THE JOY OF WORKING IN THE SUMMER

There are some who take the summer as a season for rest and relaxation. For me, the past 30 years has meant getting up at 5 AM and walking the fields seeing what is new and then deciding what to cross. The above was a pleasant surprise, a cross from 2010 which I knew had some potential but not quite this much.

It is a 48" tall plant with 4 to 6 branches and 6 buds per branch with 6" flowers. It manages to just shout out from the Garden that it is there. It seems to be a strong grower and I found a

chipmunk climbing the scapes this AM.

Thus for those Academics who seek solace in the summer there are those of us who see it as the most productive season, albeit blocking ourselves from the sun to keep the skin from too much damage.

It looks like we are beginning to see Summer, yet about two weeks later than usual.


Labels: Daylilies

MONDAY, JUNE 30, 2014

MCLUHAN AND FACEBOOK

There is an arrogance of youth that from time to time seems to get out of hand. We all have suffered from it and we will most likely will. Sometimes that arrogance is well placed, such as movements against discrimination or wars which make no sense. At other times the arrogance is less well placed. One of my favorite gripes regards the peer grading systems which are less peer grading than exposes of that very youthful arrogance gone wild. In many of the younger generation there was a feeling that any opinion, especially that of the youth, is as valid as any others. If one feels they are right then that is all that is necessary. Then they apply that in a manner which drives facts and any semblance of truth into early graves.

Now arises a terrifying experiments. As the Guardian reports:

But now Facebook, the world's biggest social networking site, is facing a storm of protest after it revealed it had discovered how to make users feel happier or sadder with a few computer key strokes.
It has published details of a vast experiment in which it manipulated information posted on 689,000 users' home pages and found it could make people feel more positive or negative through a process of "emotional contagion". In a study with academics from Cornell and the University of California, Facebook filtered users' news feeds – the flow of comments, videos, pictures and web links posted by other people in their social network. One test reduced users' exposure to their friends' "positive emotional content", resulting in fewer positive posts of their own. Another test reduced exposure to "negative emotional content" and the opposite happened. The study concluded: "Emotions expressed by friends, via online social networks, influence our own moods, constituting, to our knowledge, the first experimental evidence for massive-scale emotional contagion via social networks."

That is the researchers managed to manage what people saw and tuned it based on their known profiles. As is often the case I am reminded of the McLuhan quote from Drucker:

"Did I hear you right," asked one of the professors in the audience, "that you think that printing influenced the courses that the university taught and the role of university all together." "No sir," said McLuhan, "it did not influence; printing determined both, indeed printing determined what henceforth was going to be considered knowledge."

That is the medium, in this case a manipulated Facebook, becomes "knowledge" and "truth". Namely we see that any "social media" site can become a truth bender site. One does not have to go somewhere, one gets the distorted truth created for you by the benevolent entity who you somehow believe is altruistic. In fact they are "truth benders".

The Guardian goes on further:

Researchers have roundly condemned Facebook's experiment in which it manipulated nearly 700,000 users' news feeds to see whether it would affect their emotions, saying it breaches ethical guidelines for "informed consent". James Grimmelmann, professor of law at the University of Maryland, points in an extensive blog post that "Facebook didn't give users informed consent" to allow them to decide whether to take part in the study, under US human subjects research. "The study harmed participants," because it changed their mood, Grimmelmann comments, adding "This is bad, even for Facebook." ...But the study has come in for severe criticism because unlike the advertising that Facebook shows - which arguably aims to alter peoples' behaviour by making them buy products or services from those advertisers - the changes to the news feeds were made without users' knowledge or explicit consent.

Namely experiments like this in the social sciences need informed consent. In this case they just manipulate half a million people. One can just imaging the long term consequences. How this for a "peer review". The interesting arrogance of youth is that these folks even published their efforts. They were accompanied by academics who frankly should have known better, but one guesses did not.

Labels: Media

SATURDAY, JUNE 28, 2014

A HISTORY LESSON: 100 YEARS AGO

It was 100 years ago today that the Archduke Ferdinand was assassinated and WW I began. It was the overall lack of world leadership and an amalgam of loose terrorists that led a bumbling set of Heads of State to aim the guns and pull the triggers. Perhaps a bit of stepping back and thinking wisely and dealing with problems would be useful.

For this summer does not bode well either.

Labels: Commentary

FRIDAY, JUNE 27, 2014

FREE TO CHOOSE: JUST WHAT?

HHS announced that it will automatically re-enroll those who signed onto their ACA plans via they FED's web site again in 2015 no matter what they decide or what their employment state may be.

They state:

Today, the U.S. Department of Health and Human Services (HHS) expects to announce its plans for helping existing Marketplace consumers get auto-enrolled for next year. These plans would give existing consumers a simple way to remain in the same plan next year unless they want to shop for another plan and choose to make changes. "As we plan for open enrollment in year two and continue to build a sustainable long-term system, we are committed to simplifying the experience for consumers by allowing auto-enrollment," said Sylvia Mathews Burwell, Secretary of HHS. "We are working to streamline the process for consumers wishing to remain in their current plan."

In today's health insurance market, the vast majority of consumers are generally auto-enrolled in their plan year after year. For example, about 88 percent of employees receiving coverage through the Federal Employee Health Benefits Program don't choose to change plans and are instead auto-enrolled in their current plan with updated premiums and benefits. These guidelines aim to bring the Marketplace in line with this practice in the existing insurance market. As with existing open enrollment periods for employer-based coverage, consumers are strongly encouraged to use the open enrollment period as an opportunity to update their information and reevaluate their health coverage needs for the coming year.

Consumers always have the ability to return to the system for shopping, changing plans, or reporting life changes, or a change to their annual income to ensure they are getting the lowest cost possible on their monthly premium. And, to help ensure the program integrity of how taxpayer dollars are spent, while also protecting consumers from having to pay back tax credits they are no longer eligible for, under the approach that the Federally-facilitated Marketplace would use in 2015, the small number of consumers whose updated income information suggests they no longer qualify for a tax credit next year, will still be auto-enrolled in their current plan, but without a tax credit. State-based Marketplaces may take this approach as well, or propose an alternative.

Under the plans that HHS expects to announce today, consumers in the Federally-facilitated Marketplace will receive notices from the Marketplace informing them how to update their information to get a tailored and updated tax credit that keeps up with any income changes. Consumers will receive information from their health insurance company about the premium and the amount they are eligible to save on their monthly bill close to the beginning of the open enrollment period, when they will be able to take action should they choose to do so.

So much for freedom of choice. Next they put the VA after you!

Labels: Health Care

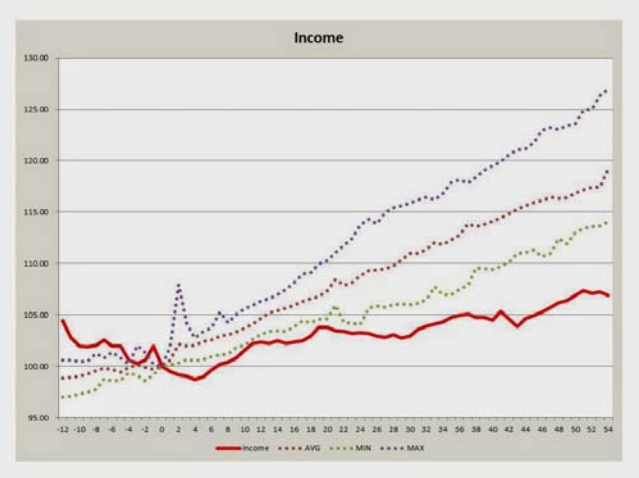
WEDNESDAY, JUNE 25, 2014

RECESSION STATS: JUNE 2014

The economy is doing quite poorly. Recovery is still a way in the distance. We examine the St Louis Fed's stats again as we have done since the beginning.

Let us begin with some basics:

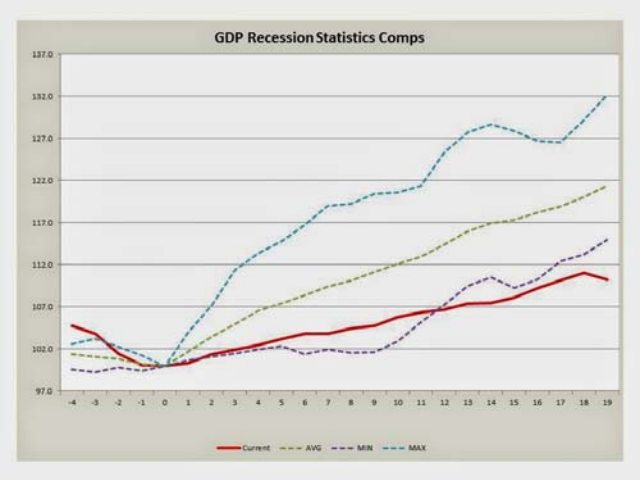
Industrial Production is not bad. That is not the problem.



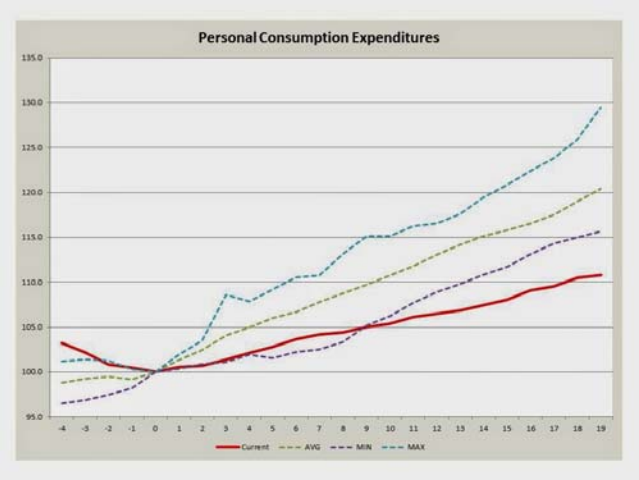
Income is dropping. That is a serious problem that few have addressed.

Ironically Retail Sales is keeping steady.

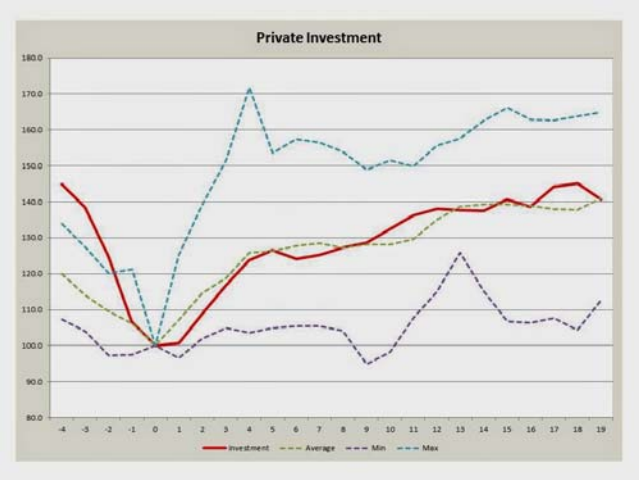
Employment is stagnant. It is hugging the bottom and there is no end in sight. The government is doing all to keep it that way.



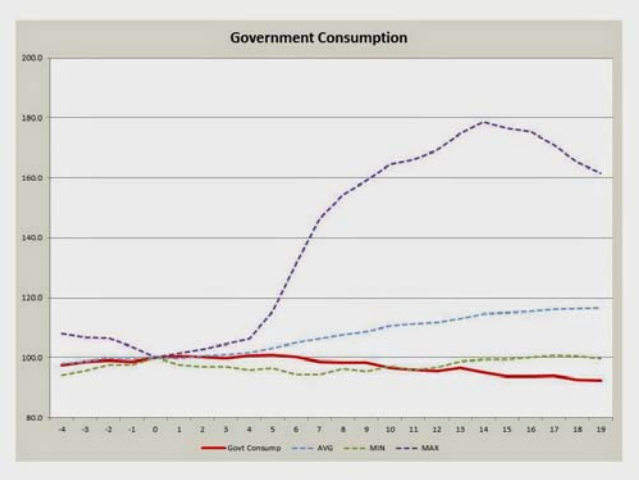
GDP on the other hand is in the tank and getting worse. Why? Let us examine the components.



Personal Consumption is increasing but slowly. Note the statement that the cold weather dampened the GDP is out right wrong. It should appear above BUT it does NOT!



Investment dropped. Why? Good question.



Government spending is down and this is a factor!

Also Exports dropped adding t the drop in GDP

Imports remain flat.

Thus we have a drop in Government Spending and in Investment.

Labels: Economy

ANOTHER BAD IDEA

There is a move afoot to have the Federal Government take more control of our Universities. Recently one Senator from Illinois bemoaned a case of some student who attended a Community College and then went to some for profit school to study Design. Somehow in the remaining two years she amassed some $130,000 in loan debt and then could not find a job. Frankly she could have known aforehand that jibs in that field were few and far between. Furthermore she should have understood that $130,000 in loans and in that field were incompatible. So what does the Senator do? Blames the school. His solution, Federal Government controls.

What duty does the student have to make realistic decisions? The student made a bad choice, now she must live with it. Perhaps the loan should be predicated on what the student majors in. English and Fine Arts majors should not be eligible, along with History and Philosophy majors.

Engineering perhaps should get the most. I will leave Finance majors for a later discussion.

Now the NY Times chimes in as follows:

The study says the federal government should set minimum performance standards for all colleges receiving federal aid: at least 17 percent enrollment of poor and working-class students; a six-year graduation rate of 15 percent; and three-year student loan default rate of no more than 28 percent. Colleges that do not meet these standards could face escalating sanctions — including the loss of federal grants and charitable interest deductions for donors. Dropout factories and diploma mills that fail to improve would face the ultimate penalty: loss of eligibility for federal aid, which would have the effect of shutting them down. The performance standards would be updated periodically as a way of steadily raising the quality of schools rated at the very bottom. The report outlines useful steps Congress can pursue should it bestir itself to listen to the president and allocate federal aid along the lines he has suggested.

This report is from Education Trust, a lobby group in DC. They published a report which they allege details the need for Government control. Their agenda appears to seek more Government control over higher education. Unfortunately as we see with the Public School system it almost always results in increased incompetence and politically correct control. One need look no further than the recent attempts in New York City to eliminate the elite schools such as High School of Science, which sent thousands of brilliant students to build our country. Now they want such high performance schools eliminated.

Imagine MIT or Harvard being controlled by some GS 10 whose former job was a VA scheduler now being responsible for over sight on MIT admissions. That could be our future.

Labels: Academy

TUESDAY, JUNE 24, 2014

RECOGNITION OF TECHNICAL INNOVATION

In a recent piece in Project Syndicate, Sachs remarks:

..."decarbonizing" the energy system is technologically complicated. America's real problem is not competition from China; it's the complexity of shifting a $17.5 trillion economy from fossil fuels to low-carbon alternatives. China's problem is not the US, but how to wean the world's largest, or second largest economy (depending on which data are used) off its deeply entrenched dependence on coal. These are mainly engineering problems, not negotiating problems.

Sachs then goes on to details some of the technological solution approaches. Yes, this is a technology problem, and technology can solve it. It is not clear that a Manhattan or Space Project is the approach. But the thread is correct. This is starkly different from the classic all political tax approach presented by the former Government official we discussed recently.

Labels: Global Warming

VERY CUTE!

I just ran across Open Garden and their offerings. Simply what they appear to do is as follows:

1. Each mobile device has three wireless access modes; a carrier, a wifi, and a bluetooth.

2. The carrier interface is one to one with the carriers base station. The carrier then connects to the Internet backbone.

3. However the wifi and bluetooth can connect to any other wifi or blutooth. Thus unlike the carrier mode one can create ad hoc mesh networks of combined wifi or bluetooth. These are off the Net networks, they are ad hoc and come and go as users come and go.

4. The range of bluetooth is short but wifi may be hundreds of meters. Thus if we have a town of say 10,000 users and 10 sq km, then we have more than adequate density if everyone has the software on their mobile devices.

5. If a critical number load the software and keep devices on then one has a local mesh network that is NOT an Internet connection. It is a Meraki network without a carrier.

This is being used in Iraq by many who want to avoid being intercepted. The BBC reports:

About 40,000 users downloaded Firechat last week, compared with 6,600 over the previous few months, the company says. The internet has been blocked in some Iraqi provinces, as authorities seek to prevent militants from communicating. Access to social media sites has also been severely restricted. Firechat allows users to take part in group chats with between two and 10,000 people, without the need for an internet connection. Using a technology known as "mesh networking", messages can be sent to people within the immediate vicinity, as long as they too have the app installed. However, discussions are not private, and can be seen by anyone in the area. The software is available for both Android and iOS devices, and has a range of roughly 70m (230ft). However, if enough people use the app, messages can travel over far greater distances, hopping between intermediary devices in a chain-like effect.

This is an interesting turn and potentially has substantial disintermediation applications! The applications is worth following.


Labels: Wireless

SUNDAY, JUNE 22, 2014

THE CARBON TAX

The people who brought us the most recent depression are suggesting another, the carbon tax. In the NY Times a former Government official makes the following statements:

I'm a businessman, not a climatologist. But I've spent a considerable amount of time with

climate scientists and economists who have devoted their careers to this issue. There is virtually no debate among them that the planet is warming and that the burning of fossil fuels is largely responsible....

Now I have not argued that we are warming. I have been tracking this with sentinel species for over 25 years. There is warming and it is significant. However it is not clear what the results will be. Namely I can see earlier blooms and I can see movement of plant species northward. Will the sea water really rise that high, well they managed in Holland, and after all New York was called New Amsterdam, and in fact the bottom half of Manhattan was underwater when my ancestors arrived in 1649. Thus the issue is not the fact of global warming but our ability to deal with the consequences.

He continues:

Some members of my political party worry that pricing carbon is a "big government" intervention. In fact, it will reduce the role of government, which, on our present course, increasingly will be called on to help communities and regions affected by climate-related disasters like floods, drought-related crop failures and extreme weather like tornadoes, hurricanes and other violent storms. We'll all be paying those costs. Not once, but many times over....

Unless I missed something a tax takes money from the people and gives it to the Government. Thus this tax he proposes takes money from those who could least afford to miss it and gives it to over paid useless Government employees to allocate as they wish. One suspects that the writer has not taken the New York subway with the masses for decades, and most likely his limo gets well less than 30 mpg. Also he could worry less about a carbon tax. The poor schlub in Queens sees the result as a regressive tax on him.

A tax on carbon emissions will unleash a wave of innovation to develop technologies, lower the costs of clean energy and create jobs as we and other nations develop new energy products and infrastructure. This would strengthen national security by reducing the world's dependence on governments like Russia and Iran.

This is one of the most illogical statements ever made. By taxing the masses then the Government decides on winners and losers regarding low carbon sources. Did we not just see that for the past six years. Was that a success? Entrepreneurs work despite the Government. They work in a Darwinian world, cruel and survival of the fittest reigns. The suggestion of this former banker and Government employee fails on all counts; realism, rationality, and reason. Pity.

Labels: Economy

WEDNESDAY, JUNE 18, 2014

PEER REVIEW, MOOCS AND TOTAL CHAOS

I am not a fan of peer review in MOOCs since it makes no sense. There are no peers as would say be the case in submitting to Science or Nature. It is assumed the Editor in each case selects a

true peer who has their own track record. Yet in a MOOC setting one gets a total and random collections of people who have generally no experience or knowledge of any depth in the subject. In addition, the cultural difference results in chaos.

But the real issue is what the so called peers see as Plagiarism. Here they walk a very fine line. It appears that the "peers" can assign a paper as plagiarized with no basis for saying so. There is no due process, there is no meeting your accuser. But there is a basis for defamation. Why the companies who allow this have not considered the legal consequences I cannot fathom. You have students from cultures where it is fine to defame others for their own achievements and practicing that randomly online and assuming there will be no consequences. That is unrealistic.

Plagiarism is a bit difficult to prove, unless one finds the source and then demonstrates the exact extraction without referring to the source. We try somewhat diligently herein to be certain at all times to delineate fair use of segments with a reference and where we seek comments. That generally is acceptable. On the other hand accusing someone of plagiarism without basis is de facto defamation.

Why MOOCs allow this practice is beyond me. It may come back to haunt them.In fact it is my opinion that it facilitates a potentially antisocial trend in a class of individuals and the result may be catastrophic.

MOOCs have a long way to go before they work. A small few, again I use Lander's course as the sine qua non example, but there have been frankly none since then. The potential is there but the anonymous discussions create cadres of the strangest types. They may be well worth a study.

Labels: MOOCs

WHAT IS ECONOMICS?

The question of the definition and scope of economics has been thrown back and forth for centuries. Clearly Economics is not a science as is Physics or Biology. Perhaps it is akin to Biology in the late 18th century, a set of descriptives of what may be out there but lacking a base of understanding without its DNA.

Skidelsky has written brilliantly over the years on Economics and its history so when he opines it is always worth considering. Skidelsky has recently written on Post Crash Economics and he says:

For starters, economics teaching and research is deeply embedded in an institutional structure that, as with any ideological movement, rewards orthodoxy and penalizes heresy. The great classics of economics, from Smith to Ricardo to Veblen, go untaught. Research funding is allocated on the basis of publication in academic journals that espouse the neoclassical perspective. Publication in such journals is also the basis of promotion. Moreover, it has become an article of faith that any move toward a more open or "pluralist" approach to economics portends regression to "pre-scientific" modes of thought, just as the results of the European Parliament election threaten to revive a more primitive mode of politics.

He continues:

For now, the best that curriculum reform can do is to remind students that economics is not a science like physics, and that it has a much richer history than is to be found in the standard textbooks. In his book Economics of Good and Evil, the Czech economist Tomáš Sedláček shows that what we call "economics" is only a formalized fragment of a much wider range of thinking about economic life, stretching from the Sumerian epic of Gilgamesh to the meta-mathematics of today.Indeed, mainstream economics is a pitifully thin distillation of historical wisdom on the topics that it addresses. It should be applied to whatever practical problems it can solve; but its tools and assumptions should always be in creative tension with other beliefs concerning human wellbeing and flourishing. What students are taught today certainly does not deserve its imperial status in social thought.

He agrees with the lack of scientific clarity. The mathematics all too often just creates shadows to hide behind. The discussion is best focused on what we want our society to hold and what to reject. Clearly the markets are not efficient, they hide information rather than display it. Manipulation is rampant in many ways, often small but profitable ways. Yet the issue is what do we want as a nation, as a people. Skidelsky presents an interesting opening.

Labels: Economics

US LOWEST IN HEALTH CARE AND UK AT THE TOP? SLANTED QUESTIONS AND MEASURES?

There is always some group trying to measure the US Health Care system to other countries, frequently for purely political purposes. A recent report by the Commonwealth Fund in my opinion is a recent thrust in that direction. It examines in its own world of metrics the US system to others and as one would expect it results in the US being last.

We have from the Guardian[53[1]]:

The NHS has been declared the world's best healthcare system by an international panel of experts who rated its care superior to countries which spend far more on health.

The same study also castigated healthcare provision in the US as the worst globally. Despite putting the most money into health, America denies care to many patients in need because they do not have health insurance and is also the poorest at saving the lives of people who fall ill, it found.

[53[1]] http://www.theguardian.com/society/2014/jun/17/nhs-health

The report has been produced by the Commonwealth Fund, a Washington-based foundation which is respected around the world for its analysis of the performance of different countries' health systems. It examined an array of evidence about performance in 11 countries, including detailed data from patients, doctors and the World Health Organisation.

"The United Kingdom ranks first overall, scoring highest on quality, access and efficiency," the fund's researchers conclude in their 30-page report. Their findings amount to a huge endorsement of the health service, especially as it spends the second-lowest amount on healthcare among the 11 – just £2,008 per head, less than half the £5,017 in the US. Only New Zealand, with £1,876, spent less.

The above uses some less that substantial metric for quality and also uses the costs metric. The conclusion is that it is less than half of the US. The NHS is hardly free of criticism. In fact it has been beaten up especially over the results of its often limited cancer care efforts.

Subsequently from the Guardian[54][2]:

A slow hand clap for Andy McGovern, a London hospital nurse who has proposed that the Royal College of Nursing supports a £10 charge to visit a GP. On its own terms, the proposal is an unacceptable assault on the very foundations of the NHS: that it is free at the point of use. But the suggestion is so menacing because of where it originates from. The many enemies of the NHS – who have to be diplomatic, knowing that the NHS "is the closest the English have to a religion", as Nigel Lawson once put it – will rejoice. "Aha!" they will think. "Now even the nurses are debating NHS charges, we have been given the political cover we need!"

That the NHS has just been declared the world's best healthcare system by the Washington-based Commonwealth Fund should be a matter of national pride. But the institution is in mortal danger. The free market crusaders who first took power in the late 1970s have long regarded NHS as an aberration. It is an irritating example of a service run on the basis of social need, rather than private profit – and, even worse, it is loved for it. As long as the NHS exists, it serves as a defiant reminder that there is an alternative to the neoliberal project.

Thus it appears as if there is a stirring in the NHS to enact a fee for service, albeit nominal. Yet from the Left in the UK that is opposed.

Let us briefly examine some of the measures used. From Commonwealth[55][3]:

Key findings related to the U.S. include:

[54][2] http://www.theguardian.com/commentisfree/2014/jun/18/10-charge-to-visit-gp-nhs

[55][3] http://www.commonwealthfund.org/publications/press-releases/2014/jun/us-health-system-ranks-last?omnicid=rsscmnw

Healthy lives: The U.S. does poorly, ranking last on infant mortality and on deaths that were potentially preventable with timely access to effective health care and second-to-last on healthy life expectancy at age 60.

What is a death preventable by timely access? Also what are the causes of infant mortality? The first is a measure based upon personal choice all too often. Take obesity. Namely in the US we have an expanding number of such cases and they are due to individual choice and not lack of care. US physicians are all too often fearful of being too emphatic with such patients and thus just over medicate. That increases the costs due to the medication, the follow on care and the sequelae.

Access to care: People in the U.S. have the hardest time affording the health care they need. The U.S. ranks last on every measure of cost-related access. More than one-third (37%) of U.S. adults reported forgoing a recommended test, treatment, or follow-up care because of cost.

This is a question of access due to cost. In the UK there is no such issue it is just getting the service in a timely manner. The cost to the patient directly is not present. Thus this question or measure begs the answer.

Health care quality: The U.S ranks in the middle. On two of four measures of quality—effective care and patient-centered care—the U.S. ranks near the top (3rd and 4th of 11 countries, respectively), but it does not perform as well providing safe or coordinated care.

Quality is elusive. We have discussed this at length. The statement that US care is not safe is somewhat without basis. The issue of coordinated care is another measure that begs the answer. Coordinated how? It was the head of Commonwealth that promulgated the Electronic Health Record system while in the Government. Was this promulgation a failure? Did the work he did fall on deaf ears despite the billions spent and mandated to be spent? Does this added costs element have no value?

Efficiency: The U.S ranks last, due to low marks on the time and dollars spent dealing with insurance administration, lack of communication among health care providers, and duplicative medical testing. Forty percent of U.S. adults who had visited an emergency room reported they could have been treated by a regular doctor, had one been available. This is more than double the rate of patients in the U.K. (16%).

How many times do they ask the same question? It is a simple technique to prove one's answer, via a tautology. The ER statement is a symptom of the people not the system. Spend some time in an ER. See the elderly who are sent back and forth because of the incompetence of many care facilities or the intent by the facility to increase their revenue. Look at the gun-shot victims, the overdoses, the assaults. Go to Mass Gen after a basketball game and see the drunks with various assault wounds. That does not reflect efficiency, it reflects a societal norm.

Equity: The U.S. ranks last. About four of 10 (39%) adults with below-average incomes in the U.S. reported a medical problem but did not visit a doctor in the past year because of costs, compared with less than one of 10 in the U.K., Sweden, Canada, and Norway. There were also

large discrepancies between the length of time U.S. adults waited for specialist, emergency, and after-hours care compared with higher-income adults.

This is a strange measure. It is a Piketty type measure, namely one where the measure is intended to provide the US with the lowest rank. Note how it is phrased, it is 39% of "below-average incomes", namely 39% of some other smaller percent, less that say 25%. That means say 16% as a guess. Well 16% is about 1 of 7 as compared to 1 in 10 for the others. The countries mentioned have a socialized medical system and that is what the report says is best. After all it posed the questions it appears to obtain that answer.

One should examine the Board of Commonwealth[56][4]. It is a mix but all with what appears to be a slanted mix. In my opinion one should give little if any weight to this report.

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http://www.theguardian.com/society/2014/jun/17/nhs-health

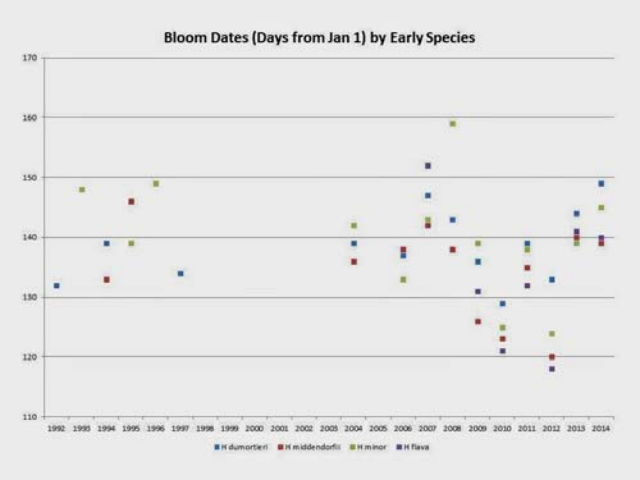
Labels: Health Care

SUNDAY, JUNE 8, 2014

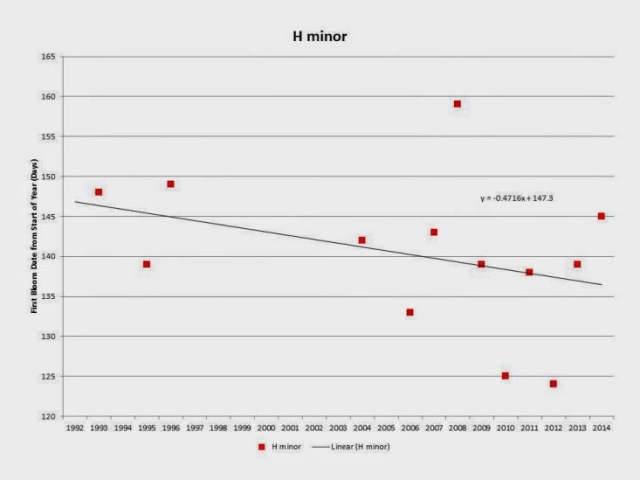
GLOBAL WARMING AND DAYLILIES

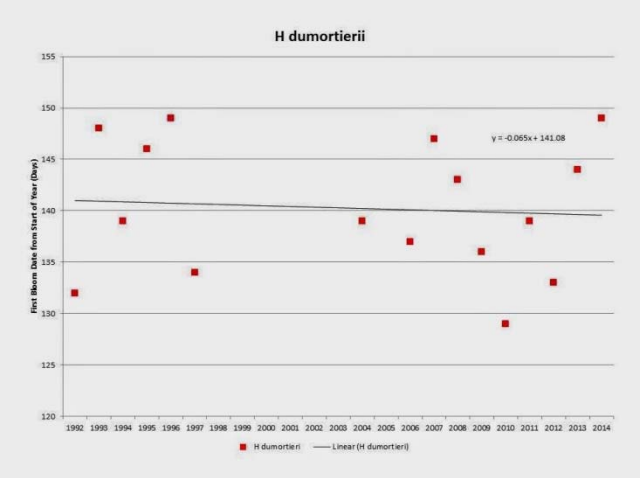
We have been measuring the date of first bloom, measured as days from the first of the year, for the past 25 years on Hemerocallis species. Four specific species are used; H minor, H middendorfii, H dumortieri, and H flava. The summary is below.

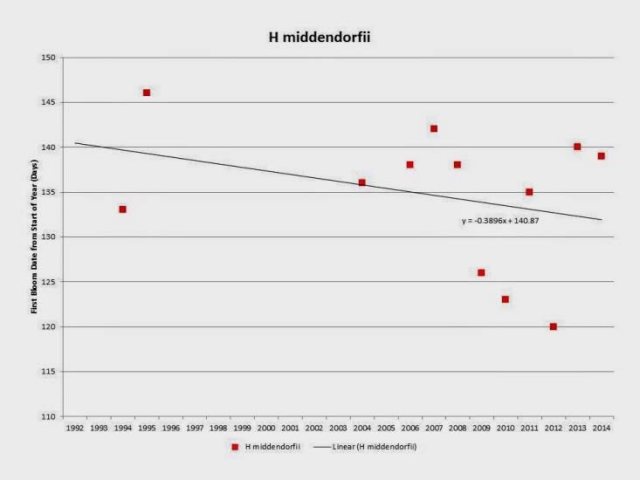
[56][4] http://www.commonwealthfund.org/about-us/board-of-directors

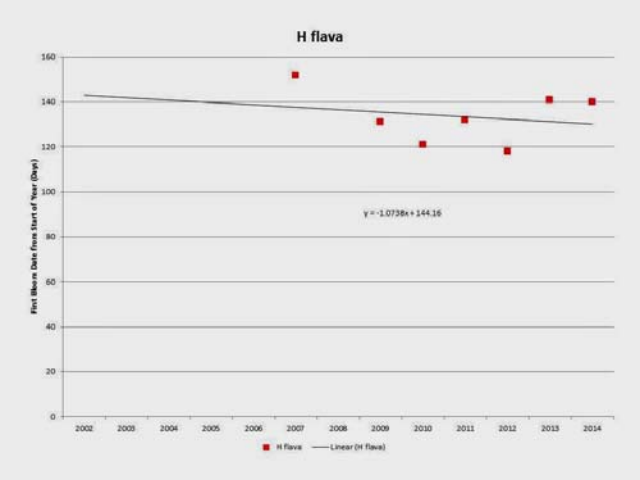


Spotty as it may be there is a consistent trend if we examine each species. We show all below.









Note that we have a consistent trend of shortening bloom dates by about 5-10 days per 25 years.

The question is; how dependent is this on micro conditions and how much is variability in general? The gross variability is significant. In addition given the severe winter of 13-14 we would have expected a later date but did not see it. However all trends are for earlier dates.

Labels: Global Warming

FRIDAY, JUNE 6, 2014

D DAY REMEMBRANCE

The wall of the battle at Normandy Cemetery.

The landing beach looking west.

The landing beach looking east.

The pool at the cemetery.


Labels: Commentary

SUNDAY, JUNE 1, 2014

PIKETTY, BASKETBALL AND CABLE TV

So what does Piketty, Basketball and Cable TV have in common. Simple, wealth transfer. Why would someone pay $2B for some basketball team? If we were to believe Piketty then the return on that asset would have to exceed the return on labor, namely some people who work must be transferring to the new owner a return in excess of their labor value in the market place. Now how does that happen. Simple!

The Government facilitates it. Cable companies charge me and hundreds of millions of others for sports channels which we never watch, and even more likely never knew they had them. Just this month Cablevsion increased my basic cable rate some 4%, annualized at 8%, for another fee for one of those useless channels. If the Government enforced the Antitrust laws regarding tying arrangements we would not have this problem. So does Piketty understand this wealth creation mechanism, I doubt it, no French economists I know understand reality. But does the Justice Department, hardly, why they fear the CATV folks, especially those who control news outlets. They may lose votes.

But is there any hope on the horizon? In wireless there is a modicum of competition and an explosion of innovation. Cable is mired in a monopolistic structure supported by wealth transfers from its subscribers. This fact is clearly proven by the recent $2B buy of some sports team. There is a clear expectation of continuing rents providing a significant wealth based rate of return. But for how long?

There has been a long standing assumption that wireless has certain limitations that make it a non-viable competitor for cable or broadband. However, in the past few years, wireless technology has made dramatic strides in many areas that will enable it soon, if not actually now, to become a truly viable competitor to cable and provider of broadband. We present here a few salient points that should be considered when examining the potential of wireless over cable.

Spectrum, Bandwidth, and Capacity; An Explosion: Most people do not understand the sea state change that has occurred in wireless with the introduction of the 4G systems. First spectrum is measured in units of Hz, and a typical allocation of spectrum would be 10 to 40 MHz, millions of Hz. Second, capacity is measured in bps, bits per second. For example the broadband world required capacity amounts well in excess of 1 Mbps, or millions of bps.

In the older generation of wireless one would get 1 Mbps of data for every 1 MHz of bandwidth. The old “rule” was that each 1 Hz of bandwidth could carry 1 bps of capacity. However, with the new 4G wireless systems and the use of OFDM technology one obtains up to 10 Mbps of data

for every 1 MHz of bandwidth. That is a tenfold increase. Thus with no additional bandwidth the wireless carriers have almost increased their capacity tenfold!

In the currently designed 5G systems, which to be deployed in less than five years, the multiplier will become as high as 100 Mbps for every 1 MHz of bandwidth. Thus we have the potential for a hundred fold increase in capacity.

This same type of change is not taking place in Cable. In fact, in many ways, Cable is mired in the past, with hubbed and sub-hubbed systems, with coax, often twenty plus years old, buried in locations where now the cost to rewire exceeds $3,500 per subscriber. Wireless can use the same towers, the same backhaul fiber, and the same basic infrastructure. All they need is new electronics at the cell site and new electronics at the user site.

Silicon and the Implosion of Data: As we see capacity of wireless explode, we also see the need for capacity for carrying video implode. Namely we see capacity required for an HDTV channel go from 200 Mbps for uncompressed video down to 4-6 Mbps in compressed video. That is a 50:1 reduction in demand. Capacity is increasing while demand is reduced.

Silicon based data processing enables this change in demand as well in supply. It had been argued before that one can see the concept; “silicon is free”, namely the computer and processing chips that enable these advances have continually dropped in price in a dramatic manner. What was costly and unrealistic two decades ago is now inexpensive and ubiquitous. Every computer terminal can now use a low cost HDTV camera and have the ability to provide compressed video and then transmit it in real time amongst large groups of participants. Likewise, the compressed HDTV can be deployed in real time video-on-demand applications. Every iPhone is now a Telepresence system and every laptop a sophisticated TV Studio!

Explosive Video Capacity on Wireless: As we see, when you increase your capacity 100 fold and decrease your demand 50 fold, there is a potential 5,000 fold change and that is the sea state change we envision in wireless. Unfortunately there is no such change in Cable.

Optimum Spectrum Available: The only significant limitation with wireless has been coverage limitations at higher frequencies, such as 1.8GHz. The 800 MHz bands are reasonably flexible, but the best propagation bands are at 600 MHz, the old UHF bands. The FCC has announced the intention to auction these off. If the major carriers can obtain them directly or even via a secondary sale, which is a highly likely outcome, then the 600 MHz spectrum, some 40 MHz, will allow 4 Gbps per cell site and at 4 Mbps per HDTV channel it will have the capacity of 1,000 video channels simultaneously! The 600 MHz spectrum can also provide excellent coverage since this spectrum “bends” around corners and hills much better than the higher frequencies; after all it is just the old UHF spectrum. This will put the wireless carriers potentially in a directly competitive position to Cable.

End User Technology: Wireless has allowed end user technology to flourish. Thus the iPhone the Android systems and other major advances in technology and technology enable content have been a corner stone of wireless. The wireless carriers merely enable an “air interface”, a small element on a chip in any device and then let the device providers add whatever they can to

the units. This strategy has profited them quite well. Many devices, services, and businesses have developed driving the wireless carriers revenues and profits. The wireless carriers now sit on the threshold of being both broadband and video content purveyors.

This is dramatically unlike cable systems which in many ways are akin to the old Ma Bell world; namely, you must get their cable modem and you must get their digital receiver, and it only comes in one color! Even more so, you must purchase their content; whether you view it or not. Wireless is playing a dramatically different game.CATV companies allow nothing at the end user interface. All we get is some old technology cable modem and cable converter. There is no Apple, Google, Qualcomm for CATV as there is in wireless. When did we ever hear of a new set of high tech start-ups for CATV tech?

The only thing keeping CATV in a position of continuing wealth generation is its monopoly. The only thing keeping the monopoly is the fear by politicians of what CATV channels can do. I suspect that the fear may soon backfire as we see continuing breakthroughs in wireless.

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Labels: CATV, Economics

WEDNESDAY, MAY 28, 2014

THE ARTIC: A NEW GATEWAY?

In a recent piece in Eureka the article refers to studies which present concerns regarding the migration of species across an open seas in the Arctic.

They state:

For the first time in roughly 2 million years, melting Arctic sea ice is connecting the north Pacific and north Atlantic oceans. The newly opened passages leave both coasts and Arctic waters vulnerable to a large wave of invasive species, biologists from the Smithsonian Environmental Research Center assert in a commentary published May 28 in Nature Climate

Change. Two new shipping routes have opened in the Arctic: the Northwest Passage through Canada, and the Northern Sea Route, a 3000-mile stretch along the coasts of Russia and Norway connecting the Barents and Bering seas. While new opportunities for tapping Arctic natural resources and interoceanic trade are high, commercial ships often inadvertently carry invasive species. Organisms from previous ports can cling to the undersides of their hulls or be pumped in the enormous tanks of ballast water inside their hulls. Now that climate change has given ships a new, shorter way to cross between oceans, the risks of new invasions are escalating.

Now some brief thoughts. First if some higher species decided Homo sapiens should not cross from Asia to the Americas I wonder what would have happened here? Second, an open Arctic passage has been sought for centuries and perhaps this may lead to substantial changes in trade; for better or worse. Third, we have argued that putting fiber across the Arctic, North America and Russia, would be highly productive. This may open up that opportunity.

Labels: Commentary

MONDAY, MAY 26, 2014

MEMORIAL DAY: REMEMBERING

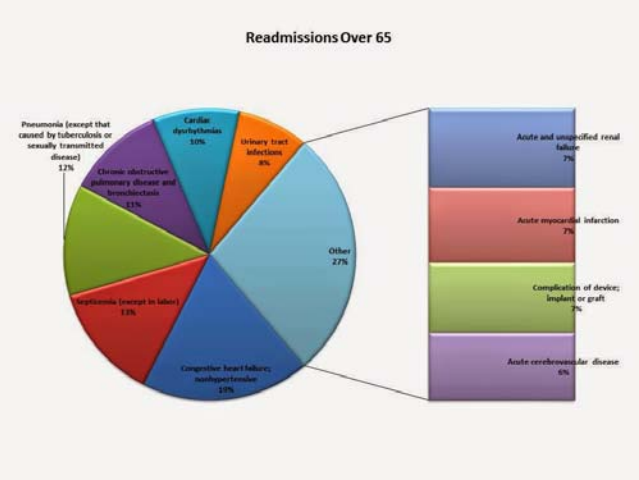
The cemetery at Normandy, row upon row of the fallen. In Remembrance to all.

Labels: Commentary

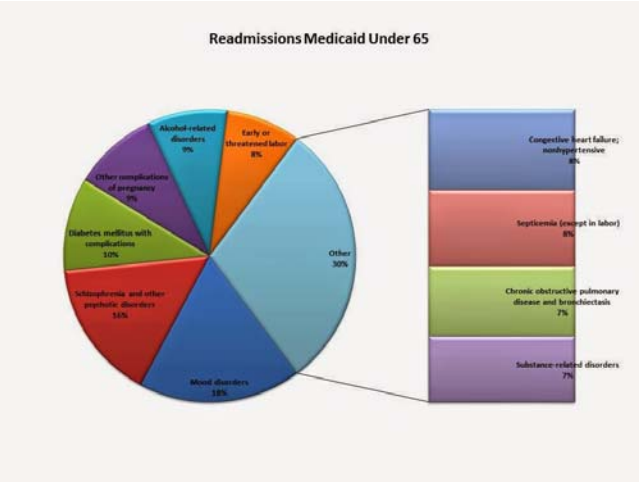
TUESDAY, MAY 20, 2014

RE-ADMISSIONS: AN INTERESTING DIFFERENCE

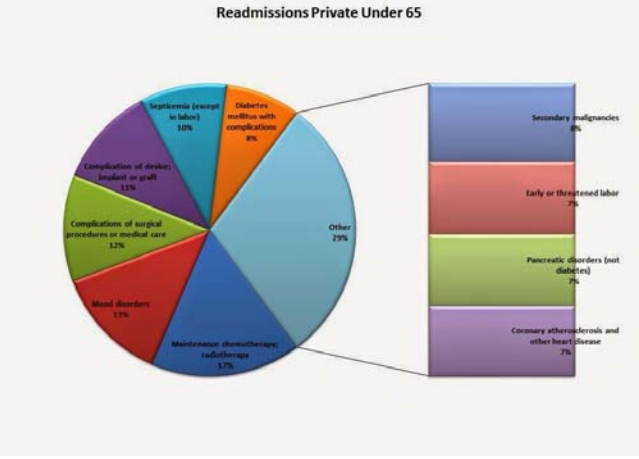
The issue of re-admissions has been a major concern for increased Health Care costs in hospitals. In a recent study by H-CUP they reported on a cross section.



The above is the summary of Re-admissions for Medicare. No real surprises here. In contrast look at Medicaid below:



They are almost dominated by psychiatric causes. Also for Private Insurance we have:



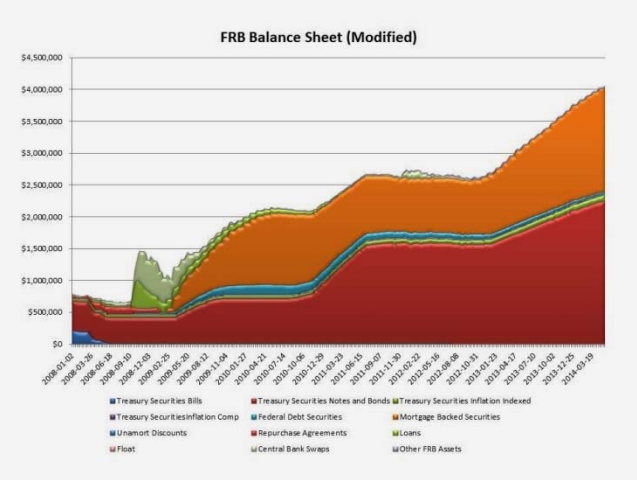
Again a somewhat similar profile.

This says a great deal about what we expect in the ACA. Two separate segments.

Labels: Health Care

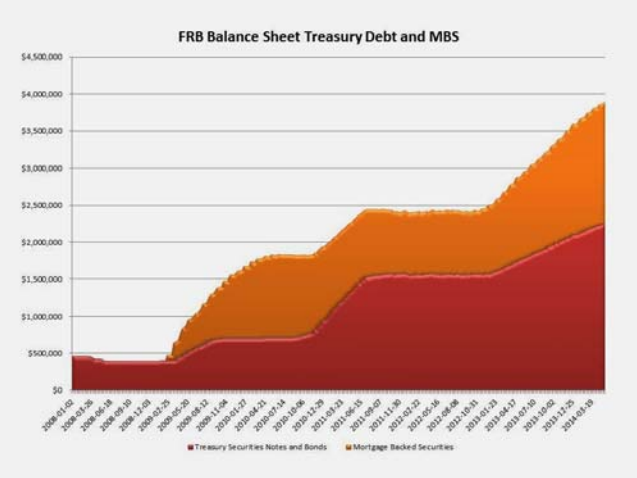
TUESDAY, MAY 20, 2014

FEDS BALANCE SHEET MAY 2014



The above is the FED's Balance Sheet as of today. Despite assertions of no further expansion if not only continues to grow but at an ever increasing rate.

The following chart depicts the key drivers.

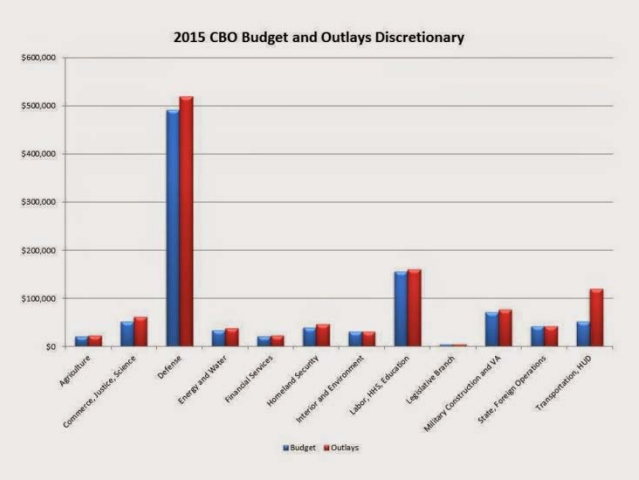


Frankly the MBS explosion is an issue. Also Treasury debt still grows at a constant rate albeit slower than during the crash.

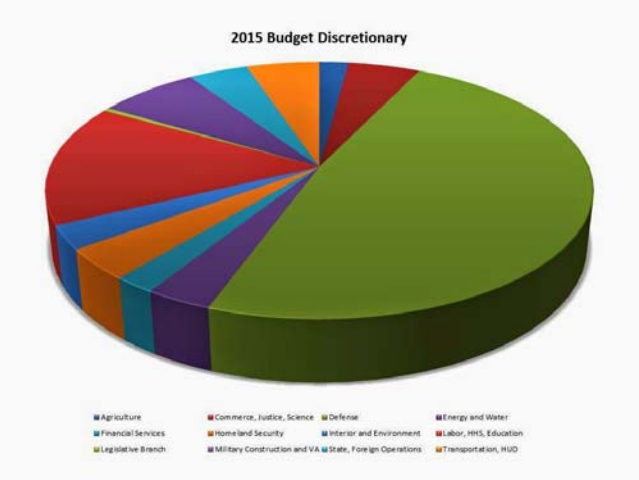
It will ne necessary to watch this continued explosion. It is well over $5 trillion when before the Crash it was only $800 billion. We will see an ten fold increase by 2016.

Labels: Economy

BUDGET AND ACTUALS ON DISCRETIONARY SPENDING

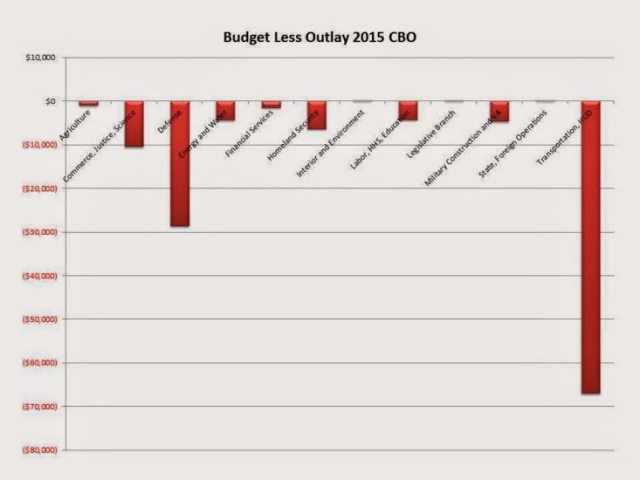


It is always useful to examine the CBOs report on Budget and Actual on Discretionary spending. The above shows both by department. Clearly DoD is the biggest spender at $500 billion plus. HHS et al are second, as expected. What is surprising is HUD and Transportation with outlays more than twice the budget. What has happened.



The above shows the budget. There is well in excess of a trillion in discretionary, and one suspects much room for cutting.

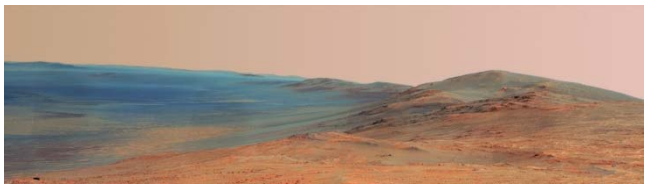
Now the following is the kicker:



Namely Defense as expected overspent, never saw a program it could not justify, but HUD outspent all together. One wonders what snake is in that woodpile?

Labels: Government

EARTH INVADES MARS!



Creatures from Earth have been sent as invaders to Mars. This is H.G. Wells in reverse!

As Nature states:

Dozens of microbial species may have accompanied the Curiosity rover to Mars, where it landed in August 2012. The stowaways withstood spacecraft cleaning methods before the rover's launch, although no one knows for sure whether the bacteria survived the inter-planetary ride. A study that identified 377 strains found that a surprising number resist extreme temperatures and damage caused by ultraviolet-C radiation, the most potentially harmful type. The results, presented today at the annual meeting of the American Society for Microbiology, are a first step towards elucidating how certain bacteria might survive decontamination and space flight.

After all the care we take in not contaminating our water etc we allow NASA to act with abandon in sending some of the most virulent of Earth's species to our nearest neighbor. Where is the EPA on this one?

The article continues:

Although spacecraft go through multiple cleaning steps to ensure that they bear no biological contaminants, previous reports suggest that Curiosity project developers did not follow these

planetary protection protocols to the letter. The regulations are a safeguard; whether microbes can tolerate conditions on the surface of Mars is still unknown. "We don't know yet if there's really a threat," says Smith. "Until we know, it's important to take a precautionary approach."

That is rather neglectful one could say. Next we will be sending our TV and movie products to totally contaminate them!

Labels: Commentary

MONDAY, MAY 19, 2014

OBESITY: A SCALE VERSUS THE GENES

There is a continual debate over the idea that:

Input-Output=Net Accumulation

This is always true, by definition.

However we should always examine what we mean by each term. Let us first examine Input.

Input= the net amount of kcal an individual obtains by the consumption of a certain type of food

Now that will depend on the food and the individual. Certain people have enzymes, products of genes, that convert the consumed more efficiently, and they also have epigenetic factors that enhance conversion of the consumed food into products that can be used or stored. Thus Input for one person consuming the same food as another is NOT the same. Genes play a part in how the physical raw input is processed in the individual to stored and used Input in the body. Thus the net Input, that which is used and/or stored, may vary in some statistical manner between humans.

For example certain southwest Indian tribes have genes that allow highly efficient absorption meaning that they can live on poor quality food but give rich foods they explode in weight and Type 2 Diabetes. Another example, epigenetic, is from Netherlands in WW II where in 1944 mothers were starved by Nazis and children born had epigenetic marks that allowed them to survive on low caloric intake by up-regulating certain genes. Thus genetic and epigenetic factors affect the conversion of Input and the net result can vary. The epigenetic factors can be passed down to children and in some cases to grandchildren. Thus environment via epigenetic changes can affect the genetic makeup.

Having said this, one can develop a distribution of net Input as a function of Gross Input, namely consumed food, and see that across a large population there is, one can assume, a Gaussian like distribution. Some people, most if you will, have a conversion rate of say 1, others may have a larger or smaller conversion rate. It does not appear that a great deal has been done examining this factor.

Output is basal metabolism rate and other factors whereby we burn calories. That also varies dramatically. You walk 5 miles and I walk 5 miles and we each urn a different amount. Again Output may vary from individual to individual. I may burn 100 kcal per mile walked and another may bur 75 or 125 kcal. Why the difference? Again it may be an amalgam of genetic or epigenetic. It may also be the way one walks. Therefore Output like Input has some form of distribution across large populations.

The problem thus is neither Input nor Output, it is Net Accumulation. Thus for zero Net Accumulation we each must understand our balance. Now that also may change as we may face different challenges.

Humans have the ability to use their intellect to measure a set point, namely a scale and to measure their weight. Secondly humans have the will power and intellectual capability to retain that set point.

Other animals spend all day hunting for feed and consuming generally low calorie food, and somehow maintain a balance. Rarely do we see a fat squirrel

The conclusions are:

1. Environment does affect what we see as net Input and net Output and thus net Accumulation

2. Genetics and Epigenetics affect what each individual does in terms of conversions

3. However as humans we have the ability/intelligence to measure the set point and the will to maintain it.

4. One size fits all does not work. Each human is different in how they convert Gross Input to Net Input and Gross Output to Net Output. Thus the only true measure is the scale, namely weighing oneself and balancing Input and Output to keep the scale at the required set point.

Thus when writes in the NY Times and other journals of note speak of diet and weight control we hear them state[57][1]:

FOR most of the last century, our understanding of the cause of obesity has been based on immutable physical law. Specifically, it's the first law of thermodynamics, which dictates that energy can neither be created nor destroyed. When it comes to body weight, this means that calorie intake minus calorie expenditure equals calories stored. Surrounded by tempting foods, we overeat, consuming more calories than we can burn off, and the excess is deposited as fat. The simple solution is to exert willpower and eat less. The problem is that this advice doesn't work, at least not for most people over the long term. In other words, your New Year's resolution to lose weight probably won't last through the spring, let alone affect how you look in a swimsuit in July.

[57][1] http://www.nytimes.com/2014/05/18/opinion/sunday/always-hungry-heres-why.html?partner=rss&emc=rss

All too often they oversimplify all factors. The basic law holds, it is a definition, a tautology. The problem is the conversion rates from Gross to Net, a factor that the authors above seem to struggle with but in apparent ignorance. Basically they argue about some set point theory. Namely humans eat until the set point and then stop. Eat too much, get fat, the set point increases and the system is unstable. Fat Squirrels! However this totally ignores the scale. If the goal is a BMI of 24.0-25.0 worst case, then just use the scale, reduce food intake by the use of the will until the scale falls back to the right range, and forget these putative set points, namely blaming some other factor. Take responsibility.

The authors continue:

If this hypothesis turns out to be correct, it will have immediate implications for public health. It would mean that the decades-long focus on calorie restriction was destined to fail for most people. Information about calorie content would remain relevant, not as a strategy for weight loss, but rather to help people avoid eating too much highly processed food loaded with rapidly digesting carbohydrates. But obesity treatment would more appropriately focus on diet quality rather than calorie quantity.

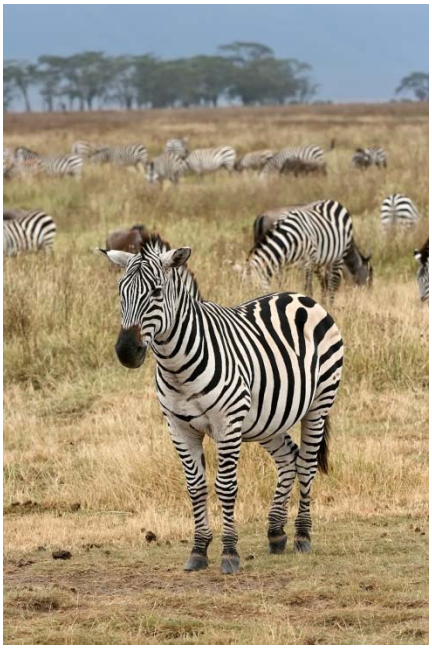
Obesity treatment is a non-issue by using a scale. Yes indeed, forget the calories, measure the pounds. Scales are cheap!

Labels: Health Care, Obesity

ALAN TURING: CALICO CATS, ZEBRAS, AND DAYLILIES

Turing in 1954 wrote his paper on Tessellation, the patterns we often see on animals and plants. The question is; is Turing's approach the right way to understand these patterns? Namely Turing proposed a hypothetical method whereby cells communicate with one another and that this communications is akin to flows of some, as of 1954, yet to be defined chemical substance or substances. Depending on the concentrations of these substances the cells then turned, for example, black or white, as in a zebra, and that this flow being coordinated in some manner yielded a pattern, not just a mass of black and white hairs.

Turing hypothesized, for example, that there may be two controlling molecules in varying densities and if one molecule was denser than the other it would turn on white and otherwise it would turn on black. But Turing said more, that the flow of the molecular density was not just random but that cells somehow participated in a distributed manner so that the densities flowed as waves, with peaks and valleys. Thus the Zebra stripes were a reflection of this flow. When the black molecule was at a high the hairs were black and when the white ones were high the hairs were white. The net result looked like waves of white and black.



Now a second model that has become of recent popularity is the explanation for the Calico Cat.

The explanation for this is dramatically different. Here Calico Cats are all female. The way it works is the epigenetic silencing of one of the X chromosomes. This allegedly is totally done at random. As seen above this of course is hardly the case. If every hair cell were random then we would expect to have a blend of two or more colors and not the patterns that we have above. This means that if this is epigenetic that spatially there is some mechanism that is not totally random. There is some form of cell to cell memory and cell to cell thresholding. Namely the hair stays black, brown or white for some spatial period and then switches to the other state. That is the Turing Tessellation effect. What then does that?

Now consider a third example; the daylily. We show a typical example below. Here we have an eyezone, the dark red around the milled and we even have red on the edges. This is again a tessellation type as described by Turing. There are areas where there is dark red and areas where there is light red or pink. Is this epigenetic, genetic, or a Turing tessellation.

In fact daylilies can show dramatic patterning as they get more sophisticated. The above is a simple form of patterning, a wave of dark and light red.

Thus what enables these patterns? In epigenetics of cats, it is the turning on and off of one X chromosome, but not really randomly, so there must be some mechanism that selects which one gets wrapped in an lncRNA and which does not. What is that activator? Not yet known.

In daylilies we know that color is driven by anthocyanin production. More of one and we get one color and more of the other another color. We also know that certain proteins, gene products, act as catalysts facilitating one anthocyanin path or another. Thus if one gene is producing then it may drive up pone anthocyanin or another. What turns these genes on and off? Perhaps epigenetic methylation as we see in many other examples. But that begs the question of what causes the methylation? It appears to be a pattern like that of the Calico Cat.

Thus the Turing Tessellation is a process that explains these patterns but the facilitator of that process, the extracellular or intercellular molecule is not known. Thus we have an interesting area of exploration. In addition we see similar effects in the field of metastatic cancers, where we get clusters of metastatic cells, and not just random aberrant one.

Labels: Commentary, Genetics

FRIDAY, MAY 16, 2014

OBESITY AND WILLPOWER

Does the law of mass balance really apply to human obesity? Namely does Input Less Output Equal Net Accumulation really work?

In a recent NEJM article one is asked to wonder. Everywhere else in the universe it applies but not for some strange reason in human obesity. The author states:

These studies, of course, reinforce what some physician–researchers have been insisting for more than a century: that obesity is innate, that weight regulation is not governed by a uniform tally of "calories in–calories out," and to quote ..., that "there is a biochemical or basic

biological element in what it is that we call `willpower.'" The views of many Americans notwithstanding, weight is clearly far from being entirely within an individual's control. Genetic predispositions, in tandem with the development of food environments that facilitate overeating and built environments requiring minimal energy expenditure, may help explain why so many Americans are obese today.

Unfortunately the statement is false, almost in toto. Yes, each person has a different set point, namely the Output level. Some people burn 1500 kcal per day and others 2200 kcal per day. There is no meter telling us that. In addition that Output number does depend on a lot of factors, stress, ages, health. But if Input exceeds Output then Net Accumulation occurs. The opposite is also true. Weight management is often a sophisticated balance, but the true meter is a scale. If one targets say a BMI of 24.0 then one just manages Input to ensure the 24.0 number is reached and maintained.

It is always nice to have that extra piece of pie, those cookies, that extra beer, I guess, but that is input. Yes there are people who eat anything and never gain a pound and those of us who measure calories each time we come near food.

As the author starts out:

The obese lack willpower; they overeat and underexercise — or so believe a majority of Americans. A 2012 online poll of 1143 adults conducted by Reuters and the market research firm Ipsos found that 61% of U.S. adults believed that "personal choices about eating and exercise" were responsible for the obesity epidemic. A majority of Americans, it seems, remain unaware of or unconvinced by scientific research suggesting that "personal choices" may not account for all cases of obesity.

No one doubts that there are a small few for whom weight control is highly problematic. No matter how low they go their Output is set well below that point. The few calories expended in exercise will never increase the output above the minimal input. But that does not account for the near global explosion of obesity. There was not a genetic change in humanity over the past thirty years to account for this. There is no epigenetic hyper/hypo methylation setting and resetting genes, causing massive reductions in basal Output. Input has increased by "choice" and all attempts to rationalize it as some effect out beyond human control is both wrong and harmful.

The law of mass balance applies. No one has ever rejected this. If it works in any chemical plant, and the human body is one, then it works in us. Remember the best meter is that scale and the best control mechanism is to not eat that extra candy bar or drink that extra soft drink. It is truly a shame that some physicians cannot call it for what it is. Oh, it appears as if the author is from the History Department at Harvard...

Labels: Health Care

FRIDAY, MAY 16, 2014

NET NEUTRALITY AND THE FCC

The FCC issued its NPRM yesterday for new Net Neutrality. The rules are short, and the basis for substantial litigation.

Here is a sample of the key proposals:

§ 8.3 Transparency. (a) A person engaged in the provision of broadband Internet access service shall publicly disclose ***accurate information*** *regarding the network management practices, performance, and commercial terms of its broadband Internet access services, in a manner tailored (i) for end users to make informed choices regarding use of such services, (ii) for edge providers to develop, market, and maintain Internet offerings, and (iii) for the Commission and members of the public to understand how such person complies with the requirements described in sections 8.5 and 8.7 of this chapter. (b) In making the disclosures required by this section, a person engaged in the provision of broadband Internet access service* ***shall include meaningful information regarding the source, timing, speed, packet loss, and duration of congestion****. (c) In making the disclosures required by this section, a person engaged in the provision of broadband Internet access service shall publicly disclose in a* ***timely manner*** *to end users, edge providers, and the Commission when they make changes to their network practices as well as any instances of blocking, throttling, and pay-for-priority arrangements, or the parameters of default or "best effort" service as distinct from any priority service.*

The issue is what is to be disclosed. Congestion is a real difficult problem and it can be obfuscated readily. I have had difficulty adequately collecting such data for fifty years. There is no definition readily acceptable.

§ 8.5 No Blocking. A person engaged in the provision of fixed broadband Internet access service, insofar as such person is so engaged, shall not block lawful content, applications, services, or non-harmful devices, subject to reasonable network management. A person engaged in the provision of mobile broadband Internet access service, insofar as such person is so engaged, ***shall not block consumers from accessing lawful websites, subject to reasonable network management; nor shall such person block applications that compete with the provider's voice or video telephony services, subject to reasonable network management.***

Wow, reasonable! That is how lawsuits are started. My reasonable and your reasonable are always at odds. This is clearly the most unrealistic document ever created!

§ 8.7 ***No Commercially Unreasonable Practices.*** *A person engaged in the provision of fixed broadband Internet access service, insofar as such person is so engaged, shall not engage in commercially unreasonable practices. Reasonable network management shall not constitute a commercially unreasonable practice.*

If you liked the confusion above, then the last one noted here is even better! What does commercially unreasonable mean and to whom! This will be in the Courts for lifetimes! The big carriers could not be happier. I wonder who wrote this in the first place? Just a thought.


Labels: FCC, Internet Neutrality

NOTCH, MIR-146A AND MELANOMA

The understanding of cancer progression has been a continuously evolving process moving from internal pathway elements, to micro RNA interactions and to a complete set of epigenetic factors including various methylation effects. We consider here a recent observation of a micro RNA initiated by change in a pathway element, BRAF V600, and its effect on proliferation and survival. This work by Forloni et al introduces putative new elements to block with a putative therapeutic result, one in fact that handles a multiplicity of factors.

In a recent paper by Forloni et al the authors state:

Oncogenic mutations in BRAF and NRAS occur in 70% of melanomas. In this study, we identify a specific microRNA, miR-146a, which is highly upregulated by oncogenic BRAF and NRAS. Expression of miR-146a increases the ability of human melanoma cells to proliferate in culture and form tumors in mice, whereas knockdown of miR-146a has the opposite effects. We show these oncogenic activities are due to miR-146a targeting the NUMB mRNA, a repressor of Notch signaling.

The focus is now clearly on these secondary factors, namely the micro RNAs and even methylation effects that are seen in many cancers. In this case it of the excess production of a specific miRNA that in turn block an mRNA and in turn allows upregulation of other pathways and in turn unregulated cell proliferation.

As Garraway states in NEJM:

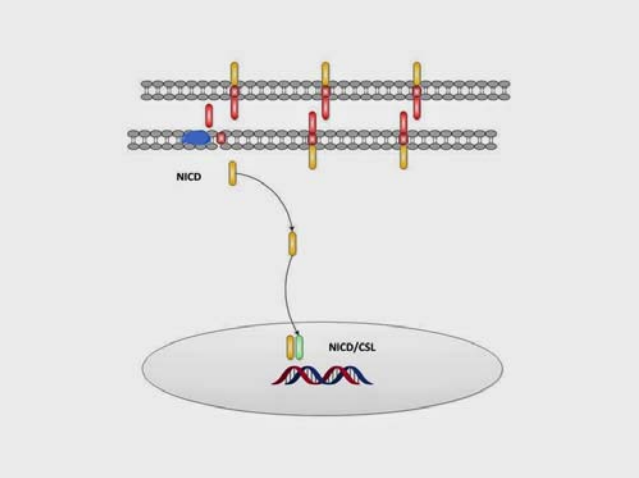
Finally, these findings invite speculation that adding γ-secretase inhibitors to inhibitors of RAF and MEK might offer an attractive therapeutic cocktail for assessment in future clinical trials of melanoma treatment. Given the substantial toxicity of γ-secretase inhibitors, additional preclinical studies of such combinations in melanoma cell lines and patient derived xenograft models would be beneficial.

Such studies could clarify the generalizability of Notch dependency in melanoma, the relevance (if any) of the pre miR146a G allele versus the C allele for patient stratification, and the possible usefulness of alternative dosing and scheduling schema to reduce toxicity. Overall, this study provides a reminder that, despite numerous advances, we have only just begun to dissect the rich interplay among noncoding RNAs, the biologic basis of cancer, and potential therapeutic strategies.

Garraway sees this as a significant breakthrough and believe it is a worthwhile pathway for new therapeutics. In this analysis we briefly examine the interaction of Notch and miR-146a and how it can be understood in the case of melanoma as a major factor of uncontrolled proliferation.

Proteolysis is the process of degradation of proteins in the cell and the release of the energy contained therein for other purposes. The Notch pathway process is a key part of the proteolysis effort[58][1]. The Notch system is a proteolytic driven system used in signal transduction in cells. Uncontrolled Notch pathways production can lead to uncontrolled cellular growth.

Let us begin with a simplified but reflective description of the Notch pathway. The Notch process starts with the two Notch ligands, which are also called DSL proteins. One is external to the cell membrane and is the other is internal. When they are broken, the intracellular part, called NICD moves to the nucleus and binds with a protein CSL which becomes a putative transcription factor. We demonstrate that below.



Recall, that a transcription factor is a protein or protein complex that can turn on (activators) or turn off (repressors) the transcription of genes[59][2]. In this case the transcription factor is an

[58][1] See Marks, Chapter 13.

[59][2] See Broad https://www.broadinstitute.org/education/glossary/transcription-factor and Watson et al 544-555. Also http://www.nature.com/scitable/definition/general-transcription-factor-transcription-factor-167 Also from Vaquerizas:

"Transcription factors are key cellular components that control gene expression: their activities determine how cells function and respond to the environment. Currently, there is great interest in research into human transcriptional regulation. However, surprisingly little is known about these regulators themselves. For example, how many transcription factors does the human genome contain? How are they expressed in different tissues? Are they evolutionarily conserved? Here, we present an analysis of 1,391 manually curated sequence-specific DNA-binding transcription factors, their functions, genomic organization and evolutionary conservation. Much remains to be explored, but this study provides a solid foundation for future investigations to elucidate regulatory mechanisms underlying diverse mammalian biological processes."

activator for MYC[60][3]. Transcription factors are frequently brought to bear to activate genes that lead to uncontrolled growth.

Goss and Kahn have presented a review of the interaction of Notch and Wnt and especially the function of excess Notch activation as a part of cell proliferation in multiple cancers[61][4]. As they state Wnt and Notch act in concert in many cancers, prostate being one which we have examined in some detail. In addition excess Notch activation appears to effect a stem cell like behavior in these cells thus resembling the cell types enable for proliferation as well as survival.

We now want to explore some of the impacts of Notch in stem cell environments and in turn in the maturation of cells. We focus on a recent paper by Katoh and Katoh. As Katoh and Katoh have written:

Notch signaling pathway is implicated in the maintenance of self-renewal potential in stem cells, binary cell-fate determination in progenitor cells, and induction of terminal differentiation in proliferating cells. Notch-ligand binding to Notch receptors leads to the cleavage of Notch receptors by metalloprotease and Á-secretase to induce nuclear translocation of Notch intracellular domain (NICD). Nuclear complex, consisting of CSL (RBPSUH), NICD, Mastermind (MAML), p300 and histone acetyltransferase (HAT), then induces transcriptional activation of Notch target genes, such as HES1, HES5, HES7, HEY1, HEY2 and HEYL. HES/HEY family members are bHLH-type transcriptional repressors for tissue-specific transcription factors. Therefore, Notch signaling activation in stem cells leads to the maintenance of self-renewal potential.

Now Katoh and Katoh provide an activation path progression as show below (as modified):

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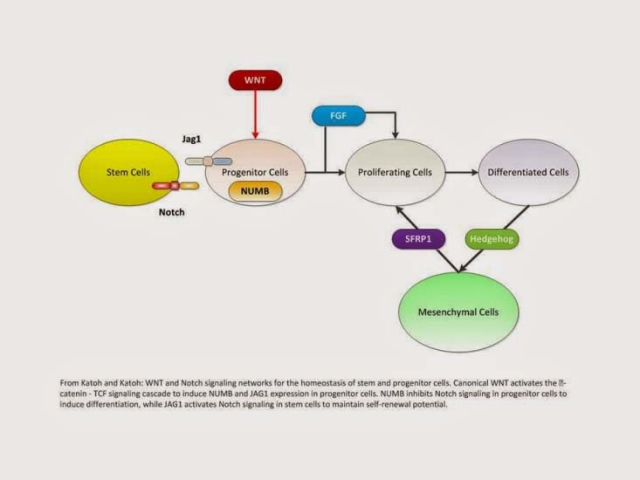
[60][3] From NCBI we have: T*he protein encoded by this gene, cMYC, is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation.* ***It functions as a transcription factor that regulates transcription of specific target genes.*** *Mutations, overexpression, rearrangement and translocation of this gene have been associated with a variety of hematopoietic tumors, leukemias and lymphomas, including Burkitt lymphoma. There is evidence to show that alternative translation initiations from an upstream, in-frame non-AUG (CUG) and a downstream AUG start site result in the production of two isoforms with distinct N-termini. The synthesis of non-AUG initiated protein is suppressed in Burkitt's lymphomas, suggesting its importance in the normal function of this gene.* See http://www.ncbi.nlm.nih.gov/gene/4609

[61][4] See Goss and Kahn, pp60-61.



The above demonstrates the progress from an overactive Notch cell which thus acts as a stem cell to more mature cell lines. The above also demonstrates the location of proliferating cells in this schema, just after the stem cell line progenitor.

Thus the activation of Notch leads to an extreme survival capability in cells so activated. They continue with the following regarding NUMB:

NUMB and NUMB-like (NUMBL), consisting of phosphotyrosine-binding (PTB) domain and SH3-binding proline-rich region, are docking proteins functioning as Notch signaling inhibitors. Here, we searched for the TCF/LEF-binding site within NUMB and NUMBL promoters. Because two TCF/LEF-binding sites were identified within human NUMB promoter, comparative integromics analyses on NUMB orthologs were further performed.

Thus one way to over-activate Notch is to suppress NUMB. NUMB is described by NCBI as follows[62][5]:

The protein encoded by this gene plays a role in the determination of cell fates during development. The encoded protein, whose degradation is induced in a proteasome-dependent manner by MDM2, is a membrane-bound protein that has been shown to associate with EPS15, LNX1, and NOTCH1.

In a similar manner NOTCH1 is described as follows[63][6]:

This gene encodes a member of the Notch family. Members of this Type 1 transmembrane protein family share structural characteristics including an extracellular domain consisting of multiple epidermal growth factor-like (EGF) repeats, and an intracellular domain consisting of multiple,

[62][5] http://www.ncbi.nlm.nih.gov/gene/8650

[63][6] http://www.ncbi.nlm.nih.gov/gene/4851

different domain types. Notch family members play a role in a variety of developmental processes by controlling cell fate decisions.

The Notch signaling network is an evolutionarily conserved intercellular signaling pathway which regulates interactions between physically adjacent cells. ...Homologues of the notch-ligands have also been identified in human, but precise interactions between these ligands and the human notch homologues remain to be determined. This protein is cleaved in the trans-Golgi network, and presented on the cell surface as a heterodimer. This protein functions as a receptor for membrane bound ligands, and may play multiple roles during development.

These are two powerful and interacting genes. NUMB suppresses Notch1 and Notch1 when activated makes for cell proliferation and survival.

There are now well over hundreds of micro RNAs, which a small non-coding RNAs which result in the control of various pathways in cellular signalling. Micro RNAs are often encoded in introns in mRNAs and some in in non-coding RNAs. They generally control mRNA in terms of its stability, degradation and/or translation. The micro RNAs can stop genes from being expressed as proteins, even though the gene is present and provides a normal mRNA. They are small, generally 22 base pairs in length.

As NCBI states[64][7]:

microRNAs (miRNAs) are short (20-24 nt) non-coding RNAs that are involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. miRNAs are transcribed by RNA polymerase II as part of capped and polyadenylated primary transcripts (pri-miRNAs) that can be either protein-coding or non-coding.

The primary transcript is cleaved by the Drosha ribonuclease III enzyme to produce an approximately 70-nt stem-loop precursor miRNA (pre-miRNA), which is further cleaved by the cytoplasmic Dicer ribonuclease to generate the mature miRNA and antisense miRNA star (miRNA) products. The mature miRNA is incorporated into a RNA-induced silencing complex (RISC), which recognizes target mRNAs through imperfect base pairing with the miRNA and most commonly results in translational inhibition or destabilization of the target mRNA.*

As Rusca and Monticelli state:

Initial evidences on the possible involvement of miR- 146a in cancer came from a study showing thatmiR-146a was upregulated in papillary thyroid carcinoma (PTC) samples compared with unaffected thyroid tissue. Interestingly, a set of five miRNAs, including miR-221, miR-222, and miR- 146, was sufficient to distinguish unequivocally between PTC and normal thyroid. Similarly to the observations performed in immunologic settings, overexpression of miR- 146a/b in the highly metastatic human breast cancer cell line MDA-MB-231 significantly downregulated

[64][7] http://www.ncbi.nlm.nih.gov/gene/406938

expression of IRAK1 and TRAF6, negatively regulating NF-κB activity. Functionally, this resulted in markedly impaired invasion and migration capacity relative to control cells.

These findings implicated miR-146 not only as a negative regulator of constitutive NF-κB activity in breast cancer cells, but also suggested that modulating miR-146 levels might have therapeutic potential to suppress breast cancer metastases. Along the same line, miR-146a was among the miRNAs found upregulated in cervical cancer tissues compared to normal cervix.

When introduced into cell lines, miR- 146a promoted cell proliferation. Although the molecular mechanism underlying such increased proliferation remains to be investigated, these observations potentially implicate miR-146a in cervical carcinogenesis. In another type of cancer, the hormone-refractory prostate carcinoma (HRPC), miR-146a levels were diminished compared to androgen-sensitive noncancerous epithelium. In this context, miR- 146a acted as a tumor suppressor, reducing levels of its target ROCK1, one of the key kinases involved in HRPC transformation.

Accordingly, forced miR-146a expression reduced ROCK1 protein levels, cell proliferation, invasion, and metastasis to human bone marrow endothelial cell monolayers. Similarly, miR-146a was lower in pancreatic cancer cells compared with normal human pancreatic cells…

There is now increasing evidence to suggest that miR-146a is involved in the regulation of the adaptive as well as innate immune response, and that miR-146a can be an important player in regulating tumor progression.

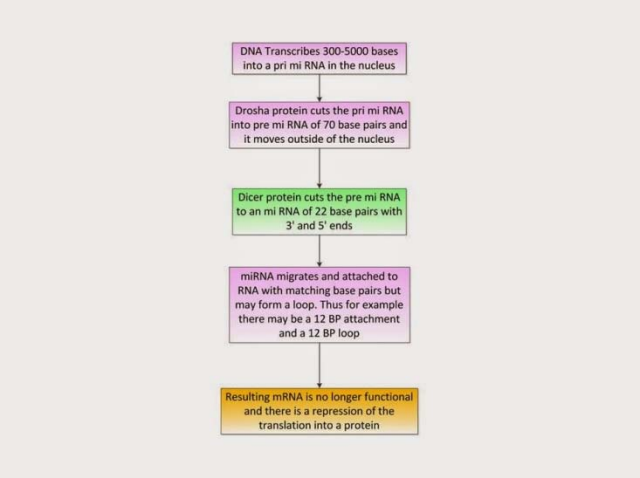
However, more work remains to be done to fully understand its role and mechanism of action in normal and pathologic conditions, so that expression of this miRNA can potentially be exploited as a new point of entry for therapy. With the identification of a vast number of miRNAs each carrying a long list of putative targets, the challenge is now to understand the details of their biological functions.

Thus miR-146a has significant roles to play in controlling cell behavior.

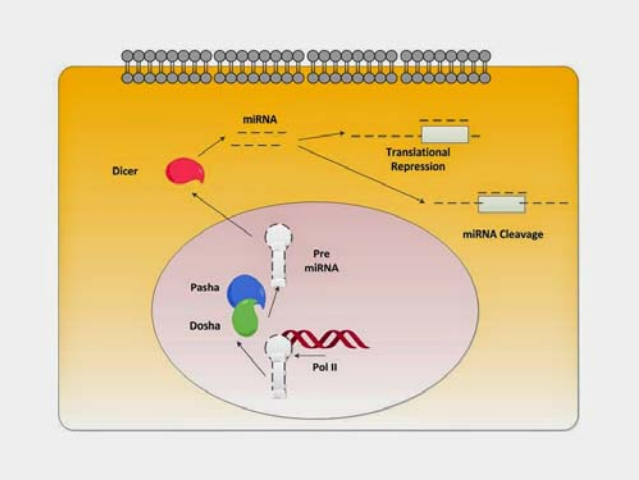
For example, miRNAs can inhibit the translation of mRNA into a protein. We show this below. The small segment attaches to the mRNA and blocks translation. This graphic is descriptive and does not contain full details[65][8].

[65][8] See Marks p 318. Note the colors are also descriptive and do not reflect any specific RNA base pair pairing. Just as with DNA we would expect similar bonding of CG and A and U.

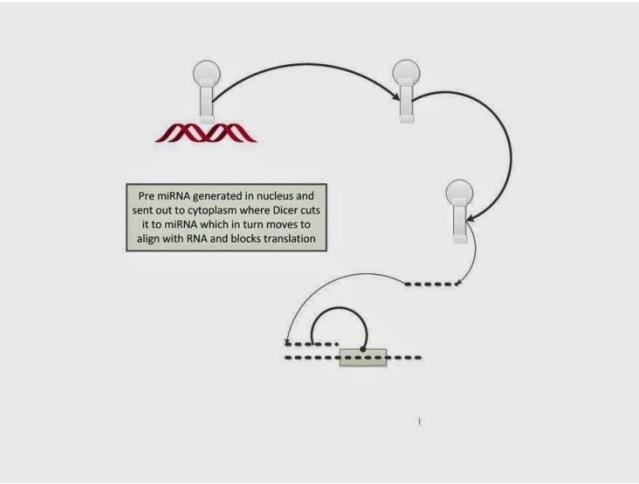
In the case being discussed, miR-146a binds to NUMB and suppresses it. That in turn allows for an overexpression of Notch which in turn can lead to an unstable system with feedback. We shall detail that a bit later.



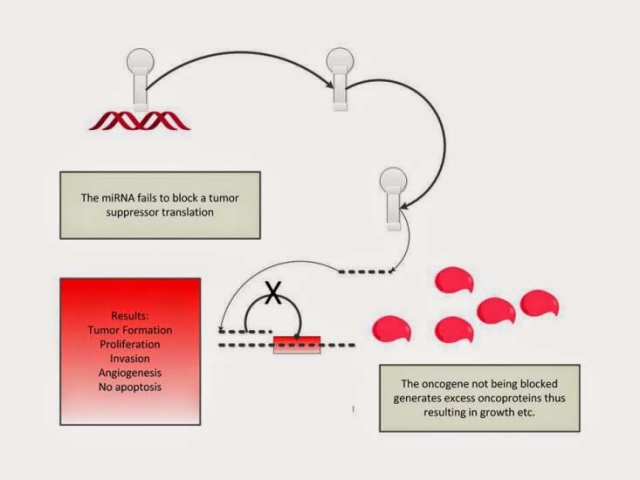
We depict that process in some detail below. For the most part all miRNAs appear to function in the same manner. There are well over a thousand identified at this point and more than likely many more to be found. The functions of most are not fully known.



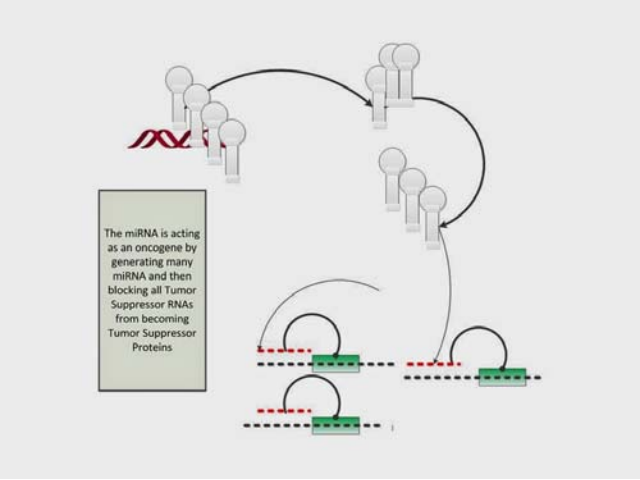
Before continuing it is worth a quick review of normal and abnormal behavior of miRNA. The normal process is shown below. This shows a classic blocking of translation. The miRNA binds to the mRNA and inhibits translation. The question is what makes the miRNA to do this? Namely what forces the generation of the miRNA? Is it a random effect or is it part of a planned process. We have shown that homeostasis is well defined in terms of a balanced expression of RNA. Yet when we have an aberrant genetic element the miRNA can express itself in deleterious ways.



Now we can examine a miRNA in the context of a cancerous environment shown below. The diagram below shows miRNA blocking a tumor suppressor gene. In a sense the example of the miR-146a is an example of this type of miRNA operation. It blocks a protein which in turn blocks a protein which leads to unbridled growth and survival, Notch.

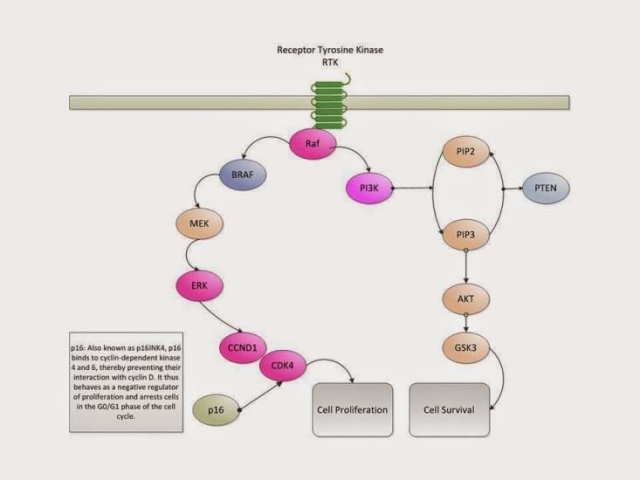


Finally we show the example of miRNA in some explosive expansion of itself thus blocking many tumor suppressor genes. This is a deadly mode for miRNAs and can be found in many cancers[66][9].



The classic pathway dynamics we understand regarding proliferation and survival is shown below. This is the BRAF and PI3K dynamics. We demonstrate this below. This is a well-known and well understood pathway and is at the core of the BRAF V600 therapeutic approach.

[66][9] It is worth examining the McGarty DRAFTs on Prostate Cancer and Melanoma to see this in some detail.



Now proliferation and survival require gene activation and maintenance.

In this report, we demonstrate a critical role for miR-146a in the initiation and progression of BRAF/ NRAS-positive melanomas, ... In addition, our results reveal a pharmacologically tractable pathway for the treatment of melanoma. We identified miR-146a as the microRNA whose expression was most upregulated by activated BRAF.

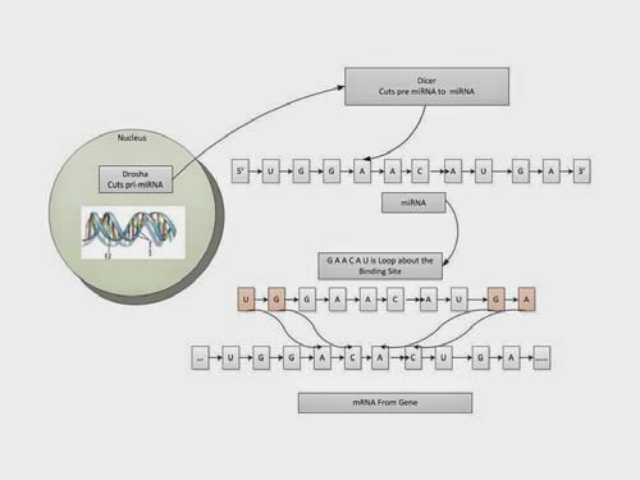
Upregulation of miR-146a by activated BRAF, as well as activated NRAS, occurs through the MAPK signaling pathway. Accordingly, we find that BRAF and NRAS mutant melanoma cell lines and short-term melanoma cultures show higher levels of miR-146a compared to those that are wild type for these genes.

A major function of the MAPK pathway is to activate transcription by regulating the stability and expression of multiple transcription factors primarily through direct phosphorylation.

We show that the MAPK pathway regulates the phosphorylation of the transcription factor MYC, which in turn binds to the promoter of miR-146a and stimulates its transcription. Notably, MYC has been found to stimulate transcription of several other miRNAs. For example, MYC has been shown to directly activate transcription of the oncogenic miR-17-92 cluster and thereby promote cell proliferation, survival, angiogenesis, and metabolic reprogramming in a number of tumor cell lines.

miRNAs and components of miRNA biogenesis pathways such as Dicer have been implicated in several aspects of melanocyte biology as well as in melanoma initiation and progression.

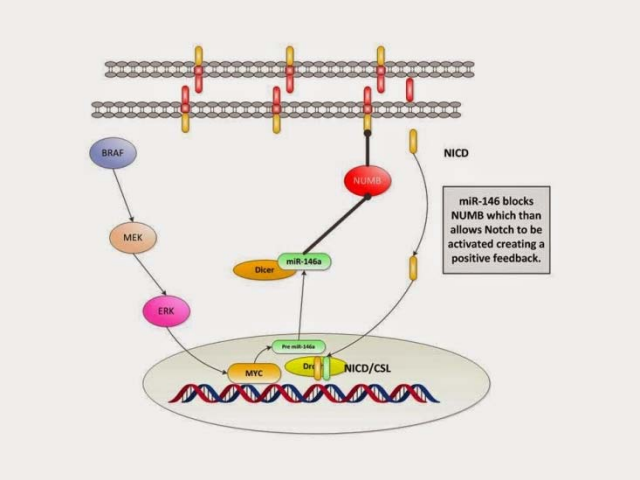
We depict some of that process below:



Previous studies have shown that miR-146a can function either as an oncogene or as a tumor suppressor depending upon the cell type. For example, miR-146a has been shown to function as an oncogene in a variety of human cancers including papillary thyroid carcinoma (PTC), triple negative sporadic breast cancers and anaplastic thyroid carcinoma. miRNAs function primarily by targeting mRNAs and either promoting their degradation or blocking their translation.

Our analysis identified 20 potential targets of miR-146a, including NUMB, which is a well-characterized Notch signaling inhibitor. It is thought that NUMB negatively regulates NOTCH, potentially through a direct protein–protein interaction that requires the phosphotyrosine-binding (PTB) domain of NUMB and either the RAM23 region or the very C-terminal end of NOTCH.

We demonstrate some of these dynamics in the Figure below (adapted from Galloway with modifications).



In simple terms:

1. BRAF activates MEK

2. and then ERK
3. which activates MYC
4. which activates pre miR-146a and
5. then via Drosha and Dicer makes miR-146a
6. which reactivates Notch by suppressing NUMB expression (we have left that out for simplicity)
7. which then goes down to the transcription on the DNA resulting in proliferation and stem like behavior.

This is an interesting and compelling mechanism for the explanation of the aggressive melanoma expansion.

Observations

This is an interesting step in the understanding of melanoma genomics. The role of micro RNAs is becoming clearer as time goes by and added to that is the effect of such epigenetic factors as methylation and we now see a much more complex field of play than a decade ago. The benefit is the recognition of more targets of opportunity that can be had for potential therapeutics. On the other hand the main concern is that the more that is learned one may ask what else is there yet to grasp.

Thus what observations can we make here? Let us examine a few:

1. Stem Cell Hypothesis. Here we have the elements of how a stem cell functions with the activated Notch and blocked NUMB. Does this imply that we have the re-emergence of stem cell like malignant cells activated in a manner such as this. Namely the miRNAs allow for the reprogramming of some modified form of totipotency.

2. Targeted Therapeutics: Galloway makes this observation We know that BRAF inhibitors get us one step there but then we need MEK inhibitors. Then what? Does an inhibitor for miR-146a take all the steps necessary or does the cell go and find another back door way to function?

3. The Dynamics of the Processes are Not Well Understood. One of the problems in understanding the impact of miRNAs and other pathway elements is that there is a concern as to the number or concentration of products. If miR-146a is to block NUMB then it should block all NUMB and in turn activate all Notch. Yet it is a molecule by molecule process which seems to be poorly understood. The paper by Choir et al and Nazarov et al present some ideas on how to deal with such issues. However they are but first steps. This is a critical factor to understand since the therapeutics depends on blocking the necessary number of miR-146a molecules. To data there seems to be limited data to assess this issue.

4. Initiation and Support: We know that V600 mutation of BRAF is drivers for metastatic melanoma. However it is not clear what is the driver ultimately for miR-146a, although it appears as we have suggested as a sequella from the other mutations. Additional insight into the proliferation is requires.

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Labels: Cancer

THURSDAY, MAY 15, 2014

CABLE UNBUNDLING ILLOGIC

There is a piece today in the NY Times which rambles about why unbundling cable channels will cost us all more. Stop right there. It will cost everyone more, more than the extortion already in place. Again, I have never seen a football game, one baseball game, one basketball game, one hockey game, really just half, and that was almost fifty years ago. Yet I pay almost $20 a month in cable charges for all the stuff I have no interest in. $70 a month for basic cable! If I get less then I pay more? Huh?

The article starts:

If you have cable TV, you probably don't watch most of the channels you get. The average American television household receives 189 channels, up from 123 in 2003. But we're watching only 17.5 of those channels — nearly unchanged from 11 years ago, according to a new report

from Nielsen.

I do not know what those channels are but I damn well pay for them. Now try this on for size:

Think of it this way: If I put my bag in an overhead luggage bin, you can't put your bag in the same spot, so it makes sense to charge me personally for my use. But if I watch Bravo, that doesn't stop anyone else from watching the same show. When a good is "nonrivalrous" like a cable signal, giving it to me doesn't stop anyone else from using it or add production costs at the margin. In those cases, it can make sense to throw lots of stuff into one package, whether or not I'll actually use it.

The fact is that they make money from advertising and for the forcible fees I pay whether I watch Duck Dynasty or not. Advertising is based on reach, measures of real customers watching. So if it were all advertising then there is no need for me to watch unless I find it of some value. No value, then I do not watch and do not buy. However the cable guys contort all logic. What is the guy saying in the above. I only speak six languages and the words above are unrecognizable.

The author also uses the argument that one bundles a newspaper. But simply one can readily unbundle the electronic content over a cable. One has more difficulty in doing so in print! In fact, if one priced cable as access plus content then content would become truly market based. It would engender true competition. As it stands now one can bundle absolute nonsense and get paid for it.

We do not argue about some bundling. It is the sports bundling that pays exorbitant salaries to athletes many of whom often get themselves into legal messes. No extortionary charges, unbundle the sports channels and reduce the salaries. Try Income Inequality on those folks for a change, Piketty, where are you when we really need you?

HAVE YOU EVER TRIED TO FIND ANYTHING AT MICROSOFT!

Now when one learns to use Microsoft products there is often the tendency by the company to change them to some new incomprehensible form. Just look at Windows 8. So when I saw this in PC World I though it is worth a comment.

Let's face it—navigating through a maze of menus isn't what any user wants to do. And that's why Microsoft is moving its intelligent search box, Tell Me, from Word Online to similar versions of PowerPoint and Excel. Tell Me, fortunately, is a very simple concept: It's a natural language search box, similar to what you might find in Microsoft's Bing search engine or Google. In Word, Excel and PowerPoint Online, it sits at the top center of the Ribbon, with the helpful cue "Tell me what you want to do." Simply type in your request, and it's off to the races. (As a handy shortcut, you can even type CTRL-' (the apostrophe) to auto-place your cursor into the Tell Me field.

As anyone who has ever tried to figure out how to work some of Microsoft's issues off of their web site knows, "Abandon all hope ye who enter", Dante's Inferno is an amusement park

compared to Microsoft Help. Go to Google, get the advice or input and then hack your way through Microsoft.

Office 2013 looks like a Kindergarten colored room, whomever chose the colors, well, no matter.

But really, use an online service to type, and then use Microsoft for help! Then use Bing! Now really guys, who put the magazine up to this one. Use Google, it works.

Labels: Microsoft

WEDNESDAY, MAY 14, 2014

MORE ON PIKETTY

The splash of Piketty's thoughts on the evil of wealth, or income inequality, has led to many commentators saying one thing or another. Now in comes Summers with his thoughts. (I had written an analysis of Piketty and Francis that may be used as an alternate view.)

He begins with statements like the following:

This should not be surprising. At a moment when our politics seem to be defined by a surly middle class and the President has made inequality his central economic issue, how could a book documenting the pervasive and increasing concentration of wealth and income among the top 1, .1, and .01 percent of households not attract great attention? Especially when it exudes erudition from each of its nearly 700 pages, drips with literary references, and goes on to propose easily understood laws of capitalism that suggest that the trend toward greater concentration is inherent in the market system and will persist absent the adoption of radical new tax policies.

What surly middle class is he talking about? Yes the current President still acts as a community rabble rouser but that should be no surprise. But erudition. How many time do we need to be reminded of Balzac! I get the point. But if one were truly erudite then one would understand that Balzac in context was protesting his own social ills. Why not the mad man Dickens. But alas in the US we do not have dynasties, except attempts at in in politics. In my opinion the book is a gross bore with multiple repetitions of the same thing.

He does make a significant point:

A brief look at the Forbes 400 list also provides only limited support for Piketty's ideas that fortunes are patiently accumulated through reinvestment. When Forbes compared its list of the wealthiest Americans in 1982 and 2012, it found that less than one tenth of the 1982 list was still on the list in 2012, despite the fact that a significant majority of members of the 1982 list would have qualified for the 2012 list if they had accumulated wealth at a real rate of even 4 percent a year. They did not, given pressures to spend, donate, or misinvest their wealth. In a similar vein, the data also indicate, contra Piketty, that the share of the Forbes 400 who inherited their wealth is in sharp decline.

Namely we do not have old style multi century European wealth. We have American

entrepreneurial wealth. High risk and high return.

He then states:

Hanging over this subject is a last issue. Why is inequality so great a concern? Is it because of the adverse consequences of great fortunes or because of the hope that middle-class incomes could grow again? If, as I believe, envy is a much less important reason for concern than lost opportunity, great emphasis should shift to policies that promote bottom-up growth. At a moment when secular stagnation is a real risk, such policies may include substantially increased public investment and better training for young people and retraining for displaced workers, as well as measures to reduce barriers to private investment in spheres like energy production, where substantial job creation is possible.

That is the question I always start with. Why? Why should we worry about this issue?

The he states near the end:

Look at Kennedy airport. It is an embarrassment as an entry point to the leading city in the leading country in the world. The wealthiest, by flying privately, largely escape its depredations. Fixing it would employ substantial numbers of people who work with their hands and provide a significant stimulus to employment and growth. As I've written previously, if a moment when the United States can borrow at lower than 3 percent in a currency we print ourselves, and when the unemployment rate for construction workers hovers above 10 percent, is not the right moment to do it, when will that moment come?

Has have ever been to Penn Station? It makes Mumbai look like a palace. The answer is Politics! The Port Authority often has control and its management is filled with in my opinion pure political hacks. Bridges rust, tolls explode, and salaries increase. Look at Kennedy, look at Penn Station, look at Port Authority Bus Station and you see what happens with politicians emptying the pockets of the taxpayers with agencies reportable to no one! Give them more money, then it ends in the pockets of the Unions. This is a no win game.

Labels: Economics

USE YAH BLINKAH!

Driving in Massachusetts I saw the lighted road warnings which said:

"Use Yah Blinkah"

Now not being from the Bay State, yet having lived there for a few decades, I assumed that perhaps it had meaning. The first thing that came to mind was the Russian word for apple, yablonka, and I wondered why I was being told to use my apple. Three more signs and I finally understood that it was a dialect. Like Sicilian in Italy. Understood from Naples and South but try not to use it in Florence and North.

The I thought that folks like me would go through the same set of distracting questions as to what this meant. In New York and New Jersey we have Turn Signals and we need to Signal Changes in lanes. Thus a Failure to Signal is an infraction. I then wondered if in the Commonwealth a Failure to Blinkah or Blinker was the same infraction.

On the other hand this is what apparently keep Massachusetts one of the highest taxed States. People coming up with these distractions. If you did that in New Jersey...well I will let the Gov tell you what happens!

Labels: Commentary

WEDNESDAY, MAY 14, 2014

INCOME INEQUALITY AND CLIMATE CHANGE

The head of the AAAS wrote a letter to its members where he states:

Based on the evidence, about 97% of climate scientists agree that human-caused climate change is happening. Yet a large fraction of this country's population and policymakers can't seem to accept the fact that the climate is changing. It's time to shift the debate from whether human-caused climate change is happening to what we can do about it.We need to make it clear that scientists believe that doing nothing now is extremely dangerous and could result in abrupt, unpredictable, and potentially irreversible changes with highly damaging impacts on future generations.

He links to the AAAS Report. The Report iterates the above in high level. The Report, like so many others, expresses imminent dire consequences unless "we" do something. The problem is the we and the problem is that people really do not understand the consequences.

Frankly Income Inequality is the same. People always want more money and if they can get it from those who already have it then many are satisfied. Climate Change however is a bit more complex since the taking away via taxes or even goods from many.

These two "threats" to our existence seem almost religious in their attempts to make "people understand".

The problem with Climate Change is; so what is the problem? It gets warmer, the ocean rises a bit, we are told it has risen a foot already and we see no change. Hurricanes? Frankly they have always been there but now we allowed people to move into areas well known for calamities and we insure them with people's taxes! Dumb? Yes, quite so. Climate Change is a "sky is falling" argument. It says that someday we will have massive problems but most people cannot relate to that. People can relate to not having more money especially if it is free, just look at Venezuela. It works for a while or at least until the economic system collapses.

Thus the key question is not the existence but the real consequences. So the oceans rise, never heard of Holland. So it gets warmer, the winters are too cold already. So some plants die off,

plant ones that survive better. It is not the science of Climate Change but the consequences which are often seen as not that bad.

The same is with Income Inequality. Why is it bad? Like why is Climate Change bad? How does it or will it harm me?

Labels: Climate Issues, Commentary, Economics

TERROR AT THE ACADEMY

The book by Losh, *The War on Learning*, is in many ways a terrifying tale of today's higher education. It is a well told and structure narrative that presents to the reader what can and is happening as technology is "introduced" or penetrates the "classes" of education. She presents this in an exceptionally clear and well documented manner and for anyone who has memories of the "old days" of higher education, to paraphrase Dante, "*abandon all hope ye who enter*" the new hallowed halls. The explosion of iPhone and instant capture and exposition of events in the class, the use of anonymous and derogatory Twitter accounts and commentary, crowd events to create chaos, are all elements that thwart modern education.

One must imagine what it must be like to teach under the constant recording eyes and ears of today's technology equipped and entitled students. There appears in Losh's student base to be a total lack of "standards" in deportment in class and that in fact there appears to be an ongoing battle between student and instructor, and in many cases the instructor may very well have been the implementer or facilitator.

Losh focuses on several key areas:

1. The almost ubiquitous explosion of recording methods and the subsequent public display of what has been recorded along with an exposition of the various "social media" outlets. She discusses the recording of some professor whose behavior, albeit well from the norm, would in bygone days become some tale told at reunions, but in today's world it becomes a memorialized video record of an individual disgraced. This memorialized record is then spread worldwide. Thus anyone who is involved in teaching enters a class in total fear of what slips they may make and thus appear to a world audience as some fool. One wonders how the Feynman lectures would have gone over in such a world.

2. The Open Course ware movement and the MOOCs are delved into in some detail. Losh is clearly no dreamer who looks at these as the salvation for education. In fact Losh does a highly credible job on the MOOC issues in examining the human side of them and what they do and frankly what they do not do. As one who has examined well over a two dozen of them, I have seen but one which is truly laudable, that of Lander at MIT, while the others range from acceptable to incredibly useless. The low completion rate should be reflective of something. In addition Losh does reflect upon the ambiguity of expectations that the MOOCs can present, where the student may think they are getting say an MIT education but in reality they are getting a canned videotape lecture at best.

3. The issue of the honor code is well presented as well. One element Losh examines and one which I am often concerned about is Peer Grading and Coursera seems most attuned to that approach. First it is a term which often has no meaning in environments such as MOOCs. There are no peers, namely there are no intellectual equals. Instruction and questions are given in English and half the students are less than proficient in English yet they proceed to use their biases to grade others. One may ask why not just have the proverbial million monkeys grade the papers and take the average! Peer grading is useless. It is a way to pretend that the student is getting fair treatment. Instead it just further facilitates the ranting of anonymous online voices to present their own world views. The second point that Losh discusses is the use of computers to examine for plagiarism. She does a superb job in presenting the many dangers of such a process. For example, if one quotes someone then all too often that quote is marked as plagiarism. In reality it is just a quote, it may have been footnoted, put in quotes italicized, and yet the software will pick it up and list the paper as plagiarized. The weaknesses of many computer based educational tools are all too often exemplified by the blatant weaknesses in these systems. Then there is what appears to be the issue of contracts by adhesion that many students enter into whereby they give up their copyright rights to their writings in order for them to be graded by some of these systems.

4. Education as a product is an excellent discussion section. However it may be useful to recall a quote from Drucker relating his interaction with McLuhan:

"Did I hear you right," asked one of the professors in the audience, "that you think that printing influenced the courses that the university taught and the role of university all together." "No sir," said McLuhan, "it did not influence; printing determined both, indeed printing determined what henceforth was going to be considered knowledge."

The change in technology changed not the way things were presented but the very understanding of knowledge, namely what was true. Thus if one follows Losh and the McLuhan view, the technologies that have been let loose in the classrooms may very well be changing what we consider knowledge, and that may be for good or ill.

5. Gaming is a new paradigm to engage the student. One assumes the assumption is that if students can get involved in games than to engage students in education one must turn it also into a game. However Losh seems to explode that myth as well. She does so with many great examples of how it become frivolous, useless and counter the original intent. Heidegger has a concept called "thrownness", part of being-in-itself. We know something only by being “thrown” or involved in it. We know what a radiologist does with an image and how he manipulates it for understanding by doing the process ourselves. Meaning is obtained in dialog, in a conversational fashion, with the ability to meet consensus. Gadamer and Heidegger both relate meaning to the social process of communicating. Both also relate the evolution of meaning to the ongoing set of discourses. But communications and thrownness is not what we see in gaming. In fact much of gaming is isolation and is the antithesis of conversation. To that end Losh does a highly commendable job.

Overall Losh has written a commendable expose of the less that laudable introductions of technologies into education and the potentials for abuse and misuse. This book is a must read for any academic or those interested in the future of the academy.

Labels: Academy

TUESDAY, MAY 13, 2014

HIGHER EDUCATION: WHAT ARE THEY GETTING?

Technology may very well be the ultimate destroyer of higher education. For example in a recent piece in Science the author states:

...says he's started using such techniques even in large classes. "My introductory biology course has gotten up to 700 students," he says. "For the ultimate class session—I don't say lecture—I'm showing PowerPoint slides, but everything is a question and I use clickers and random calling. Somebody droning on for 15 minutes at a time and then doing cookbook labs isn't interesting." .... estimates that scaling up such active learning approaches could enable success for tens of thousands of students who might otherwise drop or fail STEM courses.

Powerpoint slides are really an bane to instruction and 700 students is just a crowd and not a class. How can one learn in a crowd of 700 and worse the use of these real time entry devices are annoying interruptions to an individual trying to learn.

The old chalk board had and has a place. For example by following a lecture being delivered on a chalk board one looks, then records, and if the class is small enough then asks questions. The use of all these high tech annoyances are counter productive. Every individual thinks differently.

Problem sets, a la Lander and MITX7.01, is the best way to go. Get your hands and mind engaged in doing what is being taught, finding where your understanding fails, correct it, and iterate to learning. That is reality as well. Not clickers!

IMAGING CANCER PROGRESSION

The article in Nature shows how imaging of the growth and progression of cancer cells can be accomplished.

As they state:

First used by cancer biologists in the late 1990s, intravital imaging involves focusing powerful microscopes directly onto exposed tissue in a live, anaesthetized mouse. More labs have adopted intravital imaging as technological improvements have made it possible to peer further into tissue — now as many as 20 cells deep — and to tease out fainter signals. A growing library of molecular markers has given researchers the ability to visualize up to eight different kinds of cells and structures, including various immune-system cells and the endothelial cells that line blood vessels.

They then state:

As intravital imaging of cancer has matured, the field has moved beyond eye-catching films and has begun to generate quantitative data detailing, for example, the speed and direction of moving cells. Such data allow researchers to construct and refine mathematical models of cell behaviour. These could predict, for example, how tumour cells invade tissues, says Friedl.But generating such quantitative data is difficult and time-consuming: analysing the movies can take up to 15 times longer than making them...

We have argued that such data collection could best be accomplished in the context of having a model and then estimating the model parameters and also modifying the model accordingly.

It will be of significant interest to see this area progress. Yet with so many data collection projects having a data analysis methodology is essential.

Labels: Cancer

TUESDAY, MAY 6, 2014

NASA PICTURES

Just a thought that this was an interesting NASA pic.

Labels: Commentary

SATURDAY, MAY 3, 2014

COMMERCIALLY REASONABLE AND THE FCC

The FCC Chair posted in his Blog what he considers as "commercially reasonable" He states:

Let me be clear, however, as to what I believe is not "commercially reasonable" on the Internet:

- *Something that harms consumers is not commercially reasonable. For instance, degrading service in order to create a new "fast lane" would be shut down.*

- *Something that harms competition is not commercially reasonable. For instance, degrading overall service so as to force consumers and content companies to a higher priced tier would be shut down.*
- *Providing exclusive, prioritized service to an affiliate is not commercially reasonable. For instance, a broadband provider that also owns a sports network should not be able to give a commercial advantage to that network over another competitive sports network wishing to reach viewers over the Internet.*
- *Something that curbs the free exercise of speech and civic engagement is not commercially reasonable. For instance, if the creators of new Internet content or services had to seek permission from ISPs or pay special fees to be seen online such action should be shut down.*

In other words, the Internet will remain an open pathway.

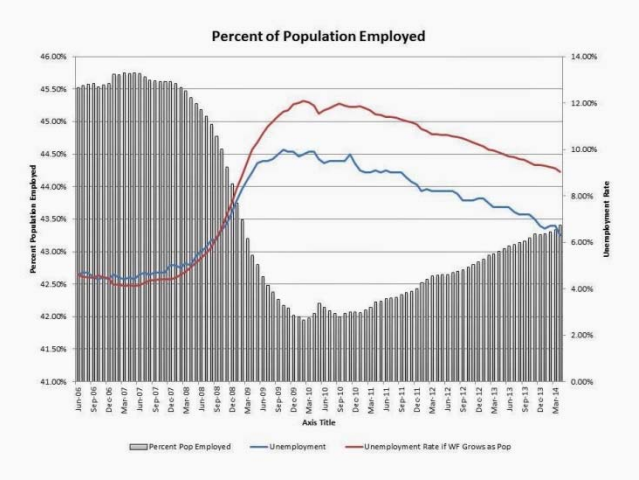
This is the basis of his proposed Internet ruling. Perhaps he does not know that legally no one relies on his blog. The Courts will decide on the term, and his Blog will not even have a footnote reference. He can try to be as clear as he wants but as centuries of legal efforts have disclosed again and again his comments bear no weight. Shame.

Labels: FCC

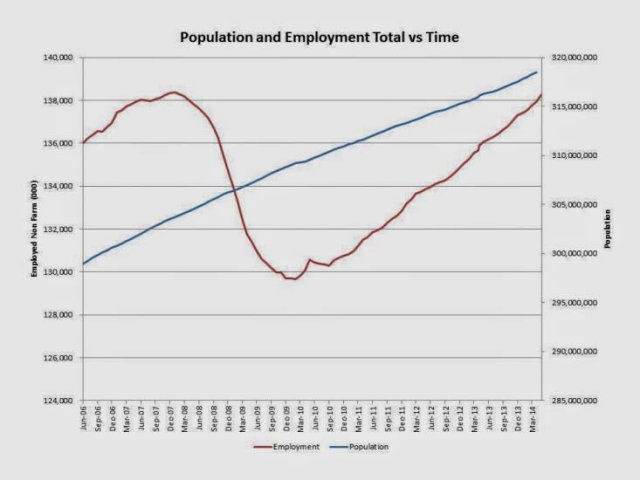
FRIDAY, MAY 2, 2014

EMPLOYMENT: MAY 2014

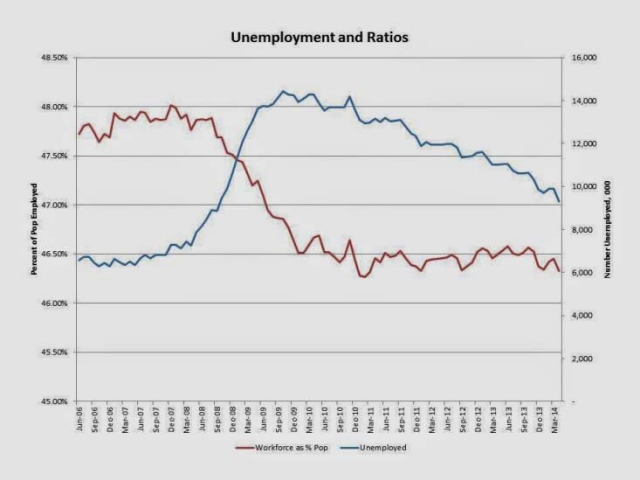
If one can believe the numbers they seem to be improving.



Unemployment has dropped while the percent employed seems to grow. However we are still well below the target percent employed even though we see a lower unemployment.



The above chart shows that good news and a bit more since the rate of increase of percent employed shows steady and steep growth

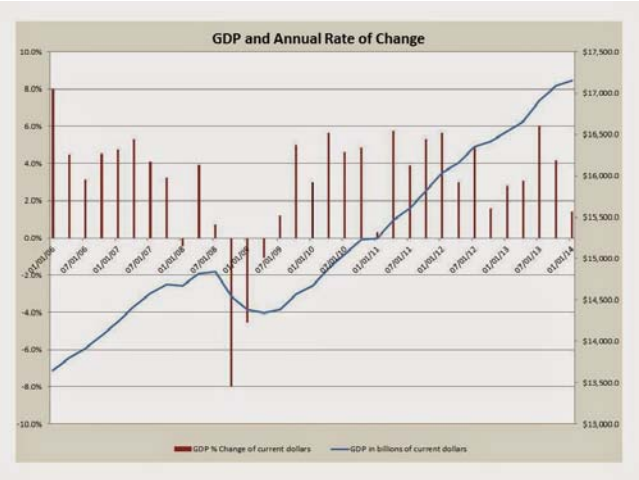


Yet that growth when shown in percent seems somewhat stalled. Thus the picture is still mixed.

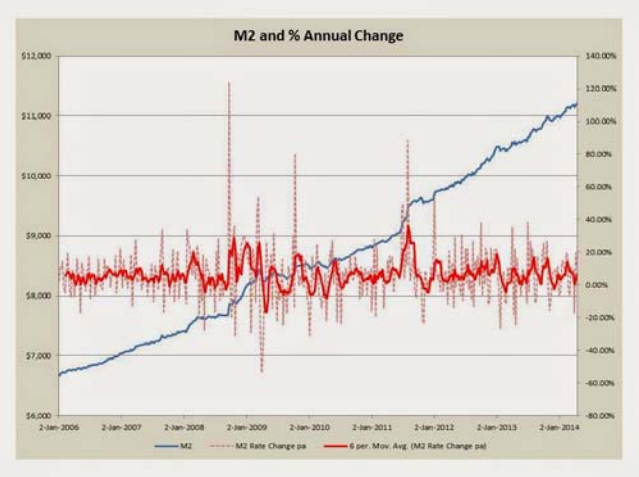
Labels: Economy

WEDNESDAY, APRIL 30, 2014

WEAK GDP AND INCREASING MONETARY BASE

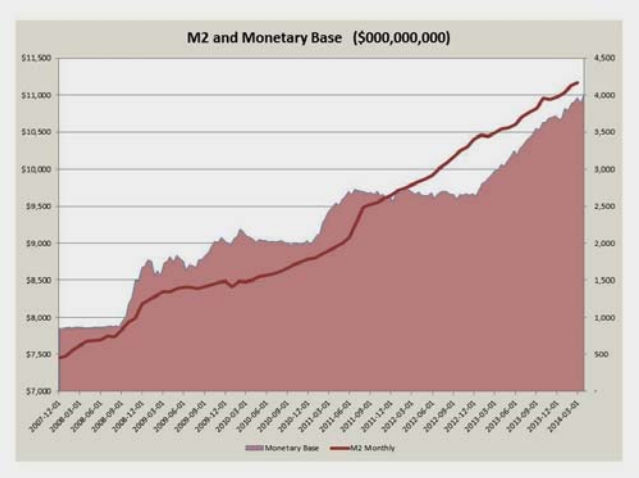


The GDP grew at a very weak rate. As seen above the Q1 2014 rate dropped to the lowest in several years. One can ascribe the sever winter, not global warming, for the drop, but still we have a significant concern.



M2 continues to rise so currency in circulation is strong but then again we have the FED backing by its continued QE efforts.

The Monetary Base also continues to rise. Banks are well off with reserves but none seems to leak into the economy to drive GDP



Comparing M2 and the Monetary Base we see the explosive growth of the MB while M2 maintains reasonable growth. Notwithstanding inflation is low.

Labels: Economy

MONDAY, APRIL 28, 2014

EVIL: FRANCIS AND AUGUSTINE

I have read Augustine and his Theory of Evil. It basically is the lack of good. But evil is a powerful word, a real powerful word. We call Hitler Evil. That has true meaning.

But today Francis tweets:

Inequality is the root of social evil.

With all due respect to The Bishop of Rome, does this mean all inequality is Evil? Some people run better than others, is that Evil? Some people make better investments than others. Is that

Evil?

When one makes such a sweeping indictment then it often tends to reduce the strength of the word.

The Guardian jumped on this quickly. As they say:

But in last autumn's essay, Evangelii Gaudium, Francis wrote that: "Just as the commandment 'Thou shalt not kill' sets a clear limit in order to safeguard the value of human life, today we also have to say 'Thou shalt not' to an economy of exclusion and inequality. Such an economy kills ... Today everything comes under the laws of competition and the survival of the fittest, where the powerful feed upon the powerless. As a consequence, masses of people find themselves excluded and marginalised: without work, without possibilities, without any means of escape. Human beings are themselves considered consumer goods to be used and then discarded." The claim that human beings have an intrinsic value in themselves, irrespective of their usefulness to other people, is one that unites Christianity and socialism. It can be even found somewhere in the shadows of Marxism, but there humans gain their value from history, and when they stand in its way, that's tough for them, as the millions of Stalin's victims could tell us. But if you think the market is the real world, it makes no sense at all, since in the market, value is simply the outcome of supply and demand.

Yes people have individual value, that is the essence of individualism. Yet humans each have a duty to perform, to maximize their potential. Humans ultimately must answer for what they have made of their lives, either to themselves or God. Survival of the Fittest is a view of nature that has a basis in fact. It may not be a norm for social interaction.

I wonder what Augustine would think of this Bishop of Rome?

Labels: Commentary

MORE THOUGHTS ON NET NEUTRALITY

There are two issues before the FCC this week. The Chairman's proposal for Net Neutrality, basically the "mail opening" proposal to charge the consumer for what is inside their mail, and the 3.5 GHz open band.

Consider if you will what may happen.

First, content providers are spread out across the world like polka dots on a map. They need to get to customers.

Second, there are many large broadband backbone entities that can get to the content providers but not to the customers. The largest are Level 3 and Google. Yes Google! Remember that fact.

Third, we poor customers need to get to that backbone so we subscribe at some extortionary rate to a local provider, say a cable company. The cable companies are now trying to lock us in and

make us pay even more.

Fourth, the 3.5 GHz frequency band with 150 MHz of bandwidth is a shared band and could in effect bypass the cable guys and allow us to get in excess of 1 Gbps connect to that backbone out there. It could do so at a low cost. A very low cost. This is the basis of disintermediation, namely a new technology which changes the way things are done.

Fifth, thus the FCC may be sending a poison pill to the cable guys and there may eventually be the demise of these trolls.

Sixth, on the other hand if Google uses its backbone and if it captures this band then perhaps we have created a new AT&T pre-Divestiture.

I really wonder if anyone at the FCC has thought this through, or are even capable of doing this?

Le plus ca change!

Labels: FCC

SUNDAY, APRIL 27, 2014

NET NEUTRALITY: THE SIMPLE VIEW

The FCC was, is and always will be a highly political entity. It, in my opinion, will follow what the strongest winds of politics are at the moment. Having said this, one looks at the current Chairman's alleged proposal for Net Neutrality and in my opinion it appears to have been crafted by Comcast. I do not have any details, but in my experience with them, it smells that way.

Let us examine how the Internet works (see my paper on Net Neutrality).

1, There is a user and a provider. That is to say me and Netflix.

2. I pay my cable company to connect on either transmit or receive to and through them to an interconnection point in the Internet backbone. Not the cable provider's necessarily.

3. Netflix pays a similar backbone provider to connect from their servers to the backbone.

Thus there is a "long-distance" provider, say Level 3, and a local provider say Comcast.

Now Netflix pays Level 3 and I pay, in my case, Cablevision.

Now along comes Comcast and says they they will open my packets, my mail if you will, and if my mail comes from the wrong person they will delay it or charge me more. After all as the customer I pay no matter what.

Net Neutrality means one simple thing; all packets are equal and the cable guy, say Comcast, must not read my mail! After all they are not the NSA, yet they may be helping. But alas that is

another story, I hope.

Thus Net Neutrality means that Netflix negotiates with Level 3 and I with my cable company. Period. And Comcast should not read my mail and interfere with my messages.

But don't count on that! Not with the folks we sent to DC this time!

Labels: FCC

SATURDAY, APRIL 26, 2014

ET GO HOME

As NHPR states they have found ET in New Mexico desert. They state:

For decades, it was mere legend: an "Atari Dump" rumored to harbor millions of copies of E.T. The Extra-Terrestrial, a video game so bad that burying it in the New Mexico desert seemed the best way to move on. But now, the Atari graveyard has been exhumed, and the latest attempt to find the cache of game cartridges has been declared a success. Helped by heavy machinery, a crew found some of the games today, in a dig ...

I remember being at Warner at the time, the Fall of 1982, and I was the Warner Cable interface with Atari. In October they were planning for a $2 billion 1983 and by December the roof collapsed. It was the best education in corporate planning gone amok. There was a flock of the most arrogant people I have ever met and then they were gone. Limousines gave way to the bus. Corporate jets gave way to People's Express.

I recall attending meetings and just wondering what was the basis for their original projections. The answer was always that is was always that way. As if change never occurs. It was one colossal mistake of arrogance after another.Perhaps a lesson for some, yet forgotten for many.

Labels: Commentary

THURSDAY, APRIL 24, 2014

DE TOCQUEVILLE AND PIKETTY: A CONTRAST AND SOME THOUGHTS

Most people who are aware of de Tocqueville know of him solely by his writings on his journeys in the United States. There are two other writings worth reading, one on his journeys through Ireland and the forced slavery imposed upon the Catholics by the Crown, and just as important his understanding of the French Revolution.

Unlike many others who wrote upon the French Revolution, one sees in de Tocqueville the same sense of “at handedness” (to use a Heidegger term) to pull together the collection of events and

circumstances that led to the explosion which became the French Revolution. de Tocqueville is in sharp contrast to the intellectual depth of Israel, he does not bring forth the deep rooted philosophical elements emanating from the Enlightenment, but he details the day to day injustices done by the Government to the people at large. Wealth, the extreme wealth in France for some in pre-Revolution times is not even an issue. It fundamentally is the oppressive control of Paris, the seat of Government on all.

Piketty is almost the anti-de Tocqueville. Whereas de Tocqueville deals with the amalgam of small facts of daily life, the burdens placed upon the people under the presence of the Government, not just the King. de Tocqueville brings to his vision a proximity with the people, not the position of an academic hidden behind a wall of suppositions and beliefs.

Let me address a few key point in the order in which he presents them and they in a sense build the argument will shall make regarding Piketty. One should recall that de Tocqueville wrote his observations of America in 1835 and the reflections on the French Revolution in 1856, after the 1848 revolution again in France. Thus his observations of American reflect those of his youth and those here on the Revolution those just before he died.

Let us start with an observation of France before the Revolution in 1789.

"It was not until the beginning of the sixteenth century…that for the first time the right to work …came to be regarded as a "privilege" purchasable from the King." (p 103)

The above details one of the major issues. Such rights, as that of choosing one's profession, were no longer left to the individual but ascribed as a privilege purchased from the Crown. The Government could dictate, mandate, isolate, individuals based upon its determination of what in its mind and preference it saw and the desired outcome. The individual, no matter what they did, had little if any choice in what they did. The second key point is that it was purchasable. One could always find an entity of the Crown, the Government, to seek out and through a payment obtain what was sought. Thus one may ask if such is the case today in the United States? To a degree, yes. One can seek out the correct lobbyist, who has the correct Congress person, who can promote the desired legislation. The environs of Washington are now akin to a setting of camp followers, all seeking to provide "favors" for payment.

Individualism was not an unknown construct to de Tocqueville. He, to an extent, observed and coined the phrase as something most American. Yet as he explains below, individualism is not solely applicable to that lone person, it is seen even in France, as the ability and even desire of persons to seek satisfaction in the small, not just in the large.

"That word "individualism" which we have coined for our own requirements was unknown to our ancestors for the good reason that in their days every individual necessarily belonged to a group and no one could regard himself as an isolated unit. Nevertheless each of the thousands of small groups of which the French nation was then composed took thought for itself alone; in fact there was so to speak a group individualism which prepared men's minds for the through-paced individualism which nowadays we are familiar." (p 96)

The most telling observation of de Tocqueville was the control over everything by Paris, by the Crown and its agents. All in France was measured, recorded, managed, and controlled via the Crow and its agents from Paris. The English had London but London did not do what Paris managed to do. Lyons was as controlled by Paris as was Bayeux, as was Annecy, as was Reims.

"Owing to this system of centralized information and controlling everything from Paris, a most elaborate machinery had to be set up for coping with the flood of documents that poured in from all sides and even so the delays of the administration were notorious…Not until the century's end when the literary methods we associate with Rousseau and Diderot had begun to make good and affected the spoken language, did the rather maudlin sensibility affected by these authors creep into the style of our administration and even our businesses. Formerly so stiff and desiccated, our official style became unctuous…" (pp 62-63)

His second comment above is quite piercing, namely it is a backhanded swipe at Rousseau and Diderot, the Enclyclopedists. Unctuous indeed was the style, and maudlin was the sense.

Then as stated below is the style of the revolution. He does not take to compare it to America, but to examine it as an act of academic investigation, leaving the details as exercises for the student.

"When we closely study the French Revolution we find that it was conducted in precisely the same spirit as that which gave rise to so many books expounding theories of government in the abstract. Our revolutionaries had the same fondness for broad generalizations, cut-and-dried legislative systems, and a pedantic symmetry; the same contempt for hard facts; the same taste for reshaping institutions on novel, ingenious, original lines; the same desire to reconstruct the entire constitution according to the rules of logic and preconceived system instead of trying to rectify its faulty parts." (p 147)

The telling point above is the contempt for hard facts. The French academic all too often enjoys the mental gymnastics, devoid of the facts that the Scot would bring. The French Enlightenment and the Scottish Enlightenment were revolutions in thought that were at the same time contradictions. Ideas devoid of facts versus Facts embodying ideas. The contrast is Rousseau versus Smith. The issue of rectifying faults is the key refrain. The current best example is the ACA in the United States. Instead of rectifying the faults, most of which were well known, the body politic reshaped reality. The result may very well be the same as that of the intellects in the Revolution.

"I have sometimes asked Americans whom I chanced to meet in their own country or in Europe whether in their opinion religion contributes to the stability of the State and the maintenance of law and order. They always answered, without a moment's hesitation, that a civilized community, especially one that enjoys the benefits of freedom, cannot exist without religion. In fact, an American sees in religion the surest guarantee of the stability of the State and the safety of individuals. This much is evident even to those least versed in political science." p (153)

Now de Tocqueville takes on the Economists, a new type of character whose entry in the eighteenth century foreshadowed this trade's power over many of our current debates.

"Towards the middle of the eighteenth century a group of writer known as the …"Economists" who made the problems of public administration their special study, came to the scene. Thought the Economists figure less prominently than our philosophers in histories of the period and perhaps did less then they towards bringing about the Revolution, I am inclined to think it is from their writings that we learn most of its true character…Their chief targets of attack were those institutions which the Revolution was destined to sweep away forever…" (p 158)

Finally we examine his examination of the ruling passions of the French. He states:

"Readers of this book who have followed carefully my description of the eighteenth century France will have noticed the steady growth amongst the people of two ruling passions…One of these, the more deeply rooted and long-standing was the intense, indomitable hatred of inequality….The other ruling passion, more recent and less deeply rooted, was a desire to live not only on an equal footing but also as free men." (pp 207-208)

The two passions were the drivers of the people; the hatred of inequality and the desire to be free. France looks at Liberty, Equality and Fraternity. Yet when one examines Equality one sees not equality of opportunity but the inequality of a class based society as the concern, as the desire of the people. The inequality was that certain people had privileges perforce of who they or their ancestors were. They were not equal before the law; there was rampant inequality, many getting to the head of the line while many were left behind.

Equality in America is the equality of individualism, that all people are equal before the law, that there is no privilege, that each individual can do with their talents as much as any other and that success is predicated on how well those talents are valued in the market. To the American in de Tocqueville's period, the Government in America empowered the individual, while to the Frenchman at the time of the French Revolution the Government established mass areas of inequality. Americans cherished equality whereas the French detested inequality. This I believe is a core element in the economic politics of Piketty.

Labels: Economics

WEDNESDAY, APRIL 23, 2014

NEW BANDWIDTH AT 3.5 GHZ

The FCC has announced its intent to release some 150MHz of bandwidth at 3.5 GHz. They state:

The Federal Communications Commission today took steps to provide more spectrum for general consumer use, carrier-grade small cell deployments, fixed wireless broadband services, and other innovative uses, through the creation of a new Citizens Broadband Radio Service. The Commission proposed rules for the Citizens Broadband Radio Service in a Further Notice of Proposed Rulemaking that advances the Commission's efforts to meet the growing demand for spectrum by proposing to make 150 megahertz available in the 3.5 GHz Band. The FNPRM proposes innovative spectrum sharing techniques to unlock the value of the spectrum between 3550 MHz and 3650 MHz, and seeks comment on extending the proposed service to 3700 MHz.

Specifically, the FNPRM proposes a three-tiered access and sharing model comprised of federal and non-federal incumbents, priority access licensees, and general authorized access users. Together, the proposals seek to promote flexibility and innovation by leveraging advancements in technology to facilitate sharing between different users and uses, including incumbent government uses.

This may represent a significant opportunity for drastic expansions of broadband. Using MIMO and OFDM alone means well in excess of 1 Gbps capabilities. The only weakness is that propagation at 3.5GHz is line of sight.

This proposal is a result of a PCAST Report. The Report proposes (also see dailywireless piece on this):

Today's spectrum users are in three categories: Federal users, licensed commercial users, and unlicensed commercial users. The proposed system will add three new categories. The first is Federal Primary Access, for legacy Federal users that share their spectrum on a first priority basis with other Federal users or commercial users. Conflict is managed by registering spectrum usage in a database. Secondary Access users are Federal or commercial users that have the next priority to shared Federal spectrum. Applications that require higher power and better quality of service than today's unlicensed devices will benefit from this category, although a fee may be required to access this spectrum. The third category, General Authorized Access, has the lowest priority, and supports less critical low power applications such as meter reading or entertainment.

We have proposed a more robust real time approach almost a decade ago when examining Software Defined Radios and had held discussions with FCC members at the time.

In fact our proposal allowed for real time adaptive spectrum management in a real time bidding approach. The bidding approach also mimicked a Bitcoin payment system. It is good to see that some of these ideas have some legs, albeit very slowly. Then again it is the FCC after all.

Labels: FCC

TUESDAY, APRIL 22, 2014

OBESITY: DISEASE, GENES, OR CHOICE?

There is an ongoing battle over obesity. The AMA decided it was a disease, something that "happens", perhaps due to what a human does, but it is not the sole result of a human decision. It is like mumps, when you go to school and the other kids have it, you get exposed, and blow up. Some look for the genetic link. The refrain, "I can't help it, it is in my genes." has been sounded again and again. Then to my surprise in Nature there is a call for personal responsibility, namely they just eat too much.

The author states:

Obesity is an important contributor to the prevailing burden of chronic disease, lying on the

causal pathway to much of what plagues modern society and its people — heart disease and diabetes to name two of the most serious. However, not only can these diseases develop in the absence of obesity, but not everyone with a high BMI develops any such condition.The categorization of obesity as a disease could have a pernicious influence on efforts to remedy the problem at its true origins. The treatment of diseases customarily involves drugs, medical technology, clinic visits and surgical procedures. If obesity is a disease, the therapeutic advances on which its management depends presumably reside in these domains.

Again, for almost all people, for every 3500 excess kcal we gain a pound. If we burn 2000 kcal per day and we eat 2500 kcal per day, that is three 12 oz sodas, then we can gain a pound a week, or 52 pounds a year!

Thus it is easy to become obese. Frankly it is just as easy to reduce that process, possibly a little slower, but it can be revered.

Thus it is good to hear a voice which lays the problem at the proper doorstep.

Labels: Health Care

MONDAY, APRIL 21, 2014

GOOGLE, FIBER AND THE FRANCHISE

There has been some recent talk of Google and its fiber Odyssey. In a recent ARS Technica piece they discuss the possibility. Having done some New York builds in my time and being still somewhat aware of the process, at no time does anyone seem to address the issue of the Franchise. What do they expect. Just start digging holes, pull the fiber and well? In New York. Ever head of IBEW Local 3? If not then you better learn quickly. You just don't send a team from Palo Alto into the city and pull whatever and wherever.

As the article mentioned above states:

Google recently announced that it chose nine metro areas around the country for potential Fiber deployments. The closest ones to New York City are Raleigh-Durham in North Carolina and Atlanta, Georgia. New York City already has fiber in the form of Verizon FiOS, and Google has focused mostly on underserved areas where municipal officials are willing to provide expedited permitting and other perks. There are still millions of Americans without broadband, so there are plenty of areas where Google Fiber is needed. One thing that is clear is that Google is building up its Fiber team. Job listings indicate that more than 60 positions are open. There is one other Google Fiber position open in New York, for a network infrastructure design manager.

But assuming you break bread with the Union types, a real big assumption, then what of the Franchise? That may take nearly forever. You can bet that if Comcast gets Time Warner that any chance another entity has of doing anything is zero, I have been there.

Lastly, the process of getting a Franchise may very well take forever. The costs are unbelievable. How then can one get any return on investment? That is the key question.

Also, if wireless keeps doing what it is doing and expanding data rates and lowering costs, then why build fiber at all?

The International Business Times lays out a more complete tale. They state:

Underneath Manhattan lies a vast labyrinth of tunnels that was originally built for telephone wire after the Great Blizzard of 1888. It runs from all the way from downtown Manhattan to the Bronx, and it's controlled by Empire City Subway (ECS), a Verizon subsidiary. Verizon claims that it maintains the tunnels, and it points to its own fiber-optic FiOS network as proof. But critics, including one of Verizon's competitors, as well as other businesses that lease the space to run their own cables through there, recently told Crain's New York that the tunnels tell a different story:

"Conduits are filled with cables from defunct Internet providers that went belly-up after the dot-com bust in 2000. Verizon itself left severed copper wire in lower Manhattan ducts after installing a fiber-optic network following Superstorm Sandy. (The company says the cables could be easily removed, if needed.)"

The conduit system that could supply New York with Google Fiber is a crowded mess, which is unlikely to change in the short term. Why would Verizon clear the way for its competition?

Indeed, there are a plethora of obstacles. First the Franchise. We wrote of our recent experiences. That process is endless, meeting after meeting with every citizen having a say. Second is rights of way as discussed above. The incumbent has those rights, not the city. Try and displace them. Third is as mentioned above is the unions. New York makes Afghanistan look like the paradigm of correctness. I suspect there are unions to manage the "Porta Johns". Fourth, is the process of getting permits for this and that. Those who succeed in Real Estate have spent decades mastering this effort. A new guy on the street just cannot master the effort.

But remember the key factor. Wireless now is a winner. OFDM allows 10 bps/Hz, add to it adaptive beamformed antennae and we may get another factor of 5 to 10. Then HDTV can be compressed to 4 Mbps. Thus we can achieve a Gbps speed per user and can send a ton of video, which Verizon already has access to via FIOS. Ever wonder why they abandoned FIOS?

Labels: Google

SUNDAY, APRIL 20, 2014

GETTING A JOB

I am always amazed when I read something about Google, namely is it true or just for the show. I recall being out there visiting the Chairman in the old building which I believe was formerly an Atari facility in one of my prior lives.

But as is stated in today's NY Times by one of the commentators who frequently tries to opine on the technology space, all too often in my opinion with little understanding, Google tries to hire people with certain skills. He states:

...the first thing Google looks for "is general cognitive ability — the ability to learn things and solve problems," he said. In that vein, "a knowledge set that will be invaluable is the ability to understand and apply information — so, basic computer science skills. I'm not saying you have to be some terrific coder, but to just understand how [these] things work you have to be able to think in a formal and logical and structured way." But that kind of thinking doesn't have to come from a computer science degree. "I took statistics at business school, and it was transformative for my career.

Analytical training gives you a skill set that differentiates you from most people in the labor market."
A lot of work, he added, is no longer tied to location. "So if you want your job tied to where you are, you need to be: A) quite good at it; and B) you need to be very adaptable so that you have a baseline skill set that allows you to be a call center operator today and tomorrow be able to interpret MRI scans. To have built the skill set that allows you to do both things requires a baseline capability that's analytical."

The overall discussion is how to get a job at Google. Perhaps it should have been how to get a job period. Now just what the second paragraph above intends to say is too complex for me. Just what does he mean being tied to a location. Back in the 60s we moved every other year, from Boston to New Jersey to Boston, to DC, to Chicago, to Atlanta. Frankly I wonder if this is what he is saying. Then the ability to be a call center operator and a Radiologist is a non sequitur of the highest level. I guess it is just what one would expect from HR and a reporter.

Having just returned from a week trip with grandson number 2 to five colleges in anticipation of his next step, the key issue is what is he doing to get a job? He may still be a High School Freshman but now is the time to start that discussion. He may want at this stage to be a Civil Engineer, a noble calling, but then at his age I wanted to be a jet pilot, not knowing that at 6'3" I

most likely would lose my head if ever ejected. But the earlier one starts the better is the process. He will not get a job as an anthropologist, there are very few of them, unless you are self funded by a large trust fund. Yet there is a continual demand for Civil Engineers, and Chem Es as well.

Thus prior planning does indeed prevent poor performance. It is not just analytical thinking but doing so in a long term perspective, looking forward to have skills which are portable, marketable, and sellable. An electrician always has a better chance that an anthropologist.

Labels: Google

ΚΑΛΑ ΠΑΣΚΑ

Happy Easter!

Labels: Commentary

FRIDAY, APRIL 18, 2014

METHYLATION AND ANCESTORS

Every time we learn more about genes and their operations we add complexity. Epigenetics has added a dimension which oftentimes surpasses much of what we have learned before. In a recent Science article the authors examine the epigenetic differences in humans and their ancestors. They state:

Ancient DNA sequencing has recently provided high-coverage archaic human genomes. However, the evolution of epigenetic regulation along the human lineage remains largely unexplored. We reconstructed the full DNA methylation maps of the Neandertal and the Denisovan by harnessing the natural degradation processes of methylated and unmethylated cytosines. Comparing these ancient methylation maps to those of present-day humans, we identified ~2000 differentially methylated regions (DMRs). Particularly, we found substantial methylation changes in the HOXD cluster that may explain anatomical differences between

archaic and present-day humans. Additionally, we found that DMRs are significantly more likely to be associated with diseases. This study provides insight into the epigenetic landscape of our closest evolutionary relatives and opens a window to explore the epigenomes of extinct species.

This is an interesting first step well worth the following!

One suspects that the more we understand methylation, miRNAs etc the better we can understand some of the vagaries of life.

Labels: Epigenetics

QALYS AND "DEATH PANELS"

One of the major controversies on the ACA roll out was the use of QALYs as a means to ascertain what treatment was best. A QALY is a British construct to control NHS expenditures. Thus if you are say 75, and have prostate cancer, then the NHS may very well deny you any treatment. After all you are dead in 7 years anyway, and so you may die a bit quicker it is cheaper than way. That in a way is a "Death Panel" After all it does not take into account you as an individual and your individual state of health. You are deemed to be part of a group of 75+ year old males.

Now the ACA was to have prohibited that. Yeah, that is what they said. But today the NY Times has a piece that says that although the ACA does not expressly state that the "Societies" are doing it on their own.

They state:

..., a visiting scientist in the ethics department at the National Institutes of Health, said the move by some societies to incorporate economic analysis "heralds an important shift in the way doctors in America are talking about cost and value."

He said that having societies do such evaluations was better than having a doctor make such trade-offs while treating an individual patient, which is sometimes called bedside rationing. Still, it is unclear if medical societies are the best ones to make cost assessments. Doctors can have financial conflicts of interest and lack economic expertise.

The cardiology societies, for instance, plan for now to rely on published literature, not commission their own cost-effectiveness studies, said ... a professor at Stanford and co-chairman of the committee that wrote the new policy.

They plan to rate the value of treatments based on the cost per quality-adjusted life-year, or QALY — a method used in Britain and by many health economists.

The societies say that treatments costing less than about $50,000 a QALY would be rated as high value, while those costing more than $150,000 a QALY would be low value. "We couldn't go on just ignoring costs," ... said.

So the Dems in DC are not expressly killing off the older folks they have apparently gotten certain allies in Health Care to do the dirty task for them. I have written extensively on QALY analysis and it is filled with many bias elements, especially against health older men. So do we read a message here or what?

Labels: Health Care

THURSDAY, APRIL 17, 2014

CRISPR PATENT

The PTO had issued a patent on CRISPR to Broad and MIT. This is the beginning of something interesting.

Filed 15 October 2013 and Issued 15 April 2014! The PTO has not moved this fast since Edison!

The prime claim is:

What is claimed is:

1. A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non- 5 naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system comprising one or more vectors comprising:

a) a first regulatory element operable in a eukaryotic cell 10 operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and

b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a 15 Type-II Cas9 protein,

wherein components (a) and (b) are located on same or different vectors of the system, whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least 20 one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

Labels: Cancer

THURSDAY, APRIL 10, 2014

PROSTATE CANCER: GENETICS AND EPIGENETICS

There has been an explosion in genetic "causes" for many cancers and prostate cancer, PCa, is not the exception. We have completed a White Paper which covers the material herein in some detal.

One of the most significant factors has been the ability by some to take metrics of multiple gene expressions and allege that with the proper weightings these single dimensional metrics are prognostic. The problem with the metrics is often that they do not relate to actual genetic control mechanisms. We consider here an example in PCa of several genes and miRNAs which taken together create a putative malignant state.

Specifically we examine three elements:

1. p53, the classic oncogene which is a control element for keeping cells in a homeostatic state and avoiding malignant changes.

2. miRNA 34, or miR-34 which is a micro RNA and is also found to have a controlling effect upon a cell.

3. MET, a tyrosine kinase receptor which can be activated by HGF, the hepatocellular growth factor ligand, and which can activate multiple pathways and if activated and done so in an uncontrolled manner can result in malignancies.

This examination is predicated on a recent paper by Cheng et al (2014) which discusses the joint regulation effects of p53 and miR-34.

This section discusses the micro RNA process and its impact on PCa. Micro RNAs, miRNA, are small single stranded RNAs which when in the cytoplasm may often bind to other RNA on complement binding sites and thus change or incapacitate the mRNA to which it binds from being translated into a protein. Craig Mello was awarded the Nobel Prize in 2006 for the discovery and his Nobel Lecture provides an excellent overview of the early stages of miRNA investigation.

In a recent paper by Cheng et al (2014) they state:

The miR-34 family was originally found to be a direct target of p53 and is a group of putative tumor suppressors. Surprisingly, mice lacking all mir-34 genes show no increase in cancer formation by 18 months of age, hence placing the physiological relevance of previous studies in doubt.

Here, we report that mice with prostate epithelium-specific inactivation of mir-34 and p53 show expansion of the prostate stem cell compartment and develop early invasive adenocarcinomas and high-grade prostatic intraepithelial neoplasia, whereas no such lesions are observed after inactivation of either the mir-34 or p53 genes alone by 15 months of age.

Consistently, combined deficiency of p53 and miR-34 leads to acceleration of MET-dependent growth, self-renewal, and motility of prostate stem/ progenitor cells.

Our study provides direct genetic evidence that mir-34 genes are bona fide tumor suppressors and identifies joint control of MET expression by p53 and miR-34 as a key component of prostate stem cell compartment regulation, aberrations in which may lead to cancer

This is a murine model which putatively demonstrates that a blocking of both miR-34 and p53 leads to PCa. Specifically, this is MET pathway dependent growth.

As noted in Bioscience Technology[67][1]:

Previous research at Cornell and elsewhere has shown that another gene, called p53, acts to positively regulate miR-34. Mutations of p53 have been implicated in half of all cancers. Interestingly, miR-34 is also frequently silenced by mechanisms other than p53 in many cancers, including those with p53 mutations.

The researchers showed in mice how interplay between genes p53 and miR-34 jointly inhibits another cancer-causing gene called MET. In absence of p53 and miR-34, MET overexpresses a receptor protein and promotes unregulated cell growth and metastasis.

This is the first time this mechanism has been proven in a mouse model, said Alexander Nikitin, a professor of pathology in Cornell's Department of Biomedical Sciences and the paper's senior author. Chieh-Yang Cheng, a graduate student in Nikitin's lab, is the paper's first author.

In a 2011 Proceedings of the National Academy of Sciences paper, Nikitin and colleagues showed that p53 and miR-34 jointly regulate MET in cell culture but it remained unknown if the same mechanism works in a mouse model of cancer (a special strain of mice used to study human disease).

The findings suggest that drug therapies that target and suppress MET could be especially successful in cancers where both p53 and miR-34 are deficient.

Also, the number of stem cells in mice with both p53 and miR-34 silenced increased substantially compared with control mice or mice with only miR-34 or p53 independently silenced.

"These results indicated that together [miR-34 and p53] regulate the prostate stem cell compartments," said Nikitin.

This is significant, as cancer frequently develops when stem cells become unregulated and grow uncontrollably, he said.

[67][1] http://www.biosciencetechnology.com/news/2014/03/gene-family-proven-suppress-prostate-cancer also http://www.news.cornell.edu/stories/2014/03/gene-family-proven-suppress-prostate-cancer

Researchers further found that p53 and miR-34 affect stem cell growth by regulating MET expression. In absence of p53 and miR-34, MET is overexpressed, which leads to uncontrolled growth of prostate stem cells and high levels of cancer in these mice.

From Tang's Lab at MD Anderson we have[68][2] (see Liu et al):

Cancer stem cells (CSCs), or tumor-initiating cells, are involved in tumor progression and metastasis1. MicroRNAs (miRNAs) regulate both normal stem cells and CSCs and dysregulation of miRNAs has been implicated in tumorigenesis6. CSCs in many tumors—including cancers of the breast, pancreas, head and neck, colon, small intestine, liver, stomach, bladder and ovary—have been identified using the adhesion molecule CD44, either individually or in combination with other marker(s).

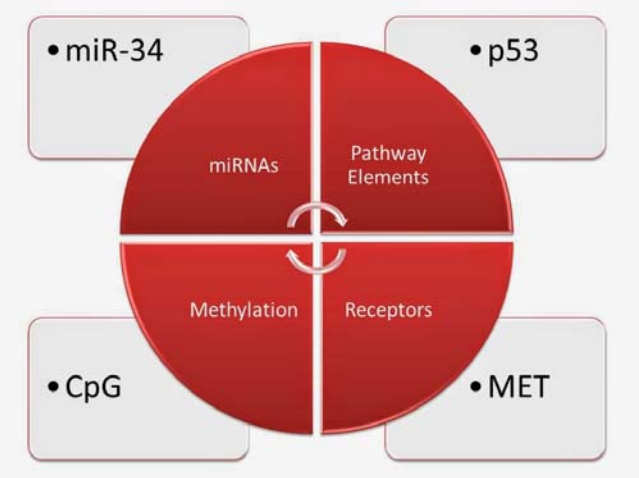
Prostate CSCs with enhanced clonogenic17 and tumor-initiating and metastatic capacities are enriched in the CD44+ cell population, but whether miRNAs regulate CD44+ prostate cancer cells and prostate cancer metastasis remains unclear. Here we show, through expression analysis, that miR-34a, a p53 target was underexpressed in CD44+ prostate cancer cells purified from xenograft and primary tumors.

Enforced expression of miR-34a in bulk or purified CD44+ prostate cancer cells inhibited clonogenic expansion, tumor regeneration, and metastasis. In contrast, expression of miR-34a antagomirs in CD44− prostate cancer cells promoted tumor development and metastasis. Systemically delivered miR-34a inhibited prostate cancer metastasis and extended survival of tumor-bearing mice.

We identified and validated CD44 as a direct and functional target of miR-34a and found that CD44 knockdown phenocopied miR-34a overexpression in inhibiting prostate cancer regeneration and metastasis. Our study shows that miR-34a is a key negative regulator of CD44+ prostate cancer cells and establishes a strong rationale for developing miR-34a as a novel therapeutic agent against prostate CSCs.

Overall we examine here a four part set of elements related to PCa; receptors, pathway elements, mi RNAs and methylation. We outline this graphically below:

[68][2] http://staging-www.nature.com/nm/journal/v17/n2/full/nm.2284.html



Note that in the above each plays a role in the development of PCa.

This has been known for a while. We see in Yamamura et al (2012) that they observed:

MicroRNA-34a (miR-34a), a potent mediator of tumor suppressor p53, has been reported to function as a tumor suppressor and miR-34a was found to be downregulated in prostate cancer tissues. We studied the functional effects of miR-34a on c- Myc transcriptional complexes in PC-3 prostate cancer cells. Transfection of miR-34a into PC-3 cells strongly inhibited in vitro cell proliferation, cell invasion and promoted apoptosis. Transfection of miR-34a into PC-3 cells also significantly inhibited in vivo xenograft tumor growth in nude mice. miR-34a downregulated expression of c-Myc oncogene by targeting its 39 UTR as shown by luciferase reporter assays. miR-34a was found to repress RhoA, a regulator of cell migration and invasion, by suppressing c-Myc–Skp2–Miz1 transcriptional complex that activates RhoA.

Overexpression of c-Myc reversed miR-34a suppression of RhoA expression, suggesting that miR-34a inhibits invasion by suppressing RhoA through c-Myc. miR-34a was also found to repress c-Myc-pTEFB transcription elongation complex, indicating one of the mechanisms by which miR- 34a has profound effects on cellular function. This is the first report to document that miR-34a suppresses assembly and function of the c-Myc–Skp2–Miz1 complex that activates RhoA and the c-Myc-pTEFB complex that elongates transcription of various genes, suggesting a novel role of miR-34a in the regulation of transcription by c-Myc complex.

It is interesting to see that we have a miRNA as a tumor suppressor. It is a key change in the way we can understand the overall pathway control paradigm. Thus the miRNA acts in a powerful manner to modulate cell growth and proliferation.

Micro RNA

The development of our understanding of micro RNAs has evolved from that of elements just left over to key control factors in major pathway expression. From Pekarik et al:

Among all previously described factors involved in the initiation and development of prostate cancer another element interconnecting several cellular processes may be traced. This element is represented by microRNAs (miRNAs), short non-coding regulatory molecules involved in multitude of processes in eukaryotic cells. They play a role in virtually each step of tumour formation and progression. miRNAs networks affect apoptotic pathways, cellular growth, responsiveness to growth factors and anticancer drugs, inhibit expression of tumour suppressor genes or permit expression of oncogenes.

Classical textbooks refer to carcinogenesis as a harmonic process caused by a loss of function of tumour suppressor genes and simultaneous activation of oncogenic genes. Recent progress in miRNAs function studying did not change this definition substantially; it only extended our understanding of regulation of this intrinsic network by miRNAs which can be likewise characterised as oncogenic miRNAs and antitumour miRNAs.

Indeed, we now see that tumor growth is a highly complex amalgam of genetic elements and supra-genetic elements as well. We have also argued that in many cases we see extracellular matrix interactions as well as free radical excitation of cells as well.

Oncogenic miRNAs are those that directly or indirectly suppress gene expression of tumour suppressors or proapoptotic genes and vice versa anti-tumorigenic miRNAs are those that reduce expression of oncogenic proteins. miRNAs are involved in nearly all types of cancer studied so far and they target classical oncological pathways. However, certain miRNAs were specifically associated with defined tumour types suggesting that they are involved in specific processes related to a cancer type or a tissue of origin. With regard to the number of genes regulated by miRNAs it is not surprising that these small regulatory molecules play a role also in the resistance of cancer cells to various anti-cancer drugs. In that respect, miRNAs become very attractive target for potential therapeutic interventions.

Recent research has revealed existence of miRNAs circulating in human blood serum. More surprisingly, it was found that levels of various miRNAs are altered in response to various physiological changes and some of these changes are well correlated with tumour existence. This makes circulating miRNAs a very attractive non-invasive cancer biomarker.

miRNAs have come to the fore as one of the several epigenetic factors which can precipitate various malignancies. The added factor of methylation as a silencing mechanism also adds to but further complicates the understanding of cancer progression. Thus, when we see loss of a miRNA, we may actually be indirectly observing the effects of methylation of the CpG region about that miRNA encoding region.

The relationship between miRNAs and pathway control elements is now being better understood. From Yamamura et al:

MicroRNAs (miRNAs) are highly conserved, single stranded, non-coding RNAs of approximately 22 nucleotides that regulate gene expression by posttranscriptional silencing of specific target mRNAs, by repressing translation or cleaving RNA transcripts. miRNAs regulate diverse cellular

processes such as cell-cycle progression, proliferation, apoptosis and development. miRNAs have been shown to function as oncogenes or tumor suppressor genes.

The p53 tumor suppressor is deleted or mutated in more than 50% of human tumors and is a key molecule which suppresses malignancies. p53 has been found to target the miR-34 family and the ectopic expression of miR-34 genes has drastic effects on cell proliferation and survival. Ectopic miR-34a causes cell-cycle arrest in the G1 phase and apoptosis. As p53 has been found to target miR-34a and since, cell-cycle arrest and apoptosis are also end points of p53 activation, the miR-34a gene may be a mediator of p53 function. The proto-oncogene c-Myc regulates cell proliferation and transformation both transcriptionally and non-transcriptionally and is frequently deregulated in human cancers

miR-34 is one of now hundreds of micro RNAs, which are short, generally 22 base pairs, and non-coding RNA segments. They are now well known as control elements in the expression of genes and have significant control mechanisms.

miR-34 Structure

From NCBI[69][3] (1p36.22; 1p36.22):

microRNAs (miRNAs) are short (20-24 nt) non-coding RNAs that are involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. miRNAs are transcribed by RNA polymerase II as part of capped and polyadenylated primary transcripts (pri-miRNAs) that can be either protein-coding or non-coding.

The primary transcript is cleaved by the Drosha ribonuclease III enzyme to produce an approximately 70-nt stem-loop precursor miRNA (pre-miRNA), which is further cleaved by the cytoplasmic Dicer ribonuclease to generate the mature miRNA and antisense miRNA star (miRNA) products. The mature miRNA is incorporated into a RNA-induced silencing complex (RISC), which recognizes target mRNAs through imperfect base pairing with the miRNA and most commonly results in translational inhibition or destabilization of the target mRNA.*

There has been a great amount of research regarding the impact of miRNA on cancer and especially on PCa. miRNAs may downregulate tumor suppressor genes such as PTEN. This has been seen in miRNA 21. Colin and Croce have provided several review article regarding miRNA and their influence on cancers. They argue that miRNA alterations are heavily involved in the initiation of many cancers. Their focus had been on CLL, chronic lymphocytic leukemia, and its initiating miRNAs, miR 15 and miR 16. Coppola et al (2010) provide a detailed summary of miRNAs and PCa.

For example miR34 can cause the activation and recapitulate p53 which in turn induces cell cycle arrest and apoptosis. Loss of the miR34 can result in the impairment of the p53 control of

[69][3] http://www.ncbi.nlm.nih.gov/gene/407040

apoptosis and permit the cells to proliferate. Coppola et al perform a detailed analysis of all of the above related miRNAs and their resultant impact on PCa. miR-21 up-regulation leads to PTEN loss and thus is an oncogene.

Recent work by Poliseno et al has shown that PTEN can be down regulated via miR-106b. It had already been known that PTEN could be down-regulated by miR-22, miR-25 and miR-302. Their work demonstrated that miR-22 and miR-106b are overexpressed in PCa miR-106b is an intronic miRNA. The work of Poliseno thus has demonstrated a proto-oncogenic miRNA dependent network that regulates PTEN and thus can have a significant role in initiating PCa.

Micro RNAs are regulators of mRNA, the post transcriptional result which is then used to generate via translation the operative protein. Currently there are nearly 1,000 identified miRNAs. They are generally 22 nucleotides long, short segments, and they usually target specific mRNA and silence it. Each one of the miRNA may act upon many mRNAs.

As He and Hannon state:

Non-coding RNAs participate in a surprisingly diverse collection of regulatory events, ranging from copynumber control in bacteria[1] to X-chromosome inactivation in mammals[2].MicroRNAs (miRNAs) are a family of 21–25-nucleotide small RNAs that, at least for those few that have characterized targets, negatively regulate gene expression at the post-transcriptional leve.

Members of the miRNA family were initially discovered as small temporal RNAs (stRNAs) that regulate developmental transitions in Caenorhabditis elegans[6]. Over the past few years, it has become clear that stRNAs were the prototypes of a large family of small RNAs, miRNAs, that now claim hundreds of members in worms, flies, plants and mammals.

The functions of miRNAs are not limited to the regulation of developmentally timed events. Instead, they have diverse expression patterns and probably regulate many aspects of development and physiology. Although the mechanisms through which miRNAs regulate their target genes are largely unknown, the finding that at least some miRNAs feed into the RNA INTERFERENCE (RNAi) pathway has provided a starting point in our journey to understand the biological roles of miRNAs.

miRNAs are simple yet complex entities and key players in the epigenetics which control gene expression.

It is clear from the above that miRNAs can positively and negatively impact many elements in the pathways we have considered in HGPIN and PCa. Coppola et al review several of the key ones. For example:

- miR-146: Down regulates the AR.
- miR-34: Can recapitulate p53 resulting in apoptosis and arrest.
- miR-23: can result in c-myc overexpression and cell proliferation.

In a recent paper by Poliseno et al they have identified several others:

- miR-106b: Down-regulates PTEN and triggers PIN in murine models.
- miR-22, miR-25, miR-302: Down-regulating of PTEN.

Similarly the papers by Petrocca et al and that by Calin and Croce detail many of the miRNAs and their impacts on many cancers. As seen in the above graphic these are but a few in the overall targeting of PCa control genes. As Coppola et al state:

The hypothesis that miRs can be regarded as new broad-spectrum oncogenes or tumor suppressor genes has opened a revolutionary field of research with exciting diagnostic and therapeutic perspectives.

The compelling hint of a widespread miR deregulation in cancer pathogenesis came from the analysis of the genomic distribution of 186 miR. In this study, it was demonstrated that more than half of them mapped in cancer-associated genomic regions, namely in chromosomal sites prone to deletions, amplifications or recombinations. These aberrations can result in miR down- or up-regulation, conferring selective advantages to mutated cells.

Additional mechanisms of miR deregulation include altered expression of miRs as a consequence of excessive or deficient processing; aberrant transcription of the precursors by epigenetic silencing of miR promoters or as a result of the activity of oncogenic transcription factors; and more rarely, point mutations in mature miRs or in target sequences that can interfere with normal target recruitment

The problem that we will have in any modeling of HGPIN and PCa is not only do we have issues regarding the somewhat well-known genes but the impact of the epigenetic factors is unknown, complex, and possibly random.

Furthermore miRNAs can act in a positive or negative manner depending upon the cell and the activated networks in the cell. From Croce (2009) we have:

Importantly, miRNAs should not be described as oncogenes or tumor suppressor genes, unless the tissue or cell type involved in their action is specified. For example, miR-221 and miR-222 target an oncogene, KIT, and inhibit the growth of erythroblastic leukaemia[30], and therefore function as tumor suppressors in erythroblastic cells. but they also target at least four important tumor suppressors — phosphatase and tensin homologue (PTEN), p27, p57 and tissue inhibitor of metalloproteinases 3 (TIMP3) — and function as oncogenic miRNAs by suppressing these tumor suppressors in various human solid tumours[31] (TABLE 1). Therefore, before describing an miRNA as a tumor suppressor or an oncogene, it is necessary to specify in which cell or tissue, as cellular context is crucial for the function of miRNAs….

Recent work on miR-34 has demonstrated its impact on p53 (Rokhlin et al) and the fact that miR-34 significantly mediates the role of p53 in apoptosis in AR dependent PCa.

As Sevli et al state:

The miRNAs have critical functions in gene expression and their dysregulation may cause tumor formation and progression. Today, it is known that tumors possess widespread deregulated miRNA levels. Over-expression or down-regulation of specific miRNAs in different tumor types make them potential therapeutic targets and diagnostic markers. Up-regulated miRNAs inhibiting tumor suppressor genes in tumor cells are commonly termed as oncogenic miRNAs or oncomirs. The miRNAs whose down-regulation promotes tumor progression are tumor suppressor miRNAs. One type of mRNA may possibly be targeted by multiple different miRNAs with variable efficiencies. Conversely, a single miRNA may target more than one mRNA. Thus, to be able to observe a tumorigenic phenotype, some significant changes should occur in microRNome content of the cells.

MiRNA and Stem Cells

As we have indicated elsewhere, the concept of the cancer stem cell has received significant attention. There has also been a great deal of work on the area of linking miRNAs and the stem cell model for PCa. In a recent work by Liu et al (2011) the authors demonstrate the nexus between miR-34a and its ability to inhibit PCa stem cells by directly repressing CD44. They observe that cancer stem cells have been observed in many solid cancers by using the fact that CD44 adheres to the cell surface. PCa stem cells with enhance clonogenic and tumor initiating and metastatic capacities are often enriched with CD44+ cell population. The work of Liu et al demonstrated that the administration of miR-34a to PCa cells inhibited PCa metastasis and inhibited PCa regeneration. This is one of the first uses of miRNA as a tumor suppressor.

In a recent paper by Xia (2008) the author states:

The key characteristics of stem cells are that they are capable of self-renewal and differentiation. The mechanisms by which stem cells maintain self-renewal and differentiation are complicated. In the past years, protein-coding genes had been broadly investigated in stem cell self-renewal and differentiation.

Recent studies indicate miRNAs as one of the most abundant classes of post-transcriptional regulators proved to be crucial in a wide range of biological processes, which suggest that miRNAs may also play essential roles in stem cell self-renewal and differentiation. Disruption of Dicer function in murine ESs influences miRNA processing and greatly impairs their ability to differentiate …

Cancer stem cells (CSCs) are the cells within a tumor that possess the capacity to self-renew and to produce the heterogeneous lineages of cancer cells that comprise the tumor. CSCs can thus only be defined experimentally by their ability of self-renewal and tumor propagation.

The implementation of this approach explains the use of alternative terms in the literature, such as "tumor-initiating cells" to describe putative CSCs. …

The identification of growth and differentiation pathways responsible for CSC proliferation and survival will help in the discovery of novel therapeutic targets. Previous studies have shown that many signal pathways may participate in regulating CSC functions, including Wnt/β-catenin,

Notch, and Sonic hedgehog homolog (SHH). The canonical Wnt cascade has emerged as a critical regulator of stem cells and activation of Wnt signalling has also been associated with various cancers …

CSC maintenance is dependent on β catenin signaling. Moreover, because Wnt/β-catenin signalling is not essential for normal epidermal homeostasis, such a mechanistic difference may thus be targeted to eliminate CSCs and consequently eradicate squamous cell carcinomas. It is therefore hypothesized that inhibition of Wnt signaling may provide an effective way to reduce the unwanted stem cell renewal which results in cancers.

Inhibition of Wnt signalling may prove to be an effective road to inhibit the uncontrolled cell renewal that drives cancer. Acting as novel and pivotal regulators of protein-encoding genes, miRNAs will have great potential in regulating CSCs' biological functions by targeting CSCs-related signal pathway molecules.

We have performed various analyses of CSCs especially for PCa. This is a critical area for ongoing research and most likely will prove quite useful.

MET

MET is a tyrosine kinase receptor. It is activated by HGF the hepatic growth factor and it in turn activates a multiplicity of pathways. It is considered a proto-oncogene and thus is of general concern. From NCBI[70][4]:

The proto-oncogene MET product is the hepatocyte growth factor receptor and encodes tyrosine-kinase activity. The primary single chain precursor protein is post-translationally cleaved to produce the alpha and beta subunits, which are disulfide linked to form the mature receptor. Various mutations in the MET gene are associated with papillary renal carcinoma.

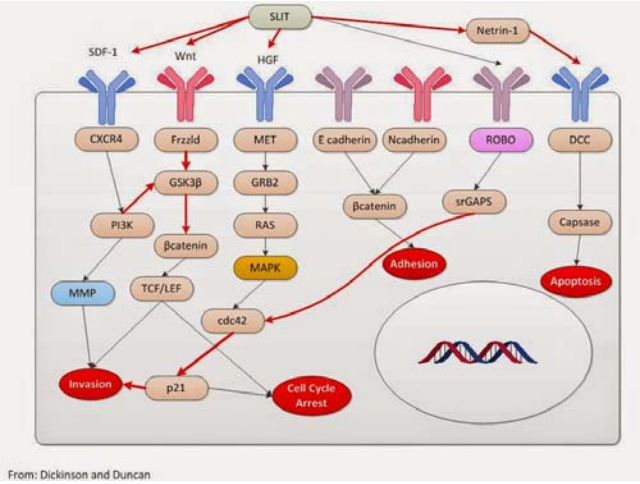
MET is located on 7q31. We now examine the MET structure and then examine its control over several pathways.

From Benvenuti and Comoglio we have:

Both MET and RON are tyrosine kinases crucially involved in the control of the ''invasive growth'' (Giordano et al., 2002). Under physiological conditions such as embryonic development and organ regeneration, they contribute to establishing the normal tissue patterning by orchestrating cellular proliferation, disruption of intercellular junctions, migration through the EMC and protection from apoptosis. In transformed tissues, receptor deregulation is responsible for cancer progression and metastasis formation and dissemination. Either upon ligand stimulation or receptor constitutive activation, cancerous cells are induced to leave the primary tumor, degrade the basal membrane, move towards different organs and there give rise to metastasis

[70][4] http://www.ncbi.nlm.nih.gov/gene/4233

MET controls many pathway elements in a cell. We show some of them in the Figure below from Dickinson and Duncan. Note the HGF binds to MET and thus it activates a set of pathways facilitating invasion and stopping cell cycle arrest.



The above demonstrates the MET pathway and its relationship to the many other key pathways.

MET can be over expressed and over activated and the result is a malignant growth. Thus MET has the potential for becoming a significant factor in cancer development. From Benvenuti and Comoglio:

It has been extensively demonstrated that when used in a deviant cellular environment and without spatial and temporal regulation, MET exerts a major role in tumor formation and progression. Cells which over-express either MET or HGF are tumorigenic when implanted into nude mice and become extremely metastatic, moreover transgenic mice for either MET or HGF develop metastatic tumors while, on the contrary, endogenously expressing cancer cells become less aggressive when MET is switched off.

In the above the issue is over expression. The question is; what is driving that over expression? Is it truly an excess production or a loss of control or modification? Is this on a cell by cell basis or is it pandemic? They continue:

Accordingly, it was demonstrated that short hairpin RNA (shRNA) mediated MET knockdown in rabdomyosarcomas (RMS)-derived cell lines greatly affects cell proliferation, survival and invasion. Furthermore in xenograft models of RMS MET silencing produced a dramatic reduction of tumor mass. Similar results were obtained silencing MET in lung cancer cell lines harboring MET amplification. In those cell lines receptor silencing (once more achieved by shRNA technology) induced a significant growth inhibition; notably the silencing sorted no effects on cell lines that did not display receptor gene amplification.

This seems to answer the question regarding complete cell line activation.

It has been extensively described, both in animal models and in normally occurring human cancers, that constitutive activation of MET can be achieved in three different ways:

(i) with establishment of ligand-receptor autocrine loops;

(ii) via receptor over-expression, and

(iii) in presence of activating point mutations in the receptor coding sequence.

Ligand-receptor autocrine circuits make cells independent from the need of growth factors; receptor over-expression triggers receptor oligomerization and reciprocal activation even in absence of ligands; point mutations generate constitutively active receptors.

This last event is extremely uncommon; however, some missense point mutations have been described in MET coding sequence in certain human cancers.

The above discussion describes the ways in some detail. The causes of over expression could then be addressed as a therapeutic methodology. They continue:

Particularly missense mutations located in the tyrosine kinase domain of MET were described in patients who suffer from hereditary and sporadic papillary renal-cell carcinomas and head and neck squamous-cell carcinomas, whereas alterations in the juxta-membrane region were mainly found in human gastric and lung cancers

The above does also present the issue of mis-sense mutations, changes that may not change anything but may cause a cessation of genetic progression.

Observations

The paper which we have used to initialize the focus on this report is one which combines: mir-34, MET, p53, and methylation. It is an amalgam of receptors of the kinase inhibitor variety, key pathway oncogenes, miRNAs and methylation. It is an interplay between all of the complex elements which are now known in cancer genetics.

The Cheng et al results are simply as follows:

1. miR-34 Cooperates with p53 in Suppression of Prostate Carcinogenesis
2. p53 and miR-34 Cooperate in the Control of Prostate Stem/Progenitor Cell Activity
3. p53 and miR-34 Regulation of Stem/Progenitor Cells Depends on MET

However in their conclusions we have also introduced the methylation effects as well. They conclude:

Our study provides direct genetic proof that miRNAs of the miR-34 family may act as tumor suppressors in concert with other genes, such as p53. These findings offer a solid physiological basis for the rational design of diagnostic and therapeutic approaches. Because the lack of mir-

34 genes alone is insufficient for cancer initiation, their downregulation is likely to occur at some point during tumor progression.

However, the preexistence of mir-34 methylation in some normal cells cannot be excluded. Further genomic studies in conjunction with animal modeling should be able to address this question. Although our current studies have been focused on prostate cancer, tissue-specific inactivation of mir-34 and p53 in other tissues will address likely interactions of these genes in other cell lineages.

Thus we have exhibited here a complex interplay between types of cell control mechanisms. The challenge will be how best to model this complex interplay. In our prior analyses we have let epigenetic factors be secondary and considered almost as noise. Here, however, they are pari passu with all other elements and must be considered expressly.

Also Liu et al from Tang's Lab state:

We have shown that miR-34a is underexpressed in tumorigenic CD44+ prostate cancer cells and that it has potent antitumor and antimetastasis effects. Our results establish miR-34a as a key negative regulator of CD44+ prostate cancer cells and CD44 as an important target of miR-34a. Our findings suggest that reduced expression of miR-34a in prostate CSCs contributes to prostate cancer development and metastasis by regulating expression of CD44 and the migratory, invasive and metastatic properties of CSCs

Tang's Lab has done extensive work on PCa CSC and the implications of reduced miR-34 are significant. The issue here is several fold. First, the measure of miR-34 activity can be prognostic. Second, the reasons for reduced miR-34 is of prime concern. As we shall note later, the cause may be methylation of CpG clusters. Thus if one were to try anti-methylation drugs, would that assist? There is always a concern here since anti-methylation therapeutics are non-selective.

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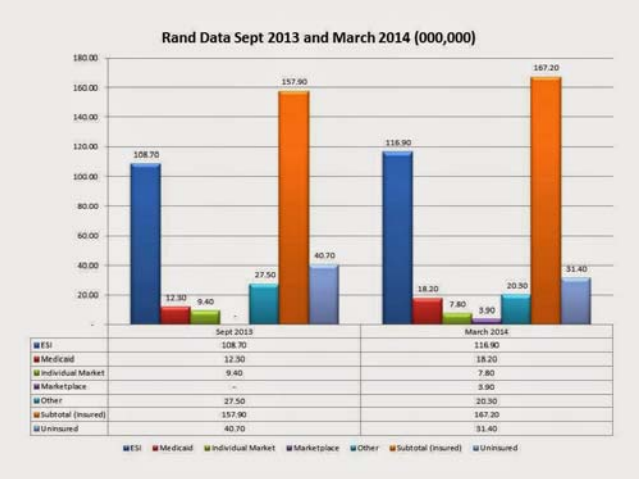
Labels: Cancer

WEDNESDAY, APRIL 9, 2014

REALITY AND RAND

Rand has published an analysis that they had completed which alleges a massive increase in insured under health care. When examining the data one gets a bit concerned. Let me explain.

First they show the following:

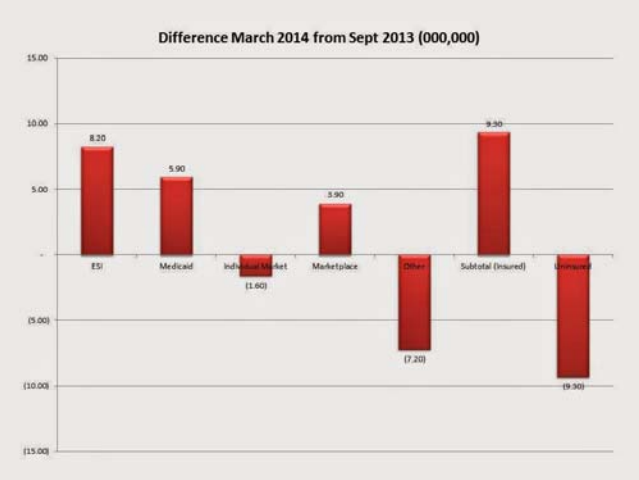


There is a massive growth in Employer Insured individuals, specifically some 8 million. Now there has only been 1 million added to the payrolls since then, see our other analyses, yet without an Employer Mandate we see this explosive growth. Why?

They argue:

Enrollment in ESI increased by 8.2 million. Most of this increase was driven by people who were previously unin- sured. Some of these newly insured individuals may have taken up an employer plan as a result of the incentive created by the individual mandate; others may have newly found a job. The U.S. unemployment rate fell slightly between September 2013 and March 2014, so part of the increase in ESI enrollment could have been due to eco- nomic recovery rather than the ACA. While the 8.2-mil- lion-person increase seems large, more than 100 million 18- to 64-year-olds were covered by ESI in 2013. Since ESI is the dominant source of insurance coverage among this age group, it is not surprising that we could see relatively large effects of the individual mandate and economic recovery in this category.

Yetthis seems not to make any sense. Look at the following chart:



Some 3 million or more went to Medicaid. Not unreasonable given the circumstances, it is free and no one cares. Some 4 million went to the "Marketplace" the web based sign ups and they are subsidized as well but not 100% Most of them seem likely to have a pre-existing condition. Some 7.2 million were lost, those on private plans most likely.

It will be interesting to see who is paying and who is not, and what the conditions are of the new entrants. The ESI number is truly confusing.

Labels: Health Care

MY PAPER ROUTE: CIRCA 1954

The NY Times has a piece today on a neighborhood called Westerleigh on Staten Island. This was my paper route in the early 1950s.

The route went from Willowbrook Road to manor Road. It was one of those routes that the "new kid" got, comprised of every non-tipping and non-paying home that every other older kid did not want. So it was a house here and a house there. Not knowing its history I plied my trade each day, six days a week, cycling from the lower part to the higher, and if lucky collecting a nickle tip from most of my 109 customers. Rain, snow, ice, heat, each day down College Avenue to Willowbrook, and then house by house up again. That was my first sales route, and it contained many a non-payer.

The best days were late Spring when on a Saturday you rode from house to house, the windows were open for the first time letting in the warm Spring air and the Top 40 played from 9AM till noon, and each house somehow had that station on. I could deliver my 109 papers and almost have continuous radio coverage. This map above was my territory, it is where one learned how to sell, how to collect, and what the ups and downs of business were.

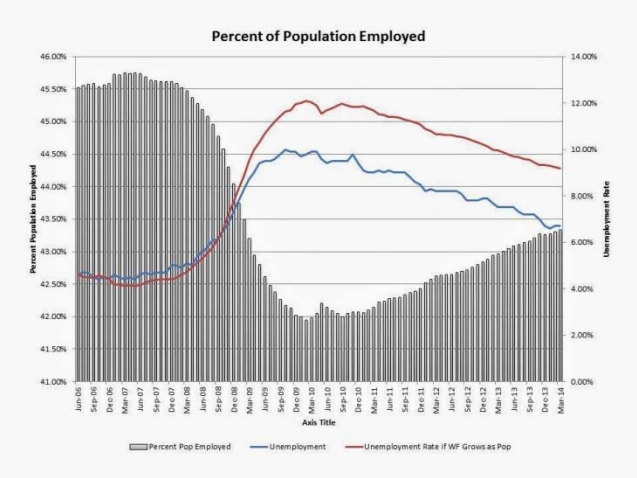
I do not see any paperboys today. None of the kids today push a bike loaded with papers from the bottom of the hill to the top, some two plus hours a day, and then have to worry about collecting enough to pay the Newspaper. You see you owed them whether you collected or not. The Staten Island Advance was a Simon Legree employer, the demanded payment and furthermore demanded that you had to service a customer whether they paid or not. Thus if you had a non-payer, well that was your problem and you had to find a way to collect.

I recall one house that never paid. I tried to terminate them but the Advance would not hear it. I finally found out they had died, I think in the in the very house, then the Advance let me cancel.

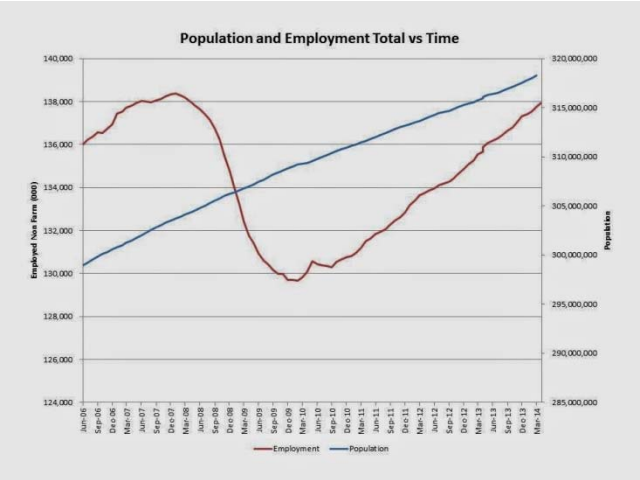
The map has many memories, street after street. Day after day. Interesting that after some sixty years I can still recall the details of the route. It is a shame that kids today do not get both the exercise and the experience.

Labels: Commentary

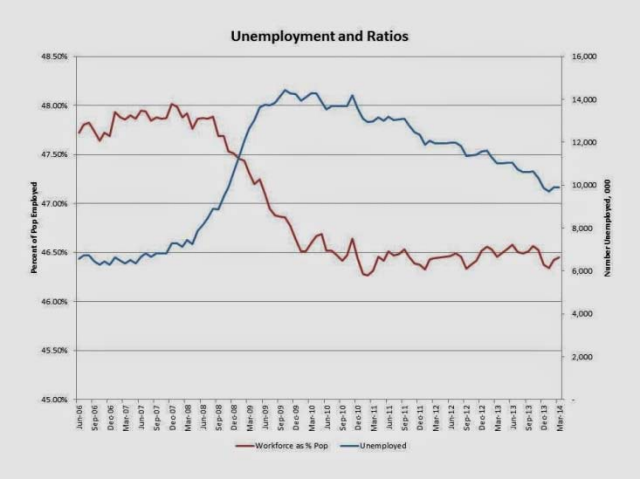
EMPLOYMENT DATA APRIL 2014



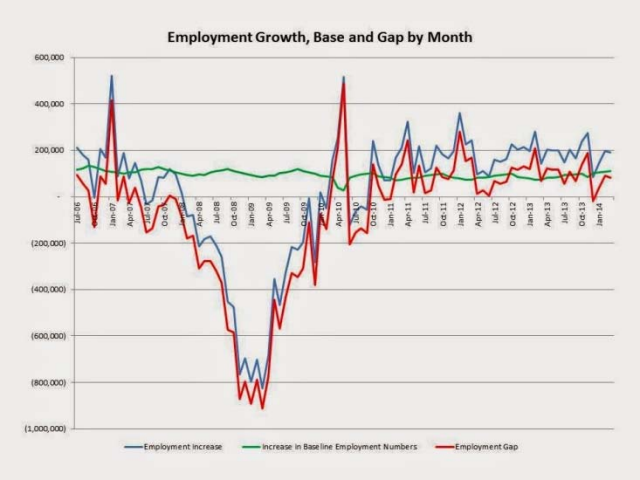
The above chart depicts the employment as released last week. As usual we still have a major gap in participation. This we have noted now since early 2008, a period in excess of six years now. Also true unemployment is still well above 10% and not improving greatly.



The above does show that employment is growing with population growth. The rate of growth however has not changed since it began, a concern.



The participation rate is a real concern. It is not clear if we just have a true systemic change and its cause. We have suggested true productivity increases and others have argued aggregate demand.



We have seen for the past two months a return to positive gaps thus indicating true added jobs in excess of population growth, a positive factor, albeit low.

Labels: Economy

TUESDAY, APRIL 8, 2014

CRISPRS AND CANCER

CRISPRs, specifically "clustered regularly interspaced short palindromic repeats"[71[1]], are portions of a cell's DNA which contain a particular type of short repetitions.. These specific repetitions are then followed by additional short segments of DNA which have been collected from some prior exposure to a virus phage. Namely CRISPRS are selective DNA snippets which have been garnered from viral phages which in some past period tried to attack the prior lineage of this cell. They are used to create Cas ("CRISPR associated" genes) which in turn have the capability of cleaving genes and inserting new ones.

CRISPR-Cas systems are now a useful toolkit for engineering eukaryotic cells, and especially human cells. They are also used in plant cells and that is a second tale but one worth examining as well.

As Jinek et al have recently said (Jinek et al 2014):

Although type I and III CRISPR-Cas systems rely on multiprotein complexes for crRNA-guided DNA targeting, type II systems use a single RNA-guided endonuclease, Cas9, that requires both a mature crRNA and a trans-activating crRNA (tracrRNA) for target DNA recognition and cleavage (8, 9). Both a seed sequence in the crRNA and conserved protospacer adjacent motif (PAM) sequence in the target are crucial for Cas9-mediated cleavage.

71[1] Recall that a palindrome is a collection of letters which can be read the same forwards of backwards. For example; GCATTACG.

The use of the crRNA and the tracrRNA are the two key elements which we shall discuss in this process. Also the Type II CRISPR-Cas system is the one which has received the most attention.

Cas9 proteins are abundant across the bacterial kingdom, but vary widely in both sequence and size. All known Cas9 enzymes contain an HNH domain that cleaves the DNA strand complementary to the guide RNA sequence (target strand), and a RuvC nuclease domain required for cleaving the noncomplementary strand (nontarget strand), yielding double-strand DNA breaks (DSBs).

These DSB open up the DNA at a desired location. Thus if one has a specific gene to be spliced out, and to be replaced, the first step is to open the DNA at the site of that desired gene. Thus the above step is a critical first step.

In addition, Cas9 enzymes contain a highly conserved arginine-rich (Arg-rich) region previously suggested to mediate nucleic acid binding. On the basis of CRISPR-Cas locus architecture and protein sequence phylogeny, Cas9 genes cluster into three subfamilies: types II-A, II-B, and II-C. Cas9 proteins found in II-A and II-C subfamilies typically contain ~1400 and ~1100 amino acids, respectively.

The ability to program Cas9 for DNA cleavage at specific sites defined by guide RNAs has led to its adoption as a versatile platform for genome engineering . When directed to target loci in eukaryotes by either dual ***crRNA:tracrRNA*** *guides or* ***chimeric single-guide RNAs****, Cas9 generates site-specific DSBs that are repaired either by nonhomologous end joining or by homologous recombination, which can be exploited to modify genomic sequences in the vicinity of the Cas9-generated DSBs.*

The opened DNA then can be targeted by crRNA:tracrRNA segments that remove and replace the targeted DNA or by a chimeric single-guide RNA which accomplishes this all in one step. This is the second step in CRISPR gene targeting and re-engineering. We shall discuss this a bit more later.

Furthermore, catalytically inactive Cas9 alone or fused to transcriptional activation or repression domains can be used to control transcription at sites defined by guide RNAs. Both type II-A and type II-C Cas9 proteins have been used in eukaryotic genome editing. Smaller Cas9 proteins, encoded by more compact genes, are potentially advantageous for cellular delivery using vectors that have limited size such as adeno-associated virus and lentivirus.

CRISPR, those collections of small sets of palindromic DNA inserted in the hosts original DNA, can be collectively called a process that is naturally occurring in nature and it is also a procedure that can then be implemented across a wide selection of cell types. In a sense it has been called the lower organism's immune system, a means of remembering previous attackers to the organisms such as bacteria, and a way to use that memory as a defense mechanism against future attacks. The mechanism can then be used in higher level organisms as a reverse process, a means of attacking bad genes and then inactivating them. It is in effect a trick to take what lower organisms have developed for protection and employ in higher level organisms for therapeutic purposes.

In a recent paper by Villion and Moineau the authors examine the two sides of CRISPR, the side that adds segments of foreign DNA to enable an immune type system and the side that deletes selected DNA.

To cope with this never-ending threat, microorganisms have developed a wide range of defense mechanisms.

Among them, CRISPR-Cas system is the new kid on the block as its silencing role was reported only five years ago. An outburst of articles, meetings, and reviews has since followed, arguably making it one of the hottest topics in microbiology.

CRISPR (clustered regulatory interspaced short palindromic repeats) loci are found in approximately 45% of sequenced bacterial genomes as well as 90% of archaeal ones and one genome can contain multiple CRISPR loci. Variable short regions, called spacers, separate each of the short repeats. The spacers are mainly homologous to viral or plasmid sequences. CRISPR-associated (cas) genes are often located adjacent to the CRISPR locus. The diversity and specificity of the cas operons has led to the identification of signature cas genes and to a polythetic classification scheme for CRISPR-Cas systems (types I to III, with several subtypes).

Notwithstanding their particularities, CRISPR-Cas systems operate through three general steps to provide immunity. In the adaptation stage, some cells will respond to the invasion of a phage or a plasmid by adding a new repeat-spacer unit into the CRISPR array, mostly polarized at the 5' end. Strikingly, the spacer sequence comes from the invading nucleic acid while the newly added repeat derives from another repeat of the array.

The mechanistic details on how this adaptation/immunization occurs are still unknown but some Cas proteins are involved. The unique spacer content is now considered a sign of past challenges and can serve as a marker for strain typing. In the second step, small non-coding CRISPR RNAs (crRNAs) are generated. A long precursor CRISPR RNA is first produced from an AT-rich leader/promoter region, which is then processed within the repeats and mature into crRNAs.

Several Cas proteins participate into the biogenesis of crRNAs. Finally, in the interference stage, the crRNACas protein complex will bind to the invading nucleic acid target and cleave it, providing a defense system to the host microbe. Therefore, CRISPRCas systems are RNA-based adaptive microbial immune systems that target nucleic acid intruders.

They end with the following, the double edged sword portion:

Although already outstanding in bridging gaps in our understanding of CRISPR-Cas systems, this fascinating story does not end here. The authors investigated the possibility of using this dual-RNA system to program Cas9 to specifically cleave any desired DNA molecules. Minimal requirements to have an efficient single chimeric RNA molecule mimicking the dual RNA structure were defined and led to site specific DNA cleavage by Cas9. In fact, several different chimeric guide RNAs were engineered and used to cleave a plasmid containing the specific target and a PAM. These findings coupled to the previous observations that CRISPRCas systems

can be functionally transferred from one organism to another open up exciting possibilities for gene targeting and genome editing of microbes and even higher organisms.

That is they have developed a way to reverse the process, using the mechanism now, not to add a piece of DNA, but to cleave a piece of DNA. This opens the door for many types of treatment of cancers where we may know the genetic defect and then can cut it out, cell by cell.

We examine briefly herein some of the recently discovered uses of CRISPR technology to address cancers of various types. The CRISPR approach is another tool in the toolbox of biologists which can become a means for medical application.

As Cain and Boinett state:

The CRISPR–Cas (clustered regularly interspaced short palindromic repeats–CRISPR associated proteins) adaptive immune system is widespread in bacteria and archaea and provides heritable protection against disruptive mobile genetic elements (MGEs), such as bacteriophages and plasmids. CRISPR loci contain a series of repetitive DNA motifs separated by spacer sequences; these spacers are derived from MGEs and incorporated after exposure to each new foreign element. The CRISPR transcript is processed into small CRISPR RNAs, which are displayed on Cas protein complexes, enabling RNA-guided degradation of the foreign DNA by Cas nucleases…. The flexibility and specificity of genome editing using CRISPR loci enables the efficient generation of mutated genotypes in diverse species. Furthermore, as CRISPR loci show strain-specific conservation at the nucleotide level, they are proving to be valuable markers for typing studies and, in conjunction with whole-genome sequencing, can provide insights into the phylogenetic relationships between different bacteria.

As reported in The Independent[72][2]:

The Crispr process was first identified as a natural immune defence used by bacteria against invading viruses. Last year, however, scientists led by Jennifer Doudna at the University of California, Berkeley, published a seminal study showing that Crispr can be used to target any region of a genome with extreme precision with the aid of a DNA-cutting enzyme called CAS9.

Since then, several teams of scientists showed that the Crispr-CAS9 system used by Professor Doudna could be adapted to work on a range of life forms, from plants and nematode worms to fruit flies and laboratory mice.

Earlier this year, several teams of scientists demonstrated that it can also be used accurately to engineer the DNA of mouse embryos and even human stem cells grown in culture. Geneticists were astounded by how easy, accurate and effective it is at altering the genetic code of any life form – and they immediately realized the therapeutic potential for medicine.

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[72][2] http://www.independent.co.uk/news/science/exclusive-jawdropping-breakthrough-hailed-as-landmark-in-fight-against-hereditary-diseases-as-crispr-technique-heralds-genetic-revolution-8925295.html

"The efficiency and ease of use is completely unprecedented. I'm jumping out of my skin with excitement," said George Church, a geneticist at Harvard University who led one of the teams that used Crispr to edit the human genome for the first time.

"The new technology should permit alterations of serious genetic disorders. This could be done, in principle, at any stage of development from sperm and egg cells and IVF embryos up to the irreversible stages of the disease," Professor Church said.

David Adams, a DNA scientist at the Wellcome Trust Sanger Institute in Cambridge, said that the technique has the potential to transform the way scientists are able to manipulate the genes of all living organisms, especially patients with inherited diseases, cancer or lifelong HIV infection.

"This is the first time we've been able to edit the genome efficiently and precisely and at a scale that means individual patient mutations can be corrected," Dr Adams said.

"There have been other technologies for editing the genome but they all leave a 'scar' behind or foreign DNA in the genome. This leaves no scars behind and you can change the individual nucleotides of DNA – the 'letters' of the genetic textbook – without any other unwanted changes," he said.

The essence of the above is twofold. First it is the use of CRISPR as a mechanism in prokaryotes and possibly in eukaryotes. The second is an important observation that we now have another tool for the genetic engineering tool box. The observation that in genetic engineering that many of the "tools" are artifacts of nature should not be overlooked.

What is a CRISPR?

We will now examine in more detail what a CRISPR is and how it functions. Let us begin by examining it in a bit more detail. As Randow et al state:

In archaea and bacteria, for example, even adaptive forms of resistance—long considered the hallmark of vertebrates—contribute to cell autonomous immunity, as exemplified by the clustered regularly interspaced short palindromic repeats (CRISPR) system, which recognizes foreign DNA in a sequence-specific manner. In metazoans, cellular self-defense synergizes with the whole-body protection provided by traditional immunity to confer pathogen resistance. Here, professional immune cells patrol their environment in search of pathogens, whereas cell-autonomous immunity guards both individual immune and non-immune cells against the immediate threat of infection.

Cellular self-defense thus has the potential to confer antimicrobial protection on most, if not all, cells….In bacteria, foreign DNA is sensed and destroyed by the CRISPR system and restriction endonucleases. Because recognition motifs for most restriction endonucleases occur frequently in the host's own genome, these enzymes are paired with matching methyltransferases, which modify host DNA to demarcate it as "self." In eukaryotic cells, rather than being modified, DNA

is largely sequestered inside the nucleus, which fosters the detection of foreign DNA in other compartments and allows the deployment of enzymes that mutate and/or degrade DNA without risk to the host genome.

Thus as noted above, the original understanding was as a bacterial self-defense system. Now as Horvath and Barrangou state also concerning the original understanding:

Microbes have devised various strategies that allow them to survive exposure to foreign genetic elements. Although out-populated and preyed upon by abundant and ubiquitous viruses, microbes routinely survive, persist, and occasionally thrive in hostile and competitive environments. The constant exposure to exogenous DNA via transduction, conjugation, and transformation have forced microbes to establish an array of defense mechanisms that allow the cell to recognize and distinguish incoming "foreign" DNA, from "self " DNA and to survive exposure to invasive elements. These systems maintain genetic integrity, yet occasionally allow exogenous DNA uptake and conservation of genetic material advantageous for adaptation to the environment.

Certain strategies, such as prevention of adsorption, blocking of injection, and abortive infection, are effective against viruses; other defense systems specifically target invading nucleic acid, such as the restriction-modification system (R-M) and the use of sugar-nonspecific nucleases. Recently, an adaptive microbial immune system, clustered regularly interspaced short palindromic repeats (CRISPR) has been identified that provides acquired immunity against viruses and plasmids.

They also state:

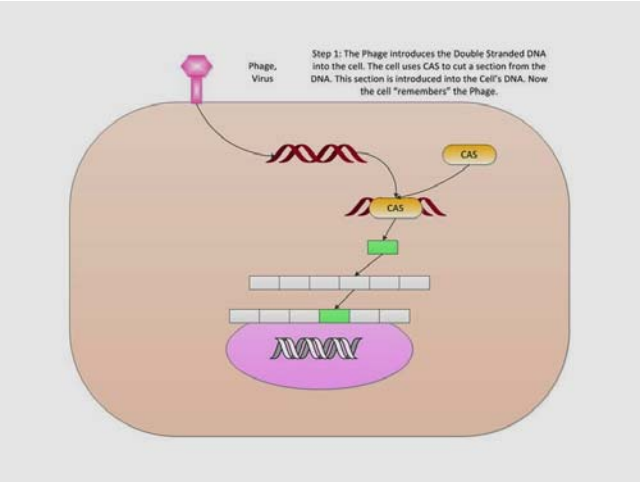
Microbes rely on diverse defense mechanisms that allow them to withstand viral predation and exposure to invading nucleic acid. In many Bacteria and most Archaea, clustered regularly interspaced short palindromic repeats (CRISPR) form peculiar genetic loci, which provide acquired immunity against viruses and plasmids by targeting nucleic acid in a sequence-specific manner.

These hypervariable loci take up genetic material from invasive elements and build up inheritable DNA-encoded immunity over time. Conversely, viruses have devised mutational escape strategies that allow them to circumvent the CRISPR/Cas system, albeit at a cost. CRISPR features may be exploited for typing purposes, epidemiological studies, host-virus ecological surveys, building specific immunity against undesirable genetic elements, and enhancing viral resistance in domesticated microbes.

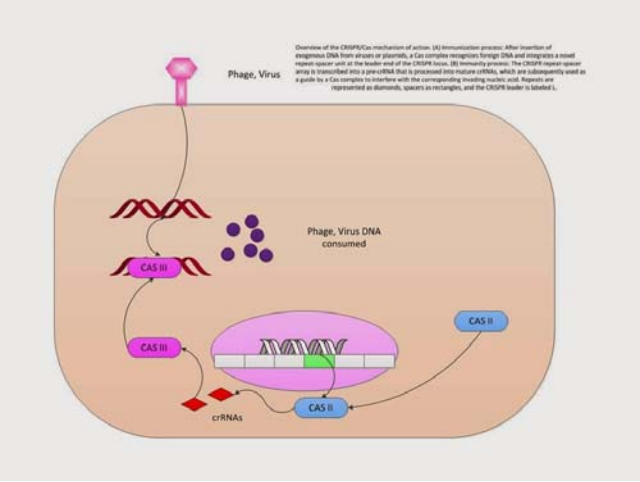
Thus we first examine how CRISPR-Cas functions in its primal environment and then we take this to human environments where we can use it as an added tool in our genetic engineering toolkit.

CRISPR DYNAMICS

We now examine some of the dynamics of the CRISPR system. We start with the use of CRISPR in a bacterial cell. We assume the cell is attacked by some viral phage and the phage sends its RNA/DNA into the cell in anticipation of replication within the host. Now from Horvath and Barrangou (as modified) we have the following description for this initial portion of the process as shown below:



The Cas protein recognizes the invading DNA and transports a portion of it to the nuclear DNA and inserts it into the cells DNA. How specifically Cas does this task is not yet well understood. The when another phage with the same or frankly similar DNA invades again, then Cas II is activated and the section of the DNA activates a Cas II which then consumes the invading DNA.



Now the above process is a natural part of the day to day activities of bacteria. But it also is a paradigm for deal with eukaryotic cells, namely cutting and pasting genes into cells.

TYPES OF CRISPR

From Jinek et al, they discuss the three types of CRISPR systems:

There are three types of CRISPR/Cas systems.

The type I and III systems share some overarching features: specialized Cas endonucleases process the pre-crRNAs, and once mature, each crRNA assembles into a large multi-Cas protein complex capable of recognizing and cleaving nucleic acids complementary to the crRNA.

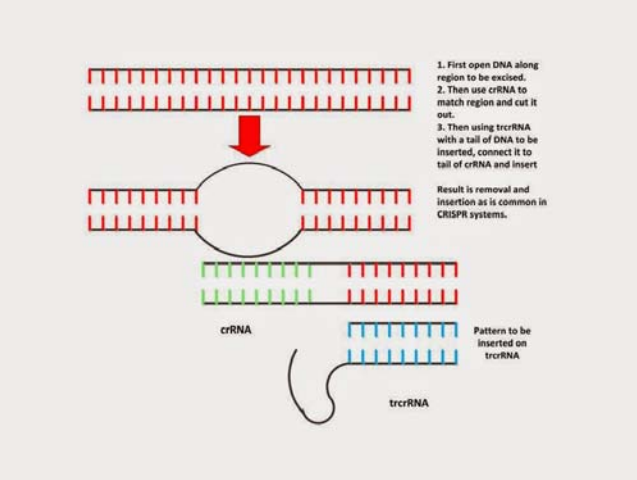
In contrast, type II systems process pre-crRNAs by a different mechanism in which a trans-activating crRNA (tracrRNA) complementary to the repeat sequences in pre-crRNA triggers processing by the double-stranded (ds) RNA specific ribonuclease RNase III in the presence of the Cas9 (formerly Csn1) protein. Cas9 is thought to be the sole protein responsible for crRNA-guided silencing of foreign DNA.

…in type II systems, Cas9 proteins constitute a family of enzymes that require a base-paired structure formed between the activating tracrRNA and the targeting crRNA to cleave target dsDNA.

Site-specific cleavage occurs at locations determined by both base-pairing complementarity between the crRNA and the target protospacer DNA and a short motif [referred to as the protospacer adjacent motif (PAM)] juxtaposed to the complementary region in the target DNA.

Thus the heart of the CRISPR engineering tool is the Type II system and specifically the Cas9 proteins used in the placement and extraction. In addition we also have just introduced above the crRNA and the tracrRNA which are used as part of the cleavage process. The crRNA provides a site specific cleavage targeting whereas the tracrRNA allows for insertion.

We now examine briefly the Jinek et al approach to a cut and paste using CRISPR. This is a Type II system and it allows for the removal of a targeted section of DNA and the replacement with another crafted piece. We show the overall construct below. This is a simplified version of Jinek et al.



We use the above as a very simplified example of how we can insert specific DNA in an excised targeted region.

CRISPR and Cancer

Now one would think that perhaps this could become a therapeutic as applied to various cancers. Consider it use as a kinase inhibitor in CML. Would it work there by targeting the aberrant kinases? What of an application in melanoma with a BRAF V400 mutation? Can we cut and paste back the proper genetic sequence? If so, how do we deliver the elements of the process, especially in a metastatic case? Furthermore, how do we determine what genes must be modified, and does that mean that we not only customize it for a patients but also for cells? Finally how do we know that there are not some deleterious sequellae from this cutting and pasting process, what if we "miss" the gene in some cell and start an secondary malignancy?

These are all reasonable questions that lead us to examine the CRISPR process in further detail

As recently stated by Stephen et al:

We are also optimistic that completely different approaches to treating cancer will contribute to eliminating Ras cancers, including new ways of knocking down/out genes using RNAi and CRISPR technologies and delivering these payloads to tumors, as well as new ways of deploying the immune system.

In this respect, it is noteworthy that anti-CTLA-4 therapy appears to be equally effective in treating melanoma driven by N-Ras or B-Raf; therefore, Ras cancers may not be excluded from these approaches as they have been from others. All of these considerations lead us to be optimistic about future prospects of finally delivering the knockout punch.

As Way et al state:

Synthetic biology is a young discipline with the declared goal of rationally engineering biological systems through approaches similar to those used by engineers to build bridges and send people to the moon. This field has rapidly developed over the past 15 years from its initial conceptualization by a few academics and government program managers into a sizeable field whose meetings attract large numbers of participants. Recently, new tools have emerged that should allow specific integration at desired sites in the genome. For example, methods based on zinc-finger, TALE, and CRISPR fusions to nucleases can be used to generate double-strand breaks at specific sites in the genome. The questions remain—where should we integrate, and how can we avoid effects of adjacent sequences?

Thus one may ask if one knows that some gene has been the cause of a cancer, can we then treat the cells with a CRISPR-Cas system to delete the gene and replace it with a normal wild type. If we have a procedure to do this then perhaps this is a therapeutic approach. It does, of course beg the question of how this is accomplished even if we have the chimeric Cas delivery system. We also must ask if we have identified all the genes. There are also many other such questions. Yet this has become a focal point of interest.

In a recent paper by Yin et al the authors discuss the delivery of a CRISPR-Cas9 mediated cutting and reintroduction of a gene into liver cells by means of an injection process. The result was conversion of the errant gene cells into normal wild type cells. They utilized the backwards flow of the CRISPER-Cas9 approach for cutting and injection. This potentially paves the way for substantial progress in alternative targeted gene replacement and return to normal states. As Yin et al state:

We demonstrate CRISPR-Cas9–mediated correction of a Fah mutation in hepatocytes in a mouse model of the human disease hereditary tyrosinemia. Delivery of components of the CRISPR-Cas9 system by hydrodynamic injection resulted in initial expression of the wild-type Fah protein in ~1/250 liver cells. Expansion of Fah-positive hepatocytes rescued the body weight loss phenotype. Our study indicates that CRISPR-Cas9–mediated genome editing is possible in adult animals and has potential for correction of human genetic diseases.

From Gene News[73][3] we have a more detailed discussion worthy of note regarding the above recent report:

MIT scientists report the use of a CRISPR methodology to cure mice of a rare liver disorder caused by a single genetic mutation. They say their study … offers the first evidence that this gene-editing technique can reverse disease symptoms in living animals. CRISPR, which provides a way to snip out mutated DNA and replace it with the correct sequence, holds potential for treating many genetic disorders, according to the research team.

"What's exciting about this approach is that we can actually correct a defective gene in a living adult animal," says Daniel Anderson, Ph.D., the Samuel A. Goldblith associate professor of chemical engineering at MIT, a member of the Koch Institute for Integrative Cancer Research, and the senior author of the paper.

The recently developed CRISPR system relies on cellular machinery that bacteria use to defend themselves from viral infection. Researchers have copied this cellular system to create gene-editing complexes that include a DNA-cutting enzyme called Cas9 bound to a short RNA guide strand that is programmed to bind to a specific genome sequence, telling Cas9 where to make its cut.

At the same time, the researchers also deliver a DNA template strand. When the cell repairs the damage produced by Cas9, it copies from the template, introducing new genetic material into the genome. Scientists envision that this kind of genome editing could one day help treat diseases such as hemophilia, Huntington's disease, and others that are caused by single mutations.

For this study, the researchers designed three guide RNA strands that target different DNA sequences near the mutation that causes type I tyrosinemia, in a gene that codes for an enzyme

[73][3] http://www.genengnews.com/gen-news-highlights/crispr-reverses-disease-symptoms-in-living-animals-for-first-time/81249682/

called FAH. Patients with this disease, which affects about 1 in 100,000 people, cannot break down the amino acid tyrosine, which accumulates and can lead to liver failure. Current treatments include a low-protein diet and a drug called NTCB, which disrupts tyrosine production.

In experiments with adult mice carrying the mutated form of the FAH enzyme, the researchers delivered RNA guide strands along with the gene for Cas9 and a 199-nucleotide DNA template that includes the correct sequence of the mutated FAH gene.

"Delivery of components of the CRISPR-Cas9 system by hydrodynamic injection resulted in initial expression of the wild-type Fah protein in ~1/250 liver cells," wrote the investigators. "Expansion of Fah-positive hepatocytes rescued the body weight loss phenotype."

While the team used a high pressure injection to deliver the CRISPR components, Dr. Anderson envisions that better delivery approaches are possible. His lab is now working on methods that may be safer and more efficient, including targeted nanoparticles.

The above described an interesting I vivo approach to the editing and insertion of a specific gene in a specific location. Although this is of interest, it is limited to a very specific site and also using a difficult delivery mechanism.

As to more extensive editing capabilities we examine Zhang et al who state:

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) protein 9 system provides a robust and multiplexable genome editing tool, enabling researchers to precisely manipulate specific genomic elements, and facilitating the elucidation of target gene function in biology and diseases. CRISPR/Cas9 comprises of a non-specific Cas9 nuclease and a set of programmable sequence-specific CRISPR RNA (crRNA), which can guide Cas9 to cleave DNA and generate double-strand breaks at target sites. Subsequent cellular DNA repair process leads to desired insertions, deletions or substitutions at target sites.

The specificity of CRISPR/Cas9-mediated DNA cleavage requires target sequences matching crRNA and a protospacer adjacent motif (PAM) locating at downstream of target sequences. Here, we review the molecular mechanism, applications and challenges of CRISPR/Cas9-mediated genome editing and clinical therapeutic potential of CRISPR/Cas9 in future.

The above stresses the strong point of CRISPR-Cas9, namely its specificity. It can target specific DNA, assuming we know what to target. It can then replace that with a substitute, assuming we know that the substitute does no harm and in fact is positively therapeutic. From Pandika we have[74][4] the following lengthy discussion regarding the evolution of this specific result:

Because a Nobel Prize winner says this breakthough is better than his breakthrough.

[74][4] http://www.ozy.com/rising-stars-and-provocateurs/jennifer-doudna/4690.article

Jennifer Doudna has always had an explorer's spirit. It's what led the UC Berkeley molecular and cell biology professor to engineer a cheaper, easier way to correct DNA defects. Her game-changing technology takes a mysterious bacterial genetic code and transforms it into a powerful tool for cutting and pasting bits of genetic material – meaning not only could the entire field of gene therapy be revived, but her genome-editing tool could one day be used to treat a range of diseases, from cancer and AIDS to hereditary disorders like Down syndrome and Huntington disease.

Every time we see some new tool for the toolkit the immediate tendency is to label it as a cure fr cancer.

Most scientists weren't even aware of these so-called CRISPRs, much less their function. But Doudna suspected they hid a crucial purpose….The bacterial enzyme Cas9 is the engine of RNA-programmed genome engineering in human cells. Doudna unearthed the first clue when she found that a protein called Cas9 acts like a pair of molecular scissors…

"I wasn't actively trying to go in any particular direction," she said. That willingness to wander, to maybe even get a little lost, could be how she was able to make a creative break from earlier genome-editing technologies. Doudna "certainly didn't set out to discover a genome editing tool by any stretch of the imagination." It all began with a puzzle she couldn't resist solving, thanks largely to her father. When Doudna was growing up, the literature professor got her hooked on one of his favorite pastimes —decoding short pieces of encrypted text, or cryptograms.

In 2005, a colleague presented Doudna with a genetic cryptogram — weird repetitive RNA sequences tucked in the genomes of many of the bacteria she studied. Most scientists weren't even aware of these so-called CRISPRs, much less their function. But Doudna suspected they hid a crucial purpose.

Sure enough, scientists discovered that CRISPRs played an important role in immunity: they recognize the DNA of viral invaders for the bacteria to chop up and fight off. But how did this search-and-destroy mechanism work? Teaming up with Umea University molecular biologist Emmanuelle Charpentier, Doudna unearthed the first clue when she found that a protein called Cas9 acts like a pair of molecular scissors. A CRISPR RNA fragment hooks up with Cas9 to precisely target the DNA of an invading virus, which it then cuts and destroys.

Here's where it gets really complicated. Martin Jinek, a postdoctoral researcher in Doudna's lab, found that Cas9 in bacteria needs two RNA guide strands – this sent the gears in their heads turning. What if they could engineer the system to require only a single, programmable RNA strand? Then biologists could use it to easily target and cut any DNA sequence. Doudna felt "a chill of excitement." Maybe they could link the two RNA strands into one, and loop it in on itself—mimicking a double-stranded structure. Those chills were warranted: Doudna's lab and other groups successfully used this simplified CRISPR system to modify genes in bacteria, plant and animal cells.

One early form of CRISPR-based gene therapy could involve editing the genes responsible for blood disorders like sickle-cell anemia in bone marrow cells, growing them into mature blood cells and injecting them back into patients.

However, the application needs a more effective insertion system. It also needs to demonstrate that it does not wander and affect other genes.

Little more than a year after Doudna first described CRISPR in the journal Science, the cut-and-paste technology has yielded promising results in labs around the world. Last month, researchers from the Netherland's Utrecht institute reported in Cell Stem Cell that CRISPR corrected the gene mutation responsible for cystic fibrosis in stem cells developed from two children with the life-threatening disease. Doudna believes a clinical trial of CRISPR-based gene therapy could begin in less than a decade.

As is all too often the case, any prediction of clinical application may be much too speculative. Single gene targeting may become the first step, albeit even there one must be cautious.

Doudna experienced "many frustrations" getting CRISPR to work in human cells. But she knew if she succeeded, CRISPR would be "a profound discovery" — and maybe even a powerful gene therapy technique.

We knew if the system could be made to work in human cells, it would be a really profound discovery.

"I hope you're sitting down," an excited colleague told Doudna in an unexpected phone call. "CRISPR is turning out to be absolutely spectacular in [Harvard geneticist] George Church's hands." He had even gotten it to work in human cells. Thrilled, Doudna immediately contacted Church. They shared their results, and both published studies in January 2013 showing that CRISPR can cut, delete and replace genes in human cells. University of Massachusetts biologist Craig Mello, who shared the 2006 Nobel Prize for another genome editing tool, hails Doudna's CRISPR technique as a "tremendous breakthrough," even admitting that "in many ways it's better" than his own technique.

Other techniques can also edit genes at specific DNA regions. But they require scientists to engineer a separate protein for each target site. In contrast, CRISPR only needs the Cas9 protein, allowing it to correct multiple defects at once. Besides being cheaper and easier to use, CRISPR is also much more precise, reducing the risk of off-target modifications introducing dangerous mutations. As a result, it could help revive the gene therapy field, whose early clinical failures — including patient deaths — led some to dismiss it as overhyped.

That doesn't mean CRISPR is perfect, though. While it's extremely precise, it occasionally modifies DNA at similar sites elsewhere in the genome instead of the target gene. Understanding and exploiting how Cas9 avoids these close matches "is an active area of investigation,"

Doudna said. Still, CRISPR is "a real game-changer," Mello told the Independent. "It's incredibly powerful."[75][5]

Indeed the observations above detail some of the powers of CRISPR-Cas9 complex.

Observations

The CRISPR-Cas9 system has proven to be a workable in vivo editing mechanism for specific gene cut and paste situations. However there are several key questions that seem to hang over it. None are so severe as to cause substantial concern but in toto they clearly indicate potential but substantial work is still required, especially in the area of cancer therapeutics.

We thus present and discuss several such questions:

1. Can the CRISPR-Cas9 system target the correct sets of aberrant cancer genes?

The issue here is that in many cancers we have a multiple set of genes which are aberrant. To make it even more complex, there are cancer cells with different mixtures of mutated or inoperable genes. How thus does one target this broad and varying complex. A single genetic mutation is one thing an broad complex set of changes is another.

2. Can CRISPER-Cas9 system be delivered in vivo in a more effective manner?

The current delivery mechanism is targeted at specific cells in a specific location. What does one do with a metastatic cancer. Oftentimes you do not even know where the cells may be. Then again one also faces the issue of the stem cell and it special characteristic. This delivery most likely be difficult.

3. Is CRISPR-Cas9 a dose related system approach rather than an all-encompassing curative approach? Namely does it cut-and-paste a large set of genes but perhaps not all?

Is the delivery system akin to dosing in normal pharmacokinetics or is it a totally different mechanism.

4. How does CRISPR-Cas deal with metastatic cells wherein there are multiple sets of genetic alterations?

The multiplicity of gene breakdowns and the process in which this happens becomes a complex driver for applying this technology. Is there a single key to solving the problem or must one continue to track changes and chase the shadows of the genetic changes?

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[75][5] http://www.independent.co.uk/news/science/exclusive-jawdropping-breakthrough-hailed-as-landmark-in-fight-against-hereditary-diseases-as-crispr-technique-heralds-genetic-revolution-8925295.html

5. What are the potential deleterious sequellae possible from a CRISPR approach and how can they best be avoided?

The ultimate question will be what else can this process do. The unintended consequences may be significant. As was noted above:

That doesn't mean CRISPR is perfect, though. While it's extremely precise, it occasionally modifies DNA at similar sites elsewhere in the genome instead of the target gene.

What then are those mistakes which can occur, especially when targeting multiple genes?

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Labels: Cancer

SUNDAY, MARCH 30, 2014

PROSTATE CANCER: CONFUSION REIGNS

In reading some of the recent reports on PCa decisions regarding "watchful waiting" and surgery, as well as the benefit of PSA, one seems to get confused. Let me examine just three recent papers:

1. The recent NEJM Scandinavia studies conclude[76][1]:

Extended follow-up confirmed a substantial reduction in mortality after radical prostatectomy; the number needed to treat to prevent one death continued to decrease when the treatment was modified according to age at diagnosis and tumor risk. A large proportion of long-term survivors in the watchful-waiting group have not required any palliative treatment.

This is a clear statement of substantial efficacy. Survival is key and this Trial demonstrates it.

2. In a recent JAMA article the author's state[77][2]:

[76][1] http://www.nejm.org/doi/full/10.1056/NEJMoa1311593

[77][2] http://jama.jamanetwork.com/article.aspx?articleid=1841972

Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 55 to 69 years. Only men who express a definite preference for screening should have PSA testing. Other strategies to mitigate the potential harms of screening include considering biennial screening, a higher PSA threshold for biopsy, and conservative therapy for men receiving a new diagnosis of prostate cancer….

They continue:

Before 2009, conflicting observational data and 2 small trials could not resolve this controversy.7- 9 Two large randomized trials published in 2009 that were expected to provide definitive conclusions yielded conflicting results. Therefore, the benefits and harms of prostate cancer screening continue to be debated….Recent interest in more patient-centered care emphasizes the importance of informing men about risks and benefits of PSA screening. However, recent clinical practice guidelines provided conflicting results..

The Trials referred to are the European and American Trials I have analyzed before on several occasions. Both, in my opinion and based upon my analysis, are flawed. The European Trial measured PSA much too infrequently thus leading to high mortality and both used a threshold of 4.0 with no attention to velocity, age, family history, or percent free. That is both Trials used a 1992 standards through a 2009 period. The standard had dramatically changed and it was never reflected in the Trial data.

3. In an earlier NEJM articles the authors conclude[78][3]:

During the median follow-up of 10.0 years, 171 of 364 men (47.0%) assigned to radical prostatectomy died, as compared with 183 of 367 (49.9%) assigned to observation (hazard ratio, 0.88; 95% confidence interval [CI], 0.71 to 1.08; P=0.22; absolute risk reduction, 2.9 percentage points). Among men assigned to radical prostatectomy, 21 (5.8%) died from prostate cancer or treatment, as compared with 31 men (8.4%) assigned to observation (hazard ratio, 0.63; 95% CI, 0.36 to 1.09; P=0.09; absolute risk reduction, 2.6 percentage points). The effect of treatment on all-cause and prostate-cancer mortality did not differ according to age, race, coexisting conditions, self-reported performance status, or histologic features of the tumor. Radical prostatectomy was associated with reduced all-cause mortality among men with a PSA value greater than 10 ng per milliliter (P=0.04 for interaction) and possibly among those with intermediate-risk or high-risk tumors (P=0.07 for interaction). Adverse events within 30 days after surgery occurred in 21.4% of men, including one death….Among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up. Absolute differences were less than 3 percentage points.

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[78][3] http://www.nejm.org/doi/full/10.1056/NEJMoa1113162

This was a Veteran's Department study. As such one must consider, in my opinion, how they function as compared to a more conventional medical establishment. The statements above do appear conflicting. On the one hand mortality was 5.8% versus 8.4% in the two groups, favoring prostatectomy. However the conclusions state that there is no difference in mortality.

How does a physician and patient interpret this data? The U.S. Government conducted Trial in my opinion is problematic at best. The JAMA result is one where we have on the one hand and on the other. The Scandinavian study seems clear cut. Yet confusion still reigns.

This is why any study of comparative clinical effectiveness is of dubious merit. The data is not available and the Trials are oftentimes contradictory.

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Labels: Cancer

SATURDAY, MARCH 29, 2014

GENOME SIZE

There is a piece in Nature which has some interest. It is the determination of the genome size of the pine tree, Loblolly. This is a pine which may make it as far north as where I am in New Jersey. It is a bit strange in that it grow branches only on the side where there is strong sunlight.

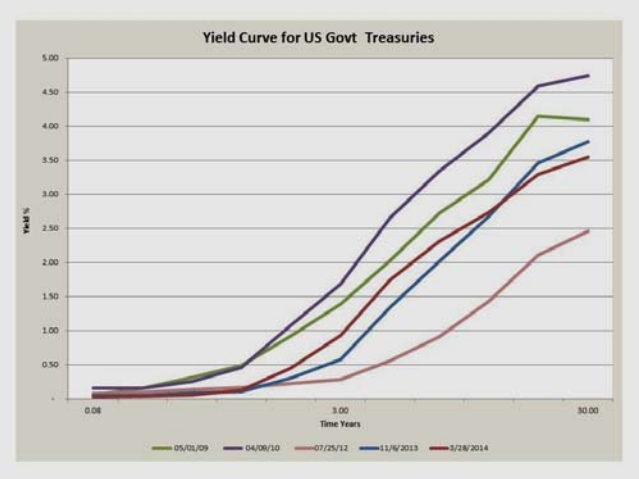
Nature states:

A species of pine tree native to the southeastern United States has a genome with 23 billion base pairs, more than 7 times the length of the human genome....Another team, made up of many of the same researchers and led by Jill Wegrzyn at the University of Connecticut in Storrs, characterized around 50,000 of the genes and estimated that 82% of the loblolly genome is made from repetitive elements. This work, the first pine genome assembled so far, provides a foundation to study the biology of conifers, the authors say.

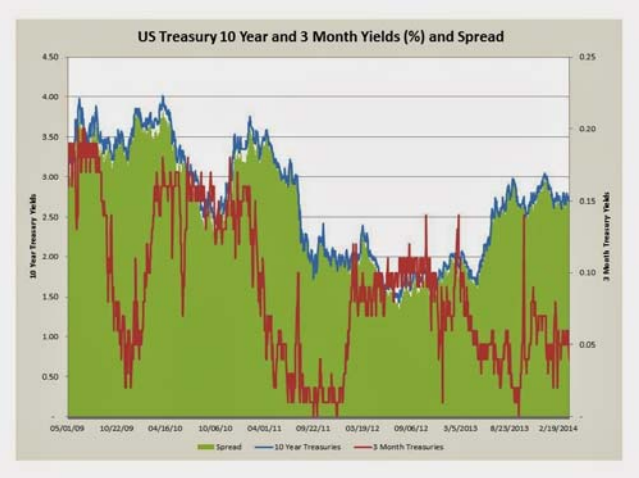
As a question to pose: How would a plot of gene length versus lifetime of species appear? Namely would say a Ginkgo have lots or excess base pairs or what? Just a thought.

Labels: Genetics

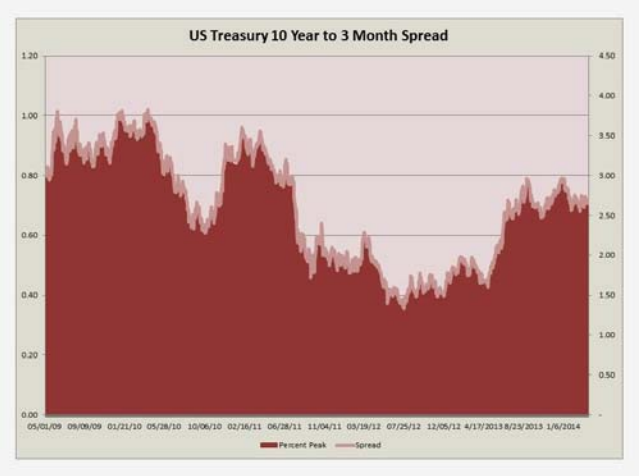
YIELD CURVE MARCH 2014



The above is a comparison of the Yield curves for the past few years. The current yield curve as of yesterday reflects a reasonable trend with no significant or drastic rise. The FED action seems to be moderate even though they are backing off.



The above demonstrates the two key measures and the spread. The spread has remained constant for a while which shows stable expectations. We again show this below:



It is a reasonable and stable spread. In a sense this may be a return to some slow normalcy.

Labels: Economics

THURSDAY, MARCH 13, 2014

TOO MUCH INFORMATION

In a recent JAMA paper on whole genome sequencing the authors examine 12 patients in detail and the results were mixed. One patient had BRCA mutation which was beneficial. The others were a mixed bag.

As the authors conclude:

In this exploratory study of 12 volunteer adults, the use of WGS was associated with incomplete coverage of inherited disease genes, low reproducibility of detection of genetic variation with the highest potential clinical effects, and uncertainty about clinically reportable findings. In certain cases, WGS will identify clinically actionable genetic variants warranting early medical intervention. These issues should be considered when determining the role of WGS in clinical medicine.

The problem is several fold. First there are many know genes with uncertain effects. Second there are many unknown genes with totally uncertain effects. Yes the genome has been mapped for over a decade but the unknow genes are "known" but their effects are uncertain. Third there are many epigenetic effects which are uncertain. Fourth many cancers are the result of subtle in lesion changes not reflective of a large scale sample.

The authors continue:

As technical barriers to human DNA sequencing decrease and the cost of whole-genome sequencing (WGS) approaches $1000, WGS and protein-coding genome sequencing (whole-exome sequencing [WES]) are increasingly used in clinical medicine. Both WGS/WES can successfully aid clinical diagnosis, reveal the genetic basis of rare familial diseases, and

explicate novel disease biology· Regardless of context, even in apparently healthy individuals, WGS/WES are expected to uncover genetic findings of potential clinical importance. However, comprehensive clinical interpretation and reporting of clinically significant findings are seldom performed. As WGS/WES are applied more broadly, questions have been raised about the duty for discovery, interpretation, and reporting of clinical findings. Recently published recommendations define genetic variant types in a minimum list of inherited disease genes that are suggested to be subject to discovery, reporting, and clinical follow-up regardless of the primary indication for sequencing, patient preference, or patient age. Despite this, the technical sensitivity and reproducibility of clinical genetic findings using WGS and the clinical opportunities and costs associated with discovery and reporting of these and other clinical findings in WGS data remain undefined.

The problems that can be seen is that many patients may demand the tests or physicians can see a way to "sell" the tests and the result will be an added load on the already burdened Health Care system to deal with what is at best conjecture. One wonders how this fits into the ACA?

Labels: Genetics

LE MOYEN AGE

There is a wonderful piece in Nature this week on the work of Grosseteste. It discusses his work on Light and the Universe. The authors conclude that his efforts were hardly those of some monk in the Dark Ages. Indeed, I have argued that before, and even more so, there were efforts during the true Dark Ages from 600-1000 AD. But Grosseteste worked during the 13th Century, a truly remarkable time.

The authors state:

De Luce (On Light), written in 1225 in Latin and dense with mathematical thinking, explores the nature of matter and the cosmos. Four centuries before Isaac Newton proposed gravity and seven centuries before the Big Bang theory, Grosseteste describes the birth of the Universe in an explosion and the crystallization of matter to form stars and planets in a set of nested spheres around Earth.

They conclude:

Because projects such as ours can be of significant scientific and cultural value, scientific granting agencies should consider funding arts and sciences projects or partnering with arts and humanities councils to translate other early scientific works, for example. The eight-century journey from Grosseteste's cosmological ideas to our own offers a rich illustration of the slow evolution in our understanding, and of the delight to be found in reaching out into nature with our imagination.

However there were two stumbling blocks they faced. he first was the lack of the mathematical tools. No calculus and they still stumbled even with Algebra. Second, was the lack of tools to

measure, and even more so agreed upon measurements. Time was difficult, distance the same, and thus velocity problematic. Yet substantial insight and progress was made.

Labels: Commentary

INCIDENTALOMAS

Incidentalomas are things a physician may find during the normal course of an exam, such as an imaging study, which may or may not be of any significance, but most likely may be followed up on. For example if a woman over 60 complains to her physician about a bloated feeling in the abdomen and then is sent for a CAT scan and the image of the ovaries is uncertain, then significant follow up is ordered even though it looks like an old cyst. She may just be eating the wrong thing but now we have a mass set of tests and specialists involved.

Now consider the same thing but apply it to a genetic testing. A patient is worried about breast cancer and BRCA gene is tested and appears to be abnormal. What next. Well we know the stats and the patient is so informed. But what if it is some other gene? Some gene where we do not really know that well, say a 5% or even 20% increase in risk. Then what. Make it even more complex. Assume we have all normal genes but that key genes are methylated in their promoter regions. Have we tests for that as well? The gene may be there but can never be expressed. Furthermore perhaps we must look at genes which are organ specific. The list goes on.

In the recent NEJM there is an excellent piece on this issue. They state:

The problem with the genomic–radiologic analogy is more than a matter of semantics. The comparison may give nonexperts a false impression of our ability to efficiently interpret genetic or genomic findings and to understand how they might affect a person's health. It perpetuates a myth about the level of our current understanding of the genome and of individual genetic variants — the notion that we can interpret all the information from genomic sequencing as quickly and accurately as we can interpret an x-ray. This myth can affect the public, patients, research participants, and clinicians who lack training or experience in genetics or genomics. And the myth will become more problematic as genomic sequencing becomes faster, cheaper, and more widespread. Despite impressive ongoing efforts that will continue to yield great progress, we are not at the point where interpreting a genomic data set is similar to interpreting a radiologic study.

Indeed, genetic test results are useful in a small body of applications. Furthermore we often do not know what to do if we discover a more complex issue. Thus the true concern as to their current use.

One need look no farther than the multiplicity of tests for Ca. Which one really works. And WHY? Yet to be answered.

Labels: Health Care

SUNDAY, MARCH 9, 2014

PCA SURVIVAL

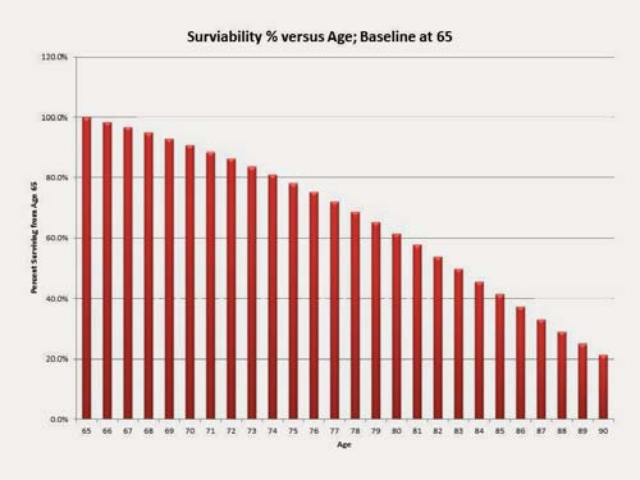
In a recent NEJM paper the authors discuss the use of a prostatectomy versus watchful waiting in prostate cancer patients[79][1]. The authors note:

A total of 447 of the 695 men enrolled in the study (64%) had died by the end of 2012. This total included 200 men in the radical-prostatectomy group and 247 men in the watchful-waiting group. The cumulative incidence of death at 18 years was 56.1% in the radical-prostatectomy group and 68.9% in the watchful-waiting group (a difference of 12.7 percentage points; 95% confidence interval [CI], 5.1 to 20.3), corresponding to a relative risk of death in the radical-prostatectomy group of 0.71 (95% CI, 0.59 to 0.86; P<0 .="">

The authors conclude:

A significant absolute reduction in the rate of death from any cause, the rate of death from prostate cancer, and the risk of metastases in the radical-prostatectomy group continued after up to 23.2 years of follow-up (median, 13.4 years), with no evidence that these benefits diminished over time. In analyses according to age and tumor risk, the effects were more pronounced in men younger than 65 years of age and in men with intermediate-risk tumors. However, among men older than 65 years of age who underwent radical prostatectomy, there was a significantly decreased risk of metastases and need for palliative treatment. We observed a substantial difference in the prevalence of disease burden between the study groups.

From SSI data we have the following Figure of percent surviving from 65 onwards[80][2]. Note that by 87 years of age only 33% of those alive at 65 are still living. This is for all causes.



[79][1] http://www.nejm.org/doi/full/10.1056/NEJMoa1311593

[80][2] http://www.ssa.gov/OACT/STATS/table4c6.html

Now the data from the study can be compared as follows:

1. Death from any cause in prostatectomy group was 56%

2. Death from any cause in the watchful waiting group was 69%

3. Death from any cause in the general population was at 66%.

4. Death from any cause in the combined groups was 68%.

The conclusion is quite interesting. Those having a prostatectomy actually lived longer no matter what than all others. Therefore, the USPTF's concern of unwarranted prostatectomies is greatly in question. Now SEER data lists 2.6 million with PCa in the US[81][3]. Making a gross calculation we could state that the 13% difference would result in an excess 338,000 cumulative deaths if we adhere to watchful waiting. That is more than 100 times those lost in 9/11.

One must be concerned that data of this sort will be denied under CER methods so as to reduce costs in the ACA world. Again this is just an observation.


Labels: Cancer

SUNDAY, MARCH 9, 2014

INPUT LESS OUTPUT EQUALS NET ACCUMULATION

A law of nature, if you burn 1800 Kcal per day and consume 2100 Kcal per day, then the excess of 300 Kcal over about 12 days will add one pound. Now today in the NY Times we have another excuse for obesity, antibiotics.

The author writes:

And yet, scientists still could not explain the mystery of antibiotics and weight gain. Nor did they try, really. According to Luis Caetano M. Antunes, a public health researcher at the Oswaldo Cruz Foundation in Brazil, the attitude was, "Who cares how it's working?" Over the next few decades, while farms kept buying up antibiotics, the medical world largely lost interest in their fattening effects, and moved on. In the last decade, however, scrutiny of antibiotics has increased. Overuse of the drugs has led to the rise of antibiotic-resistant strains of bacteria — salmonella in factory farms and staph infections in hospitals. Researchers have also begun to suspect that it may shed light on the obesity epidemic.

81[3] http://seer.cancer.gov/statfacts/html/prost.html

Now it is not only genes, advertising, it is also antibiotics. It may just as likely be global warming, climate change, or whatever the latest fad is. What it is, simply, is eating too many calories and expending too few. That law of nature has not changed. Perhaps the calories per pound of pork has increased, then eat less pork.

All one has to do is go into any American restaurant. Large plates, immense portions of high calorie food and great numbers of obese people consuming the plates, one after another. Any one of the many chain restaurants serve massive platters of excess calories and the patrons consume the food with glee. There is no price, yet, for many of them, and their obesity. Yet as it continues to grow the costs will explode.

There is no benefit to "discovering" new reasons why these people are fat. They eat too much. The whole business of blaming some exogenous factors when the fault lies within is a major failing of our society. For every 0.1 that a person is over a BMI of 25.0, there should be a tax of say $500. That ought to stem some of the tide. Sort of a new idea on income redistribution. Think about it.

Labels: Obesity

FRIDAY, MARCH 7, 2014

ECONOMISTS AND INSIGHT

There seems to be a sudden interest in the automation of the manufacturing processes as well as in many other parts of our economy. What is quite surprising is the sudden discovery of this process, especially by academics, and moreover especially by economists.

So much of classic microeconomics is predicated on the assumption of massive capital investments and long capital lives of such investment. In the past thirty years we have seen shortened lives of capital plant and in some cases the elimination of such means of production totally. Vertical integration has migrated to globalization, in the extreme.

Now in a recent piece by a Berkeley Economist on the left there appears to be a sudden discovery of automation[82[1]]. The author states:

In their compelling new book The Second Machine Age, Erik Brynjolfsson and Andrew McAfee document the progress in artificial intelligence that is enabling computers to exceed what they were capable of only a few years ago. The leaps in machine intelligence, along with the connection of human beings around the world in a common digital network, will enable the development of new technologies, goods and services. The authors are optimistic about the "bounty" or economy-wide benefits of brilliant machines. But they warn that the distribution or "spread" of these benefits will be uneven. Their fears are justified. During the last three

[82[1]] http://www.project-syndicate.org/commentary/laura-tyson-considers-appropriate-policy-responses-to-the-next-wave-of-automation

decades, even before breakthroughs in artificial intelligence, computers have been replacing and multiplying the physical labor of human beings. Improvements in computer and communications technologies have also enabled employers to offshore many routine tasks that machines cannot directly replace.

Now, as I have noted several times in this line of discussion, it was Norbert Wiener in the late 1940s who first called out the changes to our economy by the use of intelligent machines in his many writings on Cybernetics. In fact, as the father of what we know see as "automated everything", he raised the concern as to what this would do to our economy. Thus almost seventy years ago we knew what was happening and it was not just artificial intelligence.

The above sudden insight to artificial intelligence has itself been slowly evolving for almost the same period initiated also by Wiener's colleagues and co-workers. Wiener had in the 40s a keen insight into the obvious which was totally missed by all economists for decades, and they seem now to want the praise for discovering it some seventy years after it was first well-articulated.

Labels: Economics

CCE AND THE ROAD TO HELL

In a recent law proposed in Congress the intent is to eliminate liability if the physician follows a standard method of care[83][1]. Thus there is a "Safe Harbor" established. The article states:

Physicians who are Medicare and Medicaid providers would be granted increased liability protection if they can demonstrate that they followed established clinical guidelines, according to a bill introduced in Congress this week. The Saving Lives, Saving Costs Act, introduced by Reps. Andy Barr (R-KY) and Ami Bera (D-CA), would create a "safe harbor" for physicians who follow best practice guidelines. Physicians also could request that state-level malpractice suits be moved to federal courts.

The concern is that the Safe Harbor is established by following a Comparative Clinical Effectiveness standard established by the Government. The article states:

"Rather than being directed by Washington, the guidelines will be developed by the physician community based on the best available scientific evidence," according to a joint statement by the legislators. "Guidelines should be developed through a transparent process by a knowledgeable, multidisciplinary panel of experts." A physician who is being sued could "argue that he or she adhered to the relevant practice guidelines, which would cause a suspension in the proceedings while an independent medical review panel investigates." If the panel determines that the physician conformed to the guidelines, or that failure to conform was neither the cause nor the

[83][1] http://www.medscape.com/viewarticle/821588?nlid=50786_2701&src=wnl_edit_dail

proximate cause of the alleged injury, the case would be dismissed pending clear and convincing evidence that the medical review panel was in error, the statement said.

Now this has certain concerns. Specifically those relating to CCE Standards. The problem with them are:

1. They are not patient specific. They are patient general and the fact of the matter is patients are all different. Thus by following the "Standard" it may actually cause harm to the patient.

2. The development of a consensus for Standards is a timely process. It also is one that all too often reaches a least common denominator. It also, if one see the results of the ACA, may be driven by both non-physicians and worse, physicians having no expertise in the area of the "Standard". One need look no further than the USPTF and the Prostate Cancer debate as well as the proposed standards emanating from PCORI, where "patients" get to opine on what is correct.

3. Standards when delivered often are reached after extensive developments may have occurred in the treatment and studies. Thus Standards reflect a substantial time lag in the process. The adherence to "old" practices again may result in poorer levels of care.

4. Standards are also now used to manage the physician. The physician, if in fear of a law suit, will be forced to adhere to the Standard and thus not use their own judgment and patient specific information.

5. Standards can be used to penalize the physician as well as set limits on care. It can in a way be a back door way of rationing health care. Standards developed by Government bodies of political appointees are clearly a mechanism under the current Administration to delimit care and reduce costs.

Thus this Bill, with possibly some good intentions, will reduce the level of health care. One must remember that the road to Hell is lined with such "good intentions".

Labels: Health Care

TUESDAY, MARCH 4, 2014

RUSSIA AND UKRAINE

First, for all of those who have never been East of the Hamptons, it is NOT The France, The Germany, The Poland, and not The Ukraine. It is Argentina and The Argentine. But not The Ukraine. It is The United States but not The Canada.

Now on to Russia and Ukraine. Having been in both spots, and not being a George Kennan, only having companies and business partners, Russia does not like instability on its borders. I recall once meeting with a banker from London and one of my "associates" in Moscow when we discussed building a fiber across Belarus. The banker asked what about the political instability in Belarus. My Russian associate slammed his fist down and said he will send in tanks. The banker was a bit concerned as how best to fit that assurance into his due diligence report. But in nutshell that is the Russian way.

I also recall a meeting I had with Deutsche Telecom in Moscow. It was an endless ride from my hotel to the outskirts. I went to the executive conference room and it had a beautiful view of some monument below. When the head of the office came in I was fooling enough to ask what the monument was. It was German tank, it was as far as the Germans had gotten to Moscow. They DT office was allowed to get across the street but no closer. Russians have a long memory, whether it is Napoleon or Hitler. They want a buffer.

Thus an unstable Ukraine is a concern. It all depends on how one vies the current instability. Is it to get a better Ukraine or a Western organized coup. I do not suspect the latter but given recent releases from Snowdon one could guess from the past this could be their view. Thus Ukraine must remain a buffer.

So what should the West do? Good question. It depends on how far Putin will push. One could

imagine that he wants to recover Haigia Sophia in Constantinople, I mean Istanbul. That could make him a Saint Vladimir in the eyes of many. It would also resolve the straits passage problem. It would also remind us of 1914.

Labels: Russia

OVER 100,000 VISITS!

Just noticed that we have had over 100,000 visitors over the past five years. Thanks for dropping by to the idiosyncratic web site, a collection of various insights and commentary.

Labels: Commentary

FRIDAY, FEBRUARY 28, 2014

WHAT IS GOOD FOR THE GOOSE

Now I have problems with Microsoft. They are in no way customer friendly. In fact it may be possible to call them customer hostile. Now come a tale of young Master Gates returning and trying to get his new Microsoft computer to function with Windows 8.1

As the New Yorker states:

Bill Gates's first day at work in the newly created role of technology adviser got off to a rocky start yesterday as the Microsoft founder struggled for hours to install the Windows 8.1 upgrade. The installation hit a snag early on, sources said, when Mr. Gates repeatedly received an error message informing him that his PC ran into a problem that it could not handle and needed to restart. After failing to install the upgrade by lunchtime, Mr. Gates summoned the new Microsoft C.E.O. Satya Nadella, who attempted to help him with the installation, but with no success. While the two men worked behind closed doors, one source described the situation as "tense."

Tense? That is why there are more users still on XP! Windows 7 is not bad, I have it on almost all systems but I still have a few XPs hanging around and no way are they getting changed. They run in the lab anyway so it would be tough to access them.

But this has been the problem with Microsoft. Simply Windows 7 works for those of us who do real work, like spreadsheets, writing, software etc. Windows 8 is the toy stuff for pads. Try and type a book on touch screen sitting 2' from your eyes. Those trapezius muscles will get awful sore after a while. Then my android works just fine thank you Microsoft!

This may be the death knell for Microsoft. We shall see. Clearly they have screwed up again and again. They learned nothing with Vista. They just sent another arrogant team to tell the customer what they should do.

Labels: Microsoft

TUESDAY, FEBRUARY 25, 2014

PEER REVIEW AGAIN

In a recent paper in Nature the author states:

Over the past two years, computer scientist Cyril Labbé of Joseph Fourier University in Grenoble, France, has catalogued computer-generated papers that made it into more than 30 published conference proceedings between 2008 and 2013. Sixteen appeared in publications by Springer, which is headquartered in Heidelberg, Germany, and more than 100 were published by the Institute of Electrical and Electronic Engineers (IEEE), based in New York. Both publishers, which were privately informed by Labbé, say that they are now removing the papers.

Now I have no knowledge of IEEE since I no longer kept up my membership after some 45 years because I saw a dramatically declining quality of papers. My concerns were:

1. Multi author papers: There was an explosion of papers, especially at conferences, where the number of authors approach a large class size. One would logically as; who wrote what? There was the "name" author, who I often wondered had even read the paper, and then a swarm of others, and amidst the mess was probably an author.

2. Repeat of Old Stuff: No one ever seemed to examine if what they did was just a rehash. In my opinion that was especially true of IEEE papers. One wondered if they just accepted anything that was generated in the "club" and ignored everything else.

3. Awards: There has become a proliferation of various awards and the sole purpose is to gather credits for academic status. It used to be that certain journals were controlled by Bell Labs and that they set the standard, namely support AT&T or else. Now it is not clear who they are but it is just a rebirth of the same old stuff.

The article continues:

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Integrity is an essential element in science and engineering. Apparently there seems to be no check on it in certain publications. Perhaps a real house cleaning is in order. Yet, perhaps those in the house just want to shovel it under the rug and go on as the do. It is ironic that IEEE is now one of the few journals that has no open access. Perhaps that says something.


Labels: Academy

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Svante is an exceptionally good writer and the tale flows quite smoothly. If one understands the science, then one can fill in the gaps and the tales is well presented. If one does not understand the science then one can still appreciate what is happening by taking the results presented at face value.

The tale works back and forth from the fundamental science to the interrelationships between various players in the overall search. Svante shows how he managed to deal with the anthropologists and others to get samples of Neanderthals from as far away as Siberia. It also demonstrates some of the more cooperative nature of science as new techniques is shared and how Svante is assisted by many others who are but in related fields.

The efforts span from California to Eastern Russia and it shows that in today's environment the ability to communicate changed what would have been multi-lifetime efforts into a fast paced move to provide the final answers.

This book is a stark contrast to Watson's Double Helix. The Helix is a strong interplay of personalities; it portrays competitiveness and at times pettiness that is common in certain scientific endeavors. Helix was a true race, a sprint to get DNA right, and a succinct set of observations which became the underpinnings of Svante's efforts. Svante is the opposite of Watson. The ego is missing; the collegiality if present, yet one still sense the pace. Yet it is not a pace with an edge, it is a steady pace to get it right.

This is definitely a great book for those seeking to understand the Neanderthal developments as well as understanding perhaps how the research community has matured as it has expanded.

Also, upon some reflection, I recall when I first read Watson's Double Helix just after it was published I could recognize the highly competitive world of research since I was still at MIT. In contrast Svante portrays a totally different world, one more of communications and cooperation. The worlds of Watson and Svante are separated by some half century, and the difference is startling, one is near ruthless and the other collegial, with a sense of cooperation moving forward. Great job!


Labels: Books, Genetics

GOOGLE IS BECOMING MICROSOFT

Try and find out anything in Microsoft Help. First it is written in a language that has become extinct and no human can translate it. Second when you search you get nonsense to begin with. The Microsoft indirectly destroys your data. Example, PowerPoint before Office 2000 is unreadable by Office 2007 and after, even some of Office 2003.

Now what has Google done? Some Microsoft infected character took Google maps and turned it into an incomprehensible mess, no warning, no way to go back, and years of storing directions into the system leads to a total loss. Take printing a map. They say Ctrl P. No way, tried it on 7 machines. Try and find out how to do it and they send you to a blog with hundreds of complaints. Some Google genius decided that their idea was better and wham, millions left as road kill!

Are there any adults out there? It is like some 20+ year old who says follow me and off the character goes in some Shelby Cobra at 100+ and there are twenty others trying to follow on the LI Expressway on a Friday night in July out to Shelter Island! And the rest of the crowd are in Honda Civics!

Every once in a while a seminal event demonstrates the coming collapse, albeit slowly, of an entity. With Microsoft it was Vista, the Office 2003 SP3, then Windows 8. For Google it is the death of a great system. Congratulations to whoever was the brainchild of this disaster!

Maybe Verizon could acquire Google, they could probably not make things worse!

Labels: Google

FRIDAY, FEBRUARY 21, 2014

I REMEMBER THE OLD KGB

In the old Soviet Union almost every third person was in some way a KGB informant. Not that they now collect pensions but then the collected data. There was the Key Lady on every floor of an Intourist Hotel, the desk clerk the taxi drivers, the airport check in agents, the restaurant staff, the book store managers, the fellow at the news stand. After a while you just assumed everyone was watching.

Then there were the interrogators. Why are you here, where are you going, who is with you. What is in your bag. In fact when you got a safe for your room it was pretty certain that whatever you put there was examined, and they often let you know they were there.

Thus you were always on guard, especially if you were an American. Added to that was the "visitors" to your hotel room at night, knocking on the door, and you knew very well who sent them and you looked around for the cameras and microphones. They put the NSA to shame, almost.

Now comes the FCC and the assault on News Media! What type of character thought this up?

Just look and you can find out. As the FCC states:

"However, in the course of FCC review and public comment, concerns were raised that some of the questions may not have been appropriate. Chairman Wheeler agreed that survey questions in the study directed toward media outlet managers, news directors, and reporters overstepped the bounds of what is required. Last week, Chairman Wheeler informed lawmakers that that Commission has no intention of regulating political or other speech of journalists or broadcasters and would be modifying the draft study. Yesterday, the Chairman directed that those questions be removed entirely.

The very notion demonstrates what has taken over the Government. One of the very basic principles was Freedom of the Press. There are stations that just spew garbage, but economics should delimit what they say. If no one watches then they go away. There must be some trust in the American people, after all the same group votes. But this was a clear overstepping bounds. Blocking a bridge is foolish, blocking the free press is, well I let you guess.

Labels: FCC

IMPOSSIBLE!

There are times when I read things that are totally illogical but then I just say, so what. But this one beats all. Some writer at Fierce Wireless considers a merger of Verizon and Google.

He states:

However, a merger between the two of them in the next few years is not so far-fetched, according to an opinion column from FierceCable .... A Google-Verizon marriage would be the largest corporate merger ever. The companies had a combined market cap of $537 billion at Wednesday's market close. Yet there are more than a few reasons why such a deal might work, including the fact that there is no overlap (yet) between Verizon's FiOS footprint and Google Fiber deployments. The combined company could also deliver affordable high-speed Internet service through both wired and wireless networks, and it could provide competition to a combined Comcast and Time Warner Cable.

Now I could not consider two more different cultures. Verizon is fundamentally the classic "knuckle dragger" company. People do what they are told by people who often succeeded by doing what they were told! And often in my experience they made it near the top by never making a mistake or if they did to find someone else to blame.

At Google you sometimes had to be creative and profitable. At Verizon, well, if it were up to them we would still have black rotary dials! I was there, I saw it.

So putting these two together not only stretches the imagination it goes well beyond that!

Just look at fiber. Verizon very wisely saw where wireless could go and is betting the ranch, and winning. In contrast Verizon saw the folly of fiber and stopped it. The stopped it just when

Google started to get into it. With multibands, OFDM, etc wireless can do HDTV etc. In fact after Sandy Verizon is not rebuilding any physical plant, only wireless in certain areas. Great idea.

So why is Google running full bore on fiber? Good question, sooner than later they will get hit with the Comcast sledge hammer and come to a halt. The Franchise is that hammer. Doing a trial in a friendly city, one city, well that may work. But their roll out,not really. But then Google has enough money to waste learning the hard way.

When I see things like this I just shake my head. I guess someone has to fill up the world with words, meaningful or not.

Labels: Google

SUNDAY, FEBRUARY 16, 2014

I JUST LOST MY MAILBOX!

Now I am not a non-believer in global warming. I see it in my species plants. But frankly, since I have recently lost my mail box under a five foot tall or higher snow pile, I would really be grateful for a bit of that warming to return.

Now I write this in response to a Gore piece in the NY Times Book section. It is a review of some book written by some non-scientists who envisions another extinction. But Gore in his inimitable style states:

The extra heat is also absorbed in the top layer of the seas, which makes ocean-based storms more destructive. Just before Hurricane Sandy, the area of the Atlantic immediately windward from New York City and New Jersey was up to nine degrees warmer than normal. And just before Typhoon Haiyan hit the Philippines, the area of the Pacific from which it drew its energy was about 5.4 degrees above average.

Hey, I have been yelling about Hurricanes and New York Harbor for years. It was in the early 1950s that I recall, having lived there, that for three years in a row the harbor came a mile or so inland. So nothing new here, it was just that those summer "cottages" became homes and the

City allowed building where frankly there should not have been any. The same for many places on the Jersey Shore. Thus nothing new and people had seen it all before. It will happen again!

Now for the Philippines, I know that area well, It is subject to many Typhoons, the best was the classic Halsey Typhoon which hit late in 1944 just after the Battle of Leyte Gulf, where on the north side is Tacloban. You see when I wrote my book on that battle I interviewed thirty remaining crew members who sailed the much damaged vessel through that second disaster. In Tacloban they just built up to the shore line, in an area know for massive Typhoon impacts. This was State Island all over again.

Thus was this all Global Warming or just a repeat of what humans had seen and were forewarned about. I would consider the latter.

Finally he states:

Despite the evidence that humanity is driving mass extinctions, we have been woefully slow to adopt the necessary measures to solve this global environmental challenge. Our response to the mass extinction — as well as to the climate crisis — is still controlled by a hopelessly outdated view of our relationship to our environment.

I just finished reading a fantastic book on Paleobotany. I would strongly recommend it. The area is one of my night time readings for relaxation. It depicts over 400 Million years of plant evolution over some 5-6Billion years of what we currently know as history. Strange for us now to think that billions is not much after we watch out Federal budget, they spent almost ten billion on broadband in the Stimulus. Well back to Paleobotany. Frankly the extinctions allowed for new species. For almost all of that time we humans were not even capable of being assembled. But new species came and went, it is part of evolution.

Yet the author of the book, Extinction, interviewed in the Independent, focuses solely on animal "extinctions". Extinctions are quite complex. The "extinction" of the dinosaurs allowed the proliferation of the mammals. Yes, us eventually. So was that good or bad. The extinction of the conifers, yes there was such, led to angiosperms, and yet conifers survived. One could say that these extinctions are just part of evolution. Let things just go so far and then try again. Yet to have a real extinction one needs a truly catastrophic event that blocks sunlight or exhausts oxygen or water. Raising the temperature some 6F most likely will not do that. A big asteroid

may, flooding Wall Street may not. They will just move across the river, now Bay, to stay dry.

So history has a short time frame and the long time frame. Perhaps understanding the long one will help. You see plants have learned a lot more than us, animals are recent arrivals. Plants use carbon dioxide, the spew oxygen, and it is to them we owe our existence.

I think I will climb over a snow mound and thank my Ginkgoes. Perhaps I will exhale some CO2.

Labels: Global Warming

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FRIDAY, FEBRUARY 14, 2014

BRINGING A GROWN PERSON TO TEARS

The Massachusetts implementation of the ACA web services has apparently been a fiasco[84[1]]. The Globe states:

The head of the state's beleaguered health insurance marketplace, which was once a national model, broke down in tears Thursday, as she described how demoralizing it has been for her staff to struggle with a broken website that has left an unknown number of people without coverage...., the executive director of the Massachusetts Health Connector, wept at a board meeting, where it was disclosed that 50,000 applications for health insurance are sitting in a pile, and have yet to be entered into a computer system.

Now this is the state that had the infrastructure in place and had something working. They claimed 97% enrollment. So why change, simple the ACA. The result is a catastrophic collapse of the system. No computer access and apparently all those fellow "executives" managing all the paper work.

84[1] http://www.boston.com/lifestyle/health/blogs/white-coat-notes/2014/02/13/facing-application-backlog-insurance-marketplace-chief-breaks-down-tears/jeWUxJyrG9tx3lnkuJ4iCJ/blog.html

Now previously this individual, showing her exuberance in how well the ACA would be accepted, stated[85][2]:

How will the ACA, the national health care overhaul, affect the Connector? It really strengthens the Health Connector in a number of ways. As I mentioned, a very important part of what we do is to offer subsidies to a certain part of the population to help them pay for health insurance. The ACA expands that opportunity, so there will be more people able to access subsidies through the exchange. For example, low-income workers who currently have access to employer insurance but are unable to afford it will be eligible for subsidies. The ACA also makes major investments into the exchange so we can update our technology. Our goal is to offer a significantly better user experience, an easy-to-navigate process.

Now the State Web site states[86][3]:

Before joining the Health Connector, ... was Director of Contracting Strategy Analytics at Tufts Health Plan in Massachusetts, where she worked extensively on health care reimbursement issues and payer-provider collaboration initiatives. ... started her career as a management consultant with McKinsey & Company and subsequently Deloitte Consulting, where she served a wide variety of clients in the health care industry. ... graduated from Peking University of China and earned her M.B.A. from Harvard Business School.

Yes, a Harvard MBA. I guess the new strategy for Harvard is that if you can't get the web site to work you just break down in tears. Never saw that at MIT but after all we had to make things work. So here we have a case of how we take a "manager" and place them in a task which requires some technical capabilities and apparently they collapse. Even Mankiw bemoans the problem[87][4].

One of the themes that we have all heard over the past few years is that President Obama's healthcare reform is merely bringing the kind of changes Massachusetts had under Governor Romney to the nation. If that were really true, you would think that these national reforms would have minimal impact on the state of Massachusetts.

On the other hand we have Gruber from MIT still arguing for the benefits of the ACA predicating it on the benefits of the Massachusetts Plan[88][5]. He comments when criticizing the

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[85][2] http://www.bostonglobe.com/business/2013/07/20/hot-seat-with-health-connector-jean-yang/GMXAFtLV0URopJFLOoYGvN/story.html

[86][3] http://www.mass.gov/anf/budget-taxes-and-procurement/oversight-agencies/health-policy-commission/meet-the-board.html

[87][4] http://gregmankiw.blogspot.com/2014/02/obamacare-versus-romneycare.html

[88][5] http://www.newrepublic.com/article/116613/obamacare-critics-still-tell-just-one-side-jobs-story

CBO report stating that 2.5 million or so will drop from the workforce, and he like so many other Left leaning folk see that as a positive opportunity. After all who really wants to work? Gruber states:

Mulligan—like so many of the law's critics, in and out of the economics profession—gives a more one-sided view. He talks only about the marginal tax rates. A reader who relied exclusively on his column would have no idea the CBO cited multiple reasons for the shrinking workforce—and that some of these reasons were utterly defensible. Ironically, while making a surprisingly moral case against examples of 100% tax rates, he ignores the moral case for leveling the playing field by breaking the link between work and insurance, so that workers are not chained to jobs where the value of their compensation is well below their disutility of working. The Affordable Care Act, like any major reform, has its virtues and its flaws. The best economists, like the best public officials, are the ones who deal with both.

But the Massachusetts problem is not an Economics problem. Frankly there are no Economics problems, unless we are discussing political philosophy. Reality has met that philosophy. The web site and all its environs just do not work. Now I have done large scale computer system developments since 1967, starting with the Apollo mission and moving on from there. They are really tough things and need good people. Oftentimes in today's world the Beltway Bandits who end with the job are the lowest bidders, and look at these jobs as Golden Geese to feed them again and again. That is they never really finish, just get more change orders.

Reality is not economics. You do not draw two intersecting lines and jabber about some gross behavior principle which most likely will be disproved in a decade or so. Reality is making something work. Engineering is reality, Science is reality, Medicine is Reality, and even Law has elements of reality, especially when up against a jury.

Massachusetts shows a frightening example of what can happen even in the most experienced and most friendly environment. It already had 97% covered, but not by the ACA.

Labels: Health Care

WEATHER AND CLIMATE

Well here we are on Valentine's Day, another 18" of snow, a dead snow blower, and the snow plows keep putting a ton or more in the drive which I now shovel by hand. Primitive man returns. Got the driveway clean and the roof raked of excess snow. Don't want any collapses.

Now about weather and Global Warming. Based on the weather it is going into a freeze cycle. Based on 25 years of data the Hemerocallis still are blooming earlier. They integrate light and warmth. But this year we won't see grass until May! So will this change things. Microclimates are funny that way.

The interesting factor is all this snow really changes the albedo. Namely heat goes back out to space. Plants are kept at just above 32F but get no sun. Thus I am interested in the data of first bloom. The Hemerocallis is a sentinel plant, namely the bloom date of the early bloomers integrates many climactic factors, even from year to year. I am interested in how this will play out.

We will wait and see. While we do we expect another snow fall tonight and my new snow blower is not due until March 1. Perhaps I may see my car soon.

Labels: Global Warming

BURN THE BOATS

Cortes is alleged to have issued the order to "burn the boats". Simply there is no way back, you have no lifeline. You must move forward. The counter to that is the Wing Walkers Rule, "Don't let go of something until you have a firm hold on something else.". Entrepreneurs are of the former category. Corporate Executives are of the latter. Now the Left's assertion that the ACA enables someone to "take a chance" and try to become an entrepreneur is absurd at its face value. Entrepreneurs to be successful must believe that there is no way but forward. They have abandoned all that had come before and just move forward, not just "lean" forward, but to abandon all that had been safe and go where none have been.

Being an true creative entrepreneur means having faith that you can do the impossible because the challenge is there. Most good entrepreneurs I have known did not worry about health care, in fact the denied their very mortality. It did catch up from time to time, but they went into a state of total denial of any negative consequences. It was that drive that filters out the good from the wannabes.

There is a problem today that I see with the very concept of an entrepreneur. First we have academic institutions who try to "teach" it. In fact it is a Heidegger "throwness" to be an entrepreneur, you do not learn it you do it. Then the incubator concept, a comfortable transition environment to go and "think through" the plan. In reality it should be a garage, basement, spare room, and then the first office should be one where you have the early employees buy and assemble their low cost desks. If they want an expensive chair, no problem, let them buy it.

Cortes did not offer his mean health care, a pension, a nice work space, he burned the boats.

Labels: Commentary, Economics

THURSDAY, FEBRUARY 13, 2014

PROGRESSIVES AND CABLE

Comcast plans to buy Time Warner Cable. Now as a former Warner Cable executive from the early 80s I remember when some of our overseers, Board members, saw cable as an empty pit. They went on to other successes and Cable just passed them by. But this merger/acquisition would set Teddy Roosevelt and Woodrow Wilson afire, except for say MSNBC. I believe we still have Hart Scott Rodino and the Sherman and Clayton Acts. But alas, I suspect the behemoth that will be Comcast since it appears to align with the powers that be shall be passed over with no faults being seen. Clearly Cable and especially Comcast may very well capture the entire pie, as I had indicated a decade ago.

Labels: CATV

SUNDAY, FEBRUARY 9, 2014

JUST NICE FOR A WINTER DAY

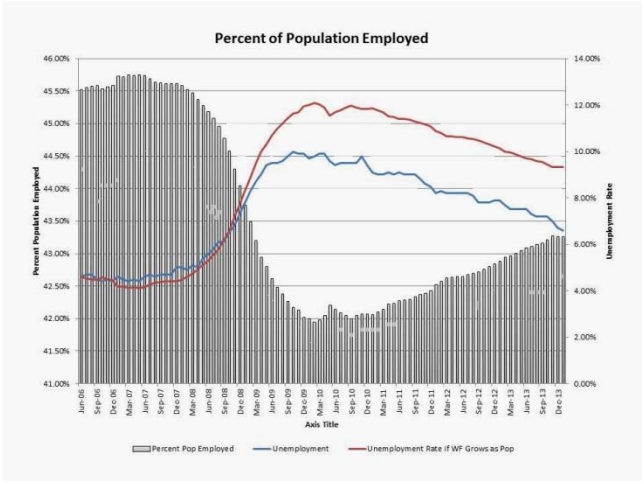
Given that we speak of genetics a bit here I thought I would provide on this snowy Winter day my introductions for 2014. They are:

Hopefully Spring will be here soon!

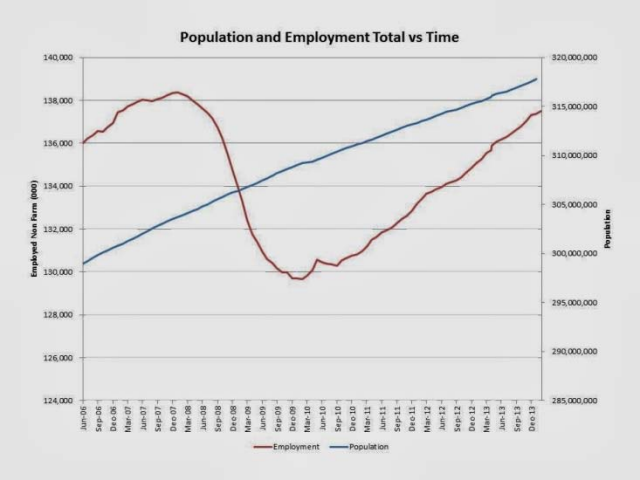
Labels: Commentary

FRIDAY, FEBRUARY 7, 2014

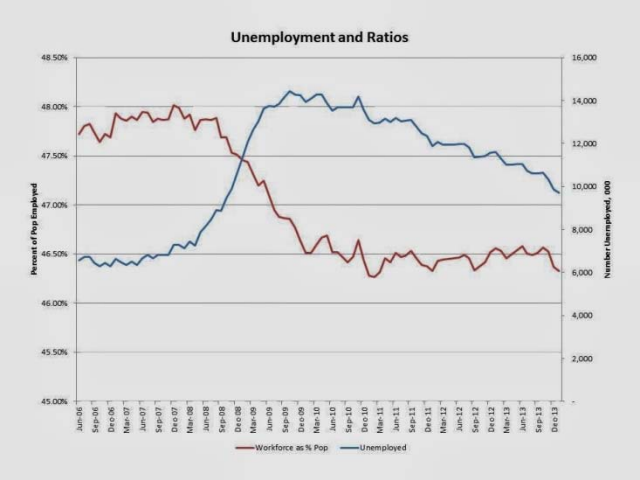
EMPLOYMENT IN 2014



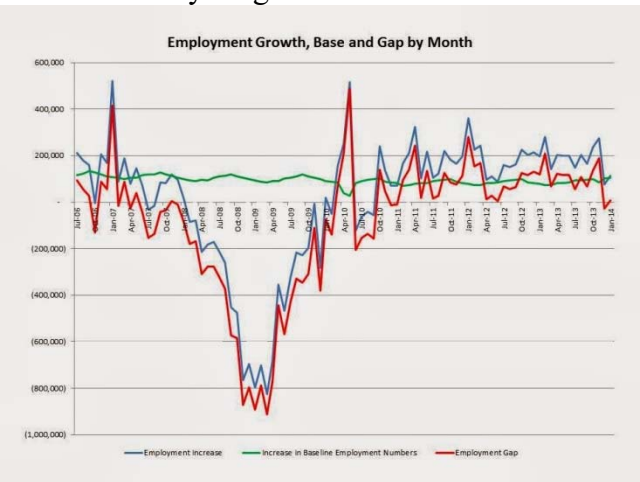
Things are really not that good. The real unemployment based on the workforce participation in January 2008 is about 9.75% and has remained constant. The percent population employed has remained steady and well below the 2008 number. The only reason unemployment is "low" is the farce concerning participation. DoL fails to count people out of work permanently.



Here we see employment and population and the gap is what is a concern. The gap is actually widening.

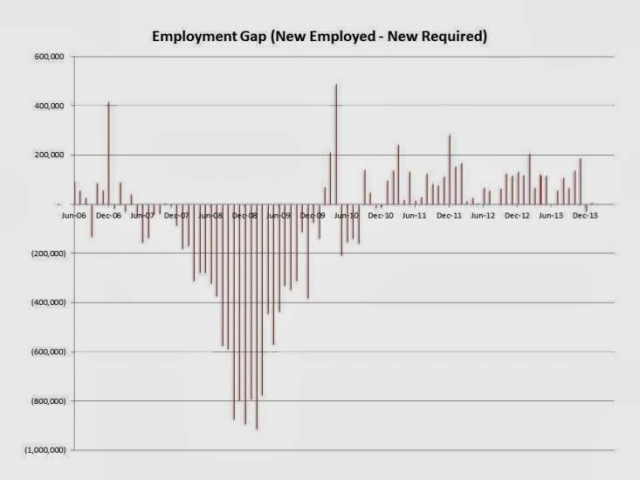


The real concern above is the workforce as percent population. It has decreased! That should send off alarm bells but alas no one any longer cares.



The above clearly shows the employment gap, that is the percent employed in 2008 times the new population less the actual new employees. This is a measure of what is necessary to go no

where! It was negative last month and is near zero this month. That means there is no way to grow!



Finally we show the gap above. This is the worst recession recovery ever! And I believe it is getting worse.

Labels: Economy

MONDAY, FEBRUARY 3, 2014

BILLIONS AND BILLIONS

The Innovation Center under CMS has gotten a bit of light shown upon it. Like PCORI and the dozens of other multi-billion dollar boondoggles spawn by the ACA this gem also got a negative write up by the NY Times.

The Times bemoans:

But now that the center has gotten started, many researchers and economists are disturbed that it is not using randomized clinical trials, the rigorous method that is widely considered the gold standard in medical and social science research. Such trials have long been required to prove the efficacy of medicines, and similarly designed studies have guided efforts to reform welfare-to-work, education and criminal justice programs. But they have rarely been used to guide health care policy — and experts say the center is now squandering a crucial opportunity to develop the evidence needed to retool the nation's troubled health care system in a period of rapid and fundamental change.

If one were to examine their web site one would see a real unorganized collections of "projects" without any apparent cohesive plan. It appears as if they just want to find ways to spend our money. This appears to be a common practice of the ACA as was promised by the San Francisco Congress person. It was passed and now we keep finding out how much it wastes!

Labels: Health Care

SATURDAY, FEBRUARY 1, 2014

COMPARATIVE CLINICAL EFFECTIVENESS: SOME THOUGHTS

The book, Comparative Effectiveness Research: Evidence, Medicine, and Policy by Ashton and Wray is an exceptionally well written presentation of the issues and politics behind CER through the current time. As the authors state, there are many definitions of what CER or its implementation as Comparative Clinical Effectiveness ("CCE") is. A simple but reasonable definition is that CER is the process of examining various modalities of medical treatment for some specific disease state and the determination of what one may be the most effective according to some metric (See pp 122-123 for various definitions).

CCE is then the dissemination of the results of the CER and its use in day to day clinical practice. An additional condition on CER is that unlike FDA randomized clinical trials the CER is conducted in "real life" clinical environments. In the current ACA the CER has been embodied in a non-Governmental entity called PCORI. This book ultimately is a justification of this entity, its purpose and goals and the very nature of its embodiment. Fundamentally the authors make presentations which covers the need for CER/CCE and then provide an exceptionally detailed and well written expose of how it was ultimately implemented in the ACA and why.

Let me first summarize the material presented and then I will provide a critique on it and the approach taken by the authors.

Part I of the book covers the principles of evidence based research and practice. Part II presents the political story of the development of PCORI and the institutionalization of CER/CCE under the ACA. Part III is the authors' presentation of their views on the politics and the implementation and usefulness of CER/CCE.

On p 23 the authors use the prostate cancer ("PCa") studies as a vehicle to discuss CER. This relates to procedures which are used to treat PCa. PCa can be treated in a variety of means, ranging from surgery, radiation therapy, nuclear implants, proton beam, and the cheapest, called watchful waiting. The problem with PCa is that about 90% of it is indolent, namely the patient will never die from it and the treatment is worse than the disease. However some 10% or so, we really do not know the number is aggressive. The typical case goes from a PSA of 4 to 40 in two years and 40 to dead in another two. The challenge is how do we save the 10% while not making the 90% have a higher morbidity? The therapies all too often depend on who the patient see and not based upon any clinical evidence of efficacy or patient satisfaction, the Patient Reported Outcomes ("PRO"). The problem the authors have here is that the problem is more complex than how they present it and it is that complexity that the physician does or should intermediate with.

On p 51 the authors again come back to PCa. Now they address the issue of robotic surgery. It is costly, is advertised, and results in less than clear advantages. Now for clarity purposes the robot is not really some autonomous entity. It merely allows for better controlled movements under the total control of the surgeon. Prostatectomies are difficult because of all the nerve involvement and one prostate is not necessarily the same as all others. The intent is to remove all the

malignancy while retaining nerve functions. Frankly a superb surgeon can do this without any "robot" and usually do. The problem is that the patients may not have a clue and somehow want the "robot". Thus the authors make a good argument for CER/CCE being targeted at not only the physicians but the patients.

Chapter 3 is an excellent expose of FDA assessment of therapeutics. The FDA has over the last half century developed a set of scientifically based procedures to ascertain the safety and efficacy of drugs. This is the randomized placebo based clinical Trials. There generally are three phases before approval and hopefully by the end of Phase III we can rely on the therapeutic doing what is says and not having any morbidity or mortality effects. Sometime that is not the case since the Trials are small and may not be large enough for some of the negative effects. The authors explain this in superb detail.

Chapter 4 will make all surgeons happy. Not really. It is a discussion on the fact that all too often surgeons perform procedures for which there may be little if any clinical evidence. To take the authors back even further, in the 40s and 50 tonsillectomies were almost a child's rite of passage. The Table on p 82 is a good example of the many surgeries performed where there is little if any evidence of efficacy.

P 103 discusses the problems with imaging. I remember in 1972 when the second CAT system was introduced to MGH. It allowed a neurologist to ascertain a block of bleed stroke. It was quick and saved lives. The problem now is that when a CAT is performed, along with massive amounts of radiation, one can find "incidental" observations which then demand follow up despite no clinical evidence of necessity other that shadows.

On p 113 the authors commence discussing the creation of clinical guidelines. The problem, however, is that all too often medical knowledge changes so quickly that the physician is incorporating this knowledge in the way they treat a patient. On the other hand the compilation of CCE procedure such as that proposed by the USPTF is based upon oftentimes decade's old data which was predicated on now outdated medical practice. This is the fundamental flaw of CCE guidelines. They are outdated and often too static. If then developed by Governmental entities they may also often end up becoming the least common denominator.

On p 130-131 the authors make the attempt in discussing the concept of "producing a public good" as the basis for arguing that only the Government can be the creator and manager of CER/CCE. Frankly this is the weakest part of the book and would best have been left aside. However it does provide a vehicle to understand from whence the authors come at this issue.

The Part II discussions are quite interesting. The authors clearly present the Washington drama behind the development of the PCORI side of the ACA, pre current Administration and in the current Administration. For anyone interested in Washington politics this compares well with Woodward and his presentations. The influence of the various stakeholders is discussed and for those not familiar with Washington the key role of Congressional Staff is portrayed effectively.

On p 193 as I comment on later, the authors go off on Rush Limbaugh. Clearly the ACA was a political issue and received not a single Republican vote. Yet the Limbaugh discussion has a

question of relevancy. They continue on p 195 regarding the death panel issues etc. Inflamed words are all too often used in politics and one must ask; what was the basis of this phrase? To some degree, being part of the discussion at the time, it related directly to CCE, and the NHS use of QALY measures in the UK. Namely if one examines the PCa problem, then using a USPTF result and the recommendation to no use PSA on any many over 75, and also mammograms in women over 75, despite what health they may be in and despite any family predispositions, was sending a chilling effect to those affected.

Chapter 10, p 208 and on, is an excellent presentation of PCORI, the non-Governmental entity set up to do CER and assist it to be converted into CCE recommendations. Any reader interested should go to their web site as well. It is too early to determine what they will accomplish but with a $500 million a year budget paid for by the taxpayers they should have no excuses. However when one looks at the FDA, it took then a good half a century to reach the point where they are today. The FDA still has some issues but it is the sine qua non entity in the world. It has developed methodologies and procedures which albeit costly had led to better safety and efficacy in devices and pharmaceuticals. PCORI lacks many of the elements of the FDA and furthermore it is not clear that it can draw on the competencies that exist in the field. The author's speak of what it can do but fail to discuss just how it will go about it.

As the authors reach their concluding comments they seem to go into niches that may or may not be warranted. On pp 248-249 there is a discussion of the public and scientific evidence. They return to their attack on the "political Right" and its "anti-science" philosophy. The problem they are discussing is that of educating patients as well as physicians. Again take the PSA issue. What should a general physician know and what should a patient know? Here we have the problem that PSA management is recording test data over significant time spans. Assume starting at 40 years of age baselines should be take and then data analyzed periodically. It is thus not any single reading, as is the case with BP or fasting blood glucose, but the temporal behavior. However physicians do not have the data and patients do not understand it. It is not because patients are politically influenced to not believe it, the Press oftentimes has a stronger confusing influence, but because they do not get the information. Thus the discussions on these pages warrant attention but not the way the authors provide it.

On pp 250-251 the authors sink into the Medicare swamp. First to make some statements of fact, more than 45% of those on Medicare have or will have paid in more than they will ever receive in benefits. 55% of participants will have paid in substantially less and will have received a dramatically greater share. Medicare is an insurance plan and not a Government benefit, albeit a bit poorly managed. On p 251 the authors say, "Medicare is a federal health insurance program, tax-supported, that was established in 1965" It is tax supported only for that portion of subscribers who have not made enough in their lifetimes. It is subscriber supported by those who have made enough and who continue to make money after 65. This is a distinction and a difference that many fail to understand. It also colors the perception of Medicare of many.

One topic that seems not to have been discussed is that of Patient Reported Outcomes ("PRO"), as an integral part of CER. PROs are complicated testing methodologies to ascertain what the patient felt was the result of a procedure. It should be an integral part of any of the CER efforts. I was disappointed that they failed to focus on this area.

To examine CER/CCE in some specific detail, let us consider the Prostate Cancer debate. The key observation that one should make is that what we understand in Medicine is changing almost daily so what we think today is common practice will be unacceptable in short order. In 2009 there were two papers published in NEJM, one American and one European, which stated that there was no significant different in death rates between men who were PSA screened and those who were not. Now one can examine the data and see some fundamental flaws, after the fact. The study regarded a PSA level of 4.0 as the point at which one should take action. That was acceptable in 1995 but by 2009 we knew that velocity of PSA, % Free PSA, volume adjusted PSA, as well as age adjusted PSA were more critical. Thus, the reports using a 1995 standard presented results that were devoid of 20 years of information.

More importantly, the question posed was: "Using a PSA of 4.0, and using a PSA testing methodology on a biennial basis, did such a testing procedure have an effect upon mortality?" The question which should have been asked was: "Is there a PSA screening methodology which when adjusted for patient classes results in a material change in patient PCa mortality?" The first question was good for 1995 with the limited knowledge available then. The second question opens the door for expanded insight into temporal PSA evaluation. The problem with many CCE trials is that they fixate on the wrong question and thus produce potentially deleterious rules of treatment.

Furthermore as the reports were published a plethora of genetic markers were being developed. Disregarding all of this, the USPTF then graded PSA testing as a D, a level which would prohibit Medicare patients from receiving its benefit. This type of CER/CCE demonstrates the fundamental flaw in CER/CCE in toto. It uses clinically collected data which may be flawed based upon the significant changes in medical knowledge over the time frame of the study and thus potentially inflicting a lethal sequella upon patients. This may not be a death panel but it is flawed medicine.

Overall the authors present a clear picture of CER and its positive benefits. However there are two basic flaws in their presentation. First they fail to fully discuss and disclose the fundamental flaws that may be part of CER/CCE. Second, they fill their presentation with comments as regards to conservative opponents which may add some color but on the other hand actually colors their own attempt at a professional presentation. Frankly the book would have been much better served without references to Rush Limbaugh and the negative comments regarding conservatives as a whole.

Finally one should more carefully examine PCORI. It is a non-Governmental entity like Ginnie Mae and Fannie Mae, albeit not a financial entity, but it has a $500 million annual fund taken from taxes on insurance plans. Recently PCORI awarded NIH a $5 million contract to study their PRO, patient reported outcome questionnaire, which has been around for a while. What is especially strange is why the Government did not fund NIH directly. In this case the taxpayer pays a tax to the insurance company, which hands it to the IRS, which gives it to The Comptroller of the Currency, which hands it over to PCORI who awards it to NIH who now has to manage the contract as external funding. One estimate is that the $5 million funding may

result in $4 million of work at a costs of $12.5 million! Only a Congressionally mandated schema like this would produce such a result. That perhaps is a dark side of the PCORI effort.

Labels: Books, Health Care

FRIDAY, JANUARY 31, 2014

INTERESTING NAVAL AIRCRAFT

The X47-B (above is USN photo) is an unmanned carrier launched aircraft. The Navy has deployed it for tests. As they state:

The X-47B Unmanned Combat Air System Demonstrator (UCAS-D) conducted flight operations aboard the aircraft carrier USS Theodore Roosevelt (CVN 71), Nov. 10. The event, the most-recent in a series of carrier-based tests, demonstrated the integration of the latest in naval aviation technology with the most advanced and capable carrier.

It is interesting in that Carrier Groups present powerful deployment platforms but are also vulnerable to sophisticated attacks.

As USNI reports they will potentially operate jointly with manned aircraft.

During the two previous X-47B at-sea periods onboard USS George HW Bush (CVN-77) and USS Theodore Roosevelt (CVN-71) in 2013, while the unmanned demonstrator had a Boeing F/A-18 chase aircraft, the two types did not operate together on the carrier flight deck. This time around the manned F/A-18 and X-47B will operate from the carrier together cooperatively.

This means that the reliance upon fixed deployment platforms may be diminished.

Labels: Law, Military

AN INTERESTING TRIAL

NCI is proposing to do a randomized trial with selected cancer patients based upon genetic profiling of the specific cancers. Namely they state:

Patients with melanoma whose tumors have mutations in the V600E region of the BRAF gene should have received and progressed on a specific BRAF inhibitor therapy to be eligible for NCI's M-PACT trial.

Patients with lung cancer should have had their tumors tested for the presence of EGFR and ALK gene mutations, and, if mutations were detected, they should have received and progressed on therapies targeting EGFR or ALK, respectively.

The specifically state:

Patients with all types of solid tumors will be considered for trial eligibility. For the randomization, patients will be assigned to Arm A (they will receive a treatment regimen prospectively identified to target their specific mutation or relevant pathway) or Arm B (they will receive a treatment regimen not prospectively identified to target their specific mutation or relevant pathway). Patients in Arm B will have the option to cross over to Arm A to receive therapy identified to target their specific mutation or relevant pathway if their disease progresses on their initial study treatment. As of January 2014, the study is open for patient accrual.

What is interesting is that this appears to be a great beginning to such a procedure. One of the concerns, however, is that with BRAF V600 we seem MEK mutations following and then we must treat that one. The challenge is to try to better understand the evolving mutations that result as the tumors proliferate and spread. Thus we may then better understand how to treat the patient progressively and even perhaps prevent subsequent mutations. But this is well worth the following.

However there is the question of epigenetic factors which should be considered as well. Methylation is a prime factor which we know plays a significant part in many cancers, such as prostate and others. Other epigenetic factors such as miRNA and lncRNA are also considered of import. Thus focusing on genes is but one step.

Therefore it would be of interest to further consider:

1. Progression of genetic changes by time and location.

2. Complexities and proliferation of epigenetic changes as well as benign somatic epigenetic factors.

3. Family genetic analysis could also be of help to determined any heritability predilection.

Labels: Cancer

THURSDAY, JANUARY 30, 2014

JE PARLE FRANCAIS, UN PEU, JE PENSE

The NY Times has a piece on the attempt to expand French as a second language in New York Schools. They state:

In the fugue of tongues on New York's streets, French has never been a dominant voice. And as surging numbers of Asian and Latino immigrants continue to tip the balance of foreign languages toward Chinese and Spanish, the idea of learning French, to some, may seem kind of quaint, even anachronistic.Yet in the city's public school system, the French dual-language program, in which half the classes are in French and the other half in English, is booming.

Now more than half a century ago after my Latin and Greek I spent four years learning French. One had to since we were taught by the French Christian Brothers. But has French been of any use? Well I had to translate several papers for my Doctorate, but that was harder than I thought since several were from the early 1900s and they were a bit arcane. Then I spent a great amount of time in France and as long as I was not in Paris things went well. In Paris my non-Parisian accent was instantly noticed and the Parisians switched to English so as to let me know of their dissatisfaction.

Now the two main languages seem to be Mandarin and Spanish. Frankly any New Yorker should just pick up Spanish as a second language on the subway alone, the signs are all in Spanish and half the conversations are as well. It is almost by osmosis that one gets to feel comfortable with it.

Recently I remarked that my grandchildren are learning Mandarin whereas I learned Russian back in the 50s and 60s. My Mandarin speaking listener immediately asked if I was a "spy". "No", I replied and continued to explain that in that period much of the technical literature in my area was in Russian. In fact if I recall I may have been one of the last MIT PhDs to have to have some modicum of language proficiency, mine, for what it was worth, was Russian.

So what is the worth of French? Almost everyone knows English, and English can be mangled totally and still be a manageable means of communications. Just speak to any New York Cab Driver, almost all of whom have some other language as their native tongue. English has so

much flexibility, assuming you do further mangle it with an accent as with the Brits, and it can be understood.

I cannot say about Mandarin, but Russian is also manageable, and Italian, well, just learn to stress all vowels and wave your hands and you too are from some part of Italy, love the language.

But French, one cannot make a mistake in syntax, form, or any part of the language, it grates the ear and mind. French has unalterable structure and is devoid of slang. You must say what you intend the way it is supposed to be said, and moreover you must remember the syllable to be stressed. So what its the value of French? Well you can read some of the worlds greatest novels, philosophers, political thinkers, poets, and the like, they are wonderful in French. In Normandy and Savoy they will listen to your attempts to pronounce it properly and are forgiving. But abandon all hope of ye who enter Paris!

So what is the best languages to teach in New York? It seems that Latin and Greek have seen better days. But Spanish and Mandarin can be fund on any street corner. The key to learning a language is the ability to integrate it to one's visual response. Russian finally made it when I could walk around Moscow and not translate words, just look at the Cyrillic collection and recognize apples, milk, bread, etc. New York presents that in Mandarin and Spanish, unfortunately not much if any French!

Labels: Commentary, Education

WEDNESDAY, JANUARY 29, 2014

THE ONE TRICK PONY

For the past five plus years as I have watched Google prosper I have always suspected it is a one trick pony, a very good one trick pony. The announcement today that it is selling the Motorola Unit that is bout a few years ago seems to more than validate my view.

One need just look at Google's stumbling:

1. Nexus, now I have several Kindles, they work, they are reliable, and Amazon understands customer care. My Nexus broke in 6 weeks and I sent it back to the Chairman who I had co-chaired the Internet 2 Presidential Panel with. I sent a letter, a personal letter. Did I ever get a response, no, did I ever get a replacement, no. One suspects management has other issues that are more important than customers.

2. Google RSS Reader: Now this could have been a goldmine. Dead.

3. Google's Personal Health Pages: I saw this as a home run for the EHR requirement. Google's response, kill it.

4. Fiber to the Home: What part of my many analyses on cities did Google not read? Forget it guys, the Cable companies will bury you. How much did you wast on this one.

The list goes on. However, Android makes sense, but that was a natural extension of software to the customer, a platform. The other things were toys that the "kids" played with.

My advice to Google, "focus, focus, focus". Being under 30 and having a high IQ is not all in life. And yes, if all else fails please listen to the customer. After the NSA does, your customers at that!

Labels: Google

TUESDAY, JANUARY 28, 2014

WHAT IS THE PURPOSE OF THE NAVY?

Admiral Mahan was a distant cousin from the same village in Ireland in County Lietrim. So perhaps, as my Irish side would say, I have a wee bit of a concern.

There is a strong proposal coming from the current Administration to reduce the size of the carrier fleet. As USNI states:

A bipartisan group of Congressmen have written a letter to the Secretary of Defense expressing their strong support for maintaining a fleet of 11 nuclear-powered aircraft carriers despite rumors the Pentagon is considering cutting the carrier fleet. "We write to reiterate our strong support that the United States Navy should continue to require a naval fleet of no-less than 11 nuclear aircraft carriers," reads the Tuesday letter address to Defense Secretary Chuck Hagel.

Now generally there is only one third of the fleet out at any one time, thus about 3 or 4 carriers, covering the Globe. They are supported by a collection of other ships in what is called a Carrier Task Force. They are our way of protecting American interests, like getting help to Libya etc, which at times does not work.

As the Navy currently reports there are 4 carriers at sea. They are:

USS Carl Vinson (CVN 70) - Pacific Ocean
USS Theodore Roosevelt (CVN 71) - 5th Fleet
USS Harry S. Truman (CVN 75) - 5th Fleet
USS Ronald Reagan (CVN 76) - Pacific Ocean

That leaves 7 in port. In the event of a problem in the Atlantic or even northern pacific we have a problem. Currently the total focus is the Middle East and the South China Seas. We have substantial exposure elsewhere. Not to mention the problem of littoral threats.

Perhaps a rethinking of the strategic need for a well deployed Navy, including submersibles, littorals and a well equipped Marine Corps is essential.

Labels: Politics

MONDAY, JANUARY 27, 2014

PROSTATE CANCER OVERDIAGNOSIS?

Prostate Cancer is the number one occurring cancer in men in the U.S. At the same time there is an ongoing debate as to the need to screen for this cancer. The problem is that most cases of PCa are indolent and will not be the cause for a man's demise. On the other hand we know that a significant number of cases, 5-15% of them, are aggressive and will result in a very painful death in a short period, two to six years or less. The problem is that there is no gold standard test to determine which is which.

Various genetic profiles have been proposed wherein they measure the expression of a panel of genes and then calculate a metric, usually some number, which if in a certain range means indolent and outside of the range is aggressive. The problem of course is; what cells are you making this measurement on? If you are doing it on the encapsulated prostate cells then you may be missing the already metastasized cells which have moved to the bone.

Now a recent paper by Gulati et al state[89][1]:

The chance that a prostate cancer detected by screening is overdiagnosed (ie, it would not have been detected in the absence of screening) can vary widely depending on the patient's age and tumor characteristics. The purpose of this study is to use age, Gleason score, and prostate-specific antigen (PSA) level to help inform patients with screen-detected prostate cancers about the chances their cancers were overdiagnosed.

First I would be concerned with the definition of overdiagnosed. It states; "it would not have been detected in the absence of screening". One should examine this. If one screens and detects a PCa then that is an overdiagnosis. If, however, one gets a patient who comes into your clinic with massive back pain and dysuria, then that patient is not overdiagnosed. The latter patient is however terminal. Thus I would strongly quibble with this definition of overdiagnosed.

They continue:

A computer microsimulation model of prostate cancer natural history was used to generate virtual life histories in the presence and absence of PSA screening, including an indicator of whether screen detected cancers are overdiagnosed. A logistic regression model was fit to nonmetastatic patients diagnosed by screening with PSA less than 10ng/mL, and a nomogram was created to predict the individualized risk of overdiagnosis given age, Gleason score, and PSA at diagnosis. The calibrated microsimulation model closely reproduces observed incidence

[89][1] http://jnci.oxfordjournals.org/content/early/2014/01/06/jnci.djt367.abstract

trends in the Surveillance, Epidemiology, and End Results registries by age, stage, and Gleason score. The fitted logistic regression predicts risks of overdiagnosis among PSA-detected patients with an area under the curve of 0.75. Chances of overdiagnosis range from 2.9% to 88.1%. The chances of overdiagnosis vary considerably by age, Gleason score, and PSA at diagnosis. The overdiagnosis nomogram presents tailored estimates of these risks based on patient and tumor information known at diagnosis and can be used to inform decisions about treating PSA-detected prostate cancers.

Now I would also have concern as regards to such a model. We have been examining them in several cancers and they are complex and require data which we are yet able to provide. Moreover a logistic analysis is rant with many problems; it merely hypothesizes a relationship based on a correlation model which may bear no resemblance to reality. In its place one really needs a tempero-spatial model which includes genetic mutations in some Markov manner. Also I would be concerned with an overdiagnosis range of from 2.9% to 88.1%.

Now a comment by Rathner in the same issue states as follows[90][2]:

Using a nomogram that incorporates age, Gleason score, and prostate-specific antigen (PSA) level at diagnosis, individual risks that a screen-detected prostate cancer has been overdiagnosed can be estimated, according to a new study published January 6 in the Journal of the National Cancer Institute . The authors used a standard definition of overdiagnosis to refer to a cancer that would not have become symptomatic or clinically identifiable if it had not been detected by screening. Overdiagnosed cancers do not pose a risk to the patient and do not require treatment, which is associated with significant risks of impotence and incontinence.

Here there is a clarification of overdiagnosed as meaning indolent. Indolent means slow growing and of de minimis risk of death from the lesion. However it is highly problematic to make such a determination unless one uses genetic metrics on a whole body basis. Techniques using exosomes may be beneficial if the profiles are stable.

Previous studies have estimated the risk of overdiagnosis for the U.S. population, with results ranging from 23% to 42% of screen detections. However, risks of overdiagnosis can vary considerably depending on the patient's age and tumor characteristics, highlighting the need for a personalized tool to predict the likelihood of overdiagnosis. … The authors used a microsimulation model to generate virtual life histories for a representative population of u S men between 1975 and 2005. Men who develop cancer can be detected based on elevated PSA levels or development of symptoms. ,,,,

A prediction model was then developed to predict individual chances of overdiagnosis (i.e., the chance that other-cause death would precede diagnosis in the absence of PSA screening) given information known at screen detection. The prediction model estimates that the chances of overdiagnosis range from 2.9% to 88.1% depending on patient age, PSA, and Gleason score. …

[90][2] http://jnci.oxfordjournals.org/content/early/2014/01/06/jnci.dju001.full.pdf+html

Freidlin and Korn question whether the Gulati et al model of the risk of overdiagnosis is useful in guiding treatment decisions of patients with screen-detected prostate cancer: "...once an individual has been screened and found to have prostate cancer, the relevant question is the outcomes of various treatments (treatment morbidity, prostate cancer symptoms and death), and not the probability of an event [detection of prostate cancer] that could have happened if the individual had not been screened."

One then must ask if it is ethical to perform a fully blinded randomized trial to ascertain the predictions made herein. As much as I am a fan of models, this is not a phenomenological model. It merely uses data from previous diagnostic tests to ascertain the importance of certain metrics. As such it lack what I believe is a sine qua non to approaches like this, a physical model with predictability.

Now comments in Healio state the following[91[3]]:

Researchers assessed risk for overdiagnosis — defined as a cancer detected through screening that otherwise would have been asymptomatic or clinically unapparent— using a microsimulation model of virtual life histories of men aged 50 to 84 years from 1975 to 2005. Researchers then applied SEER prostate cancer incidence and PSA screening data to the virtual models. Results indicated that the odds for overdiagnosis increased by 12.9% (95% CI, 12.2-13.6) for each additional year of age at the time of diagnosis.

One of the concerns is that using SEER from 1975 to 2005 may insert a bias in age since PSA was not used to any extent until 1995 at the earliest. Thus half the data was without PSA testing and thus the older men may very well already have PCa.

A Gleason score of at least 7 was associated with a 19.5% (95% CI, 11.7-26.5) decrease in the risk for overdiagnosis when compared with a Gleason score of 6 or lower (P<.001). The odds of overdiagnosis decreased by 16.6% (95% CI, 14.2-18.9) with each additional 1 ng/mL of serum PSA up to 10 ng/mL.

A Gleason of 7 on biopsy may be really a Gleason of 8 upon prostatectomy. It may even be higher. PSA is also an issue related to age, prostate volume, BPH, and the better measurements are those reflecting temporal changes. Single PSA measures have the same problem as spot blood pressure measures. Researchers found age to be the most statistically significant risk. Among men with a Gleason score of 6 or lower and PSA levels from 4 ng/mL to 4.9 ng/mL, those who were aged 50 to 54 years had an 11.6% risk for overdiagnosis, whereas those who were aged 70 to 74 years had a 59.9% risk and those who were aged 80 to 84 years had an 83.4% risk.

91[3] http://www.healio.com/hematology-oncology/prostate-cancer/news/online/%7Bc5dae162-daa5-4940-a849-31151a911d3f%7D/age-gleason-score-psa-indicate-risk-for-prostate-cancer-overdiagnosis

Age has always been a significant factor and the results presented here in my opinion just reiterate that fact.

The question is; does such a nomogram have any clinical value? That is in my opinion problematic. The handful or so of first line Urologists at major centers will have thousands of cases where they can ascertain based on a plethora of data a patient's prognosis, yet even they are wont to go too far. Patients, in my opinion, may find such an approach as just another element to add to an already confusing pile of suggestions.

References

Gulati R et al, Individualized Estimates of Overdiagnosis in Screen-Detected Prostate Cancer, JNCI J Natl Cancer Inst (2014) doi: 10.1093/jnci/djt367 First published online: January 7, 2014

Rathner, Z., Nomogram to determine individualized estimates of screen-detected prostate cancer overdiagnosis, JNCI J Natl Cancer Inst (2014) doi: 10.1093/jnci/dju001 First published online: January 7, 2014

Labels: Cancer

HYPERMETHYLATION AND PCA

Methylation is an epigenetic process which often results in the silencing of genes and for example in the case of hematologic cancers is often the driver for loss of proper maturation of cells and to the proliferation of blast cells. The MDS condition is a prime example. This precursor of AML is often a result of hypermethylation which in turn can be treated by demethylating drugs.

In PCa there is still a debate as regards to the cell types initiating the process, luminal vs basal, and also the existence and significance of the PCa stem cell. In a recent paper by Pellacani et al the authors note[92[1]]:

Prostate cancer (CaP) is mostly composed of luminal-like differentiated cells, but contains a small subpopulation of basal cells (including stem-like cells), which can proliferate and differentiate into luminal-like cells. In cancers, CpG island hypermethylation has been associated with gene downregulation, but the causal relationship between the two phenomena is still debated. Here we clarify the origin and function of CpG island hypermethylation in CaP, in the context of a cancer cell hierarchy and epithelial differentiation, by analysis of separated basal and luminal cells from cancers.

[92[1]] http://www.nature.com/cdd/journal/vaop/ncurrent/pdf/cdd2013202a.pdf

For a set of genes (including GSTP1) that are hypermethylated in CaP, gene downregulation is the result of cell differentiation and is not cancer specific. Hypermethylation is however seen in more differentiated cancer cells and is promoted by hyperproliferation. These genes are maintained as actively expressed and methylation-free in undifferentiated CaP cells, and their hypermethylation is not essential for either tumour development or expansion.

We present evidence for the causes and the dynamics of CpG island hypermethylation in CaP, showing that, for a specific set of genes, promoter methylation is downstream of gene downregulation and is not a driver of gene repression, while gene repression is a result of tissue-specific differentiation.

The observation is interesting since it differentiates hypermethylation from cause to effect.

As stated in the article in Medical Express concerning the above article, the writers note[93][2]:

Scientists at the University of York have discovered that a process called 'methylation', previously thought to drive the development of cancer, occurs in cells that are already cancerous. The findings mean therapies aimed at reversing this process might not be effective against cancer stem cells, allowing the cancer to return…The work, … reveals a major difference between the cells normally treated in cancer and the underlying 'stem' cells.

The discussion of stem cells in PCa is something we have examined for the past few years. There is as of yet no clear definitive demonstration of such stem cells and even more so there is no description of what a stem cell is especially as regards to any genetic changes. They continue:

Dr Pellacani said: "To develop cancer, certain proteins found in healthy cells need to be switched off". Sometimes this is caused by methylation - a process where DNA is changed to block instructions for making a specific protein. "There are obvious differences in the methylation of genes in prostate cancer cells and non-cancer cells. This previously suggested that the process could be driving the progression of cancer, and that this could be reversed by using specific drugs, but our research has suggested that this may not be the case."

Methylation is a powerful and ubiquitous process. It has only been understood as a significant epigenetic factor in the past decade and even now is going through a steep learning curve. Methylation is often found in cancer cells and like so many of the suggested genetic profiles one wonders if it is cause, effect, or just correlative. One may even wonder if methylation is some archaic attempt by the cells to deal with the genetic changes causing the cancer. It is not yet clear just what the function may be.

The authors continue:

Prostate cancer is made up of two types of cell; rare basal cells, including stem cells, from which the tumour is formed, and luminal cells, which form the tumour mass. The team found that a

[93][2] http://medicalxpress.com/news/2014-01-prostate-cancer-drugs-root-disease.html

change from basal to luminal cells – a process called differentiation – is strongly linked to the methylation difference, suggesting that the methylation in prostate cancer cells is not the primary driving force for the cancer.

This is a strong statement which some may not fully agree with. There have been many studies which we have reported on here that question whether we have a basal or luminal cell origination of PCa. In fact one might even imagine some other cell altogether. Yet the methylation factor in basal to luminal change is interesting.

Dr Pellacani continued: "There are clear implications for the effectiveness of new drugs currently being developed to change the methylation pattern in cancers. At the moment we only treat a proportion of the cells. By breaking the cancer down into its component cell types, we get insights into why cancers come back after treatment. Only by treating all the cells in a cancer will we approach long term treatment or even cure." Professor Maitland and his team at the YCR Cancer Research Unit achieved international recognition in 2005 when they were the first to identify prostate cancer stem cells, which are believed to be the 'root cause' of prostate cancer.

This discussion is of interest and it blends well with our model of cancer cell propagation. The two observations are critical. They are: (i) that there are various cancer cells characterized by specific gene expressions or lack thereof, (ii) that there exists a cell called the stem cell which has characteristics we have discussed at length. The hypermethylation, and even hypomethylation, are but two characteristics of epigenetic changes. We would also expect to see miRNA, lncRNA and the like to also play roles.

The problem still is; what cells are we profiling? Are we profiling cells proliferating in the prostate or one which have already spread elsewhere?

Overall this is an interesting and compelling report.

References

Pellacani, D et al, DNA hypermethylation in prostate cancer is a consequence of aberrant epithelial differentiation and hyperproliferation, Cell Death & Differentiation, (24 January 2014).

Labels: Cancer

SUNDAY, JANUARY 26, 2014

IT IS GOOD THAT WE ARE NOT IN THE MIDDLE AGES

The Guardian reports that when the Bishop of Rome let loose some white doves from his balcony that they were attacked by seagulls and crows. If this were say 1092 we might have the source for some bad omens.

The Guardian states:

...thousands of people watched in St Peter's Square on Sunday, a seagull and a large black crow swept down on the doves after they were set free from an open window of the Apostolic Palace.

One wonders where this may fit within the message. It could be a great basis for some novel.

Labels: Commentary

INCOME INEQUALITY: WHAT DOES IT REALLY MEAN?

The current concern on the issue of Income Inequality is really not new. As I have noted before it started in the early 19th century and seemed to peak during the first Progressive era from 1890 to 1920. The issue then was that with the influx of immigrants and the extreme wealth of a few, that the country was going to Hell in a hand basket.

Recent authors such as the left wing Irishman at the New Yorker states:

Now for the bad news: the Horatio Alger myth is still a myth. Relative to many other advanced countries, the United States remains a highly stratified society, and most poor kids still have few prospects of making big strides. I've already mentioned the finding that the odds of a child moving from the bottom fifth of the income distribution to the top fifth are less than one in ten, and have been that way for decades. For children who are born in the second fifth of the income distribution, those who might be categorized as working class or lower-middle class, the probability of moving up to the top quintile has fallen significantly. For someone born in 1971, it was 17.7 per cent; for someone born in 1986, it was 13.8 per cent.

Frankly to see that this does not really add up all one has to do is to look at the backgrounds of the top earners at Goldman Sachs. Unlike the UK we in the US do not have a Constitutionally mandated Aristocracy. The UK does and they believe there is a Divine right to, well money. Here in the US frankly any person if they are smart, so inclined, and can fast talk themselves to the right places, can get to Goldman.

In a similar fashion, I look at the many students from China who come here and with just a bit of searching one finds near poverty a generation or so in the past.

The problem as I see it is what we expect of our children. When I approached college it was; what was I going to do for a living? In the late 1950s most kids in Catholic Schools in New York saw the police or fire departments as a path forward. Many looked for union jobs, sinecures that guaranteed high pay for low yield. Only some 20% or more went to college. A few of us looked past the good Brothers and even Vatican 2 and saw opportunity. Thus one got a degree, by hook or by crook, so as to get a well paying job, not to be "educated". The problem today is we seem to send our children to college and seem never to ask them how they will earn a living.

The kids coming out and going to Goldman had asked that question early on and were directed to

go there. Goldman and the like are one of the many opportunities available. Entrepreneurs have a much better chance than when I started with my first start up in 1969. There were at best a handful of venture companies, if such was even an appropriate term. Now, there are still thousands. And there are globalization trends. There are very few silver spoons. This is not the UK. Fortunes are made and lost. Then they are made again. That is the glory of the United States.

Perhaps, as I suppose, the drop in some incomes, is because we failed to ask, "What are you going to do for a living?" Instead we allowed a generation or two to take up their interests never worrying about their lives!

Labels: Government, Politics

LEFT HAND POCKET TO THE RIGHT HAND POCKET

In a recent announcement, PCORI, the Government sponsored and funded entity which get about $500M pa from the added taxes on our new health care plans has awarded some $5M contract to NIH to fund work on its internal PRO system. They state:

The Patient-Centered Outcomes Research Institute (PCORI) has approved $5 million in funding for research focused on the Patient Reported Outcomes Measurement Information System (PROMIS) of the National Institutes of Health (NIH). "Funding PCORI projects focused on PROMIS will allow us to substantially advance the use of these tools in comparative effectiveness research," said PCORI .... "Working with the NIH allows us to build on its investment in a comprehensive, flexible, and patient-centered measurement system."

Now this means that the money we all pay for our health care now has a tax which is collected by the Government and then handed over to PCOR which then as a non-governmental entity adds its costs and then transfers the $% M to NIH a governmental entity. One wonders how much money there was before it got down to the $5 M going to NIH. Why not just give NIH the money outright rather than burdening the taxpayers with the added overhead. Only the Government could conceive of this mess.

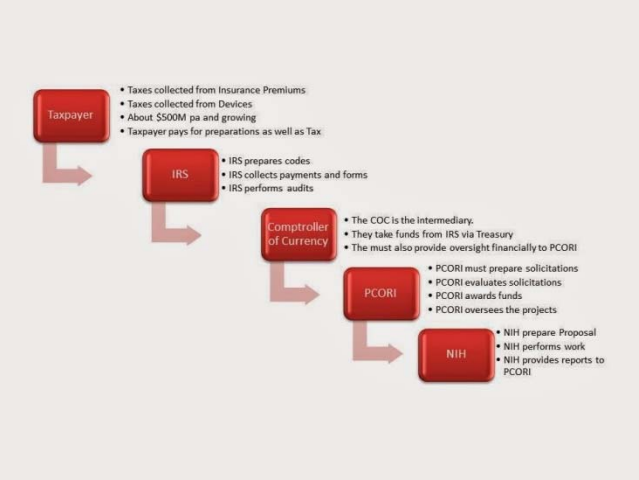
But read the words, "*advance the use of these tools in comparative effectiveness research"* Namely, this is a CCE tool, and although it focuses on PRO information it will be used for CCE or CER results.

Now just a remark on CCE. FDA does randomized trials using well accepted gold standard statistical techniques. CER examines procedure in a real life clinical setting. Patients just do what they want. That means if we compare weight reduction to metformin for Type 2 Diabetes, we all know that most people just do not do what they are supposed to in managing food intake. Thus we know a priori that there is a bias. Also the people will not tell the truth, they fear being criticized. Thus CER has at best highly questionable results.

So why do this work? If NIH is doing this for drug approval support then we have the FDA involved. If it is for CER/CEE work then PCORI is now the new kid on the block. But somehow

this flipping the money around so everyone gets a bite is rather silly, and wasteful of the taxpayers money, but alas it is what we have come to see in the ACA. Just a little corner of the effort.

Now let us examine what this $5M may cost the Taxpayer. Below is a reasonable flow chart of what Government entity handles each step.



The money is paid by the Taxpayer. It is collected and validated by the IRS who hands it to the Comptroller of the Currency, who pays PCORI. Remember PCORI us guaranteed a minimum of $500M per year!. Now PCORI works through RFPs etc and ultimately the $5 million goes to NIH. Along the way I estimate that the Taxpayer had to pay in $25 million to get the $5 million out the other end! Why not just give it directly to NIH? Simple, ACA will not allow that! And folks, you are just seeing the beginning. Don't say we did not warn you!

Labels: Government, Health Care

SUNDAY, JANUARY 26, 2014

CANCER GENES

Genes encode anti-proliferative proteins, in which loss-of-function mutations would be expected to contribute to oncogenesis	Genes encode proteins that are clearly involved in cell proliferation	Genes encode proapoptotic factors, in which loss-of-function mutations would be expected to promote oncogenesis	Genes encode proteins related to genome stability	Genes are associated with chromatin regulation	Genes encode proteins whose loss is expected to help tumours evade immune attack	Genes are associated with RNA processing and metabolism	Gene involved in protein homeostasis
ARHGAP35	RHEB	ALPK2	CEP76	SETDB1	HLA-B	PCBP1	TRIM23
MGA	RHOA	BCLAF1	RAD21	MBD1	TAP1	OKI	
IRF6	SOS1	MAP4K3	TP53BP1	EZH1	CD1D	RPL5	
DNER	ELF3	ZNF750	TPX2	CDH8			
	SGK1	TNF	ZRANB3	HIST1H4E			
	MYOCD		STX2				

In a recent paper by Lawrence et al in Nature the authors present a structured collection of genes elated to a selection of cancers. We summarize them above. The details are in the paper.

The details shown above are another way to view the results. This is interesting in that it demonstrates steps in cancer formation, proliferation, and metastasis. Although the paper does present a mass of unconnected genetic markers, one suspects that the spatio-temporal characteristic can be somewhat readily ascertained.

As the authors conclude:

Although a few cancer genes are mutated in a high proportion of tumours of a given type (>20%), most are mutated at intermediate frequencies (2-20%). To explore the feasibility of creating a comprehensive catalogue of cancer genes, we analysed somatic point mutations in exome sequences from 4,742 human cancers and their matched normal-tissue samples across 21 cancer types. We found that large-scale genomic analysis can identify nearly all known cancer genes in these tumour types. Our analysis also identified 33 genes that were not previously known to be significantly mutated in cancer, including genes related to proliferation, apoptosis, genome stability, chromatin regulation, immune evasion, RNA processing and protein homeostasis. Down-sampling analysis indicates that larger sample sizes will reveal many more genes mutated at clinically important frequencies.

It is worth following this in some detail.

Labels: Cancer

PAINE VERSUS MADISON AND HAMILTON

Common Sense was written by Thomas Paine and he put his own name on it as well as paid for it out of his own pocket. In contrast when Madison, Hamilton et al wrote the Federalist Papers in support of the Constitution they did so anonymously. The NY Times today bemoans the influence of American like the Kochs who use their First Amendment rights to present their

political views, a practice quite common here in the US. After all many of the broadcast stations as well as the Times itself present their views in a continuous manner.

The Times appears to believe that the Kochs can make Democrats vote against their own interests by using their political speech rights whereas the Times has no such influence. The logic befuddles me.

The Times states:

Democrats have been staggered by a $20 million advertising blitz produced by Americans for Prosperity, the conservative advocacy group organized and financed by the Koch brothers, billionaire industrialists. The ads take aim at House and Senate candidates for re-election who have supported the health law, and blame them for the hyped-up problems with the law's rollout that now seem to be the sole plank in this year's Republican platform.

Now the ACA as we have noted herein for the past five years is rant with problems. The recent ones are but the tips of the iceberg. We have written extensively about the EHR and its costs and ability to disclose personal records, the CCE effort bolstered by PCORI, a non-governmental entity, set outside the control of Congress, however supported by the new taxes on our Health Care programs, starting at $500M per year, which will "advise" CMS on what procedures should be allowed by Medicare and Medicaid, now covering some 130 million Americans, yes 50% of the population! The list continues as we will see in the next few years. Despite the person from San Francisco who said "you must pass it to see what is in it" we saw what was in it as it was rolled out, a disaster, and a potential for the collapse of the Country.

Thus do the Kochs have a right? Absolutely. Moreover they have a duty as citizens to present the facts. Take a look at what we wrote five years ago, it is just starting to unfold. There are times when facts do matter!

Labels: Health Care

WEDNESDAY, JANUARY 22, 2014

NATIONAL SERVICE: THE NEW PUSH OR A GREAT LEAP FORWARD?

I have recently heard Defense Secretary Gates and Admiral Mullen amongst other former DOD types advocate for Universal Government Mandated Service for all 18-22 year olds. I have opposed that before and since they seem to be promoting it again, I thought a review of rational reasons against it is worth a try. I fear that if this idea gets any legs it will drag this country into the sewer of history. This analysis is in no way any form of ad hominem attack; it is however an attempt to logically frame a counter-view in light of the now apparently a common-call from former DOD leaders for this idea of Universal Service.

Let me begin by summarizing my reasons against this proposal.

Costs: Overall as I have examined before, the costs of enrolling, managing, feeding, and directing a mass of 18-22 year olds, assuming no outs for any reason, exceeds $T per year! That now is on par with the total Government Budget. This should be the first question asked. DOD is costly enough, the idea of placing tens of millions of 18-22 year olds into Government programs would collapse our economy in short order. Whether this is reflective of classic DOD spending mentality of not is questionable, however it does reflect a broad and consistent lack of full thought on the proposal by all Generals, Admiral and Secretaries concerned.

Loss of Economic Productivity: Many entrepreneurs start in the late teens and early twenties. I recognize that entrepreneur thinking is not fostered in the Military, just the opposite, but it is that thinking and mind set, tat risk taking, that provides the future economic engine of our country. Take Edison, Jobs, Gates, and the like and send them at their prime to sweep streets in El Paso and one wonders how much we lost.

Loss of Educational Continuity: As any educational professional knows if one takes a high performing High School student out of the productive environment and place them into a prison like entity, after all it is the Government and managed by the Government, their enthusiasm will drop like a brick! Why would anyone desire to destroy the creativity of youth in this manner?

Loss of Entrepreneurial Capability: Entrepreneurs start early. The are motivated by challenges to create, to produce. Sending entrepreneurs into 3 year mandated Government programs is four years of entrepreneurial loss.

Cost of Delay on Education: Delaying education, taking someone from High School and sending them to some backwater for four years is costly. When they get back home they are now

competing with the Chinese students who took their place and fact an escalating tuition rate, four years more costly than what they would have faced without the Government internments.

Failure to do Anything Beneficial: Do we forget the Stimulus jobs and shovel ready projects so quickly. What Government effort is ever productive? Perhaps some of NIH, but that is the exception. Most Government workers sort yellow papers from green ones, unless that is perhaps too much. So we are asking these young people to do just what? Gates suggested teaching. Has he not heard of unions? An 18 year old teaching what? To whom? These suggestions keep coming forth with not a single thought of how they would ever be implemented. No wonder our wars are often in chaos from the top down.

Loss of International Competitiveness: Imagine if the Chinese head of government mandated that instead of going to college and competing in the world economy that the 18-220 year olds go to the country side and farm and teach. Oh yes, that did happen under Mao, the Great Leap Forward. How did that d for China? Not that well. Lost a generation. Now China sees its youth as its future, not some fodder for Governmental control. They would rather set up new companies; compete with US technology and entities. China wants to lead and it will lead through its youth. It would never think of another Great Leap Forward. So why does our ex-Military higher up seem to think it is such a great idea, have they not read Mao? Or have they?

These are just a few of the reasons that such a proposal is devoid of merit. But is speaks a great deal of the mindset of those who propose, and in a somewhat terrifying manner.

Now the men proposing this seem to be speaking from the same script. Not uncommon in Washington, especially today. The all seem never to have held a real job, never have been in the position of creating jobs and have been masters of the political environment in DC. They all seem to echo the statement: “18-22 years olds should pay back their country…”

Now I do not know what they think 18-22 year olds have costs the US of late but given the state of the US school system they may be demanding a refund. In addition they may face a $250,000 or more price tag to further their education so as to best allow them to be productive members of our country. They are the ones who hopefully are investing their time and talents into productive results. That is the essence of a capitalist society; we want people to invest their youth into things that will continue to drive us forward. By saying that they have a duty to pay back at 18 seem almost laughable. One wonders what salon they have all been gathering these thoughts in.

Instead of entering into this foray, which the Military types are all too often ill-equipped to comment, costs and sources of revenue never seem to be in their fore, they should be having a conversation on how does the US defend its interests in the 21st Century. Threats have evolved, the most recent wars are examples, and we need a mindset to enter successfully into that fray. The Military needs effective covert operations, it needs high quality intelligences often gathered via classic human Intel sources. We may have the best satellites but we need the best and most up to date human Intel, however we can obtain it. The Navy has a schizophrenic challenge. On the one hand it must defend against large scale players such as China so that threats cannot be made too effective but at the same time they must support the covert ops efforts. The Navy must

also provide flexible platforms for deployment, defense and offense. More thought on these issues and less on another Great Leap Forward would be useful.

Labels: Government

OBESITY, TYPE 2 DIABETES AND MORTALITY RATES

We have discussed extensively over the past six years the nexus between Obesity, Type 2 Diabetes and now mortality. In a recent study by Tobias et al in NEJM there is an assumed nexus between obesity, as determined by BMI, and the impact of the combo on mortality.

Tobias et al conclude:

We observed a J-shaped association between BMI and mortality among all participants and among those who had ever smoked and a direct linear relationship among those who had never smoked. We found no evidence of lower mortality among patients with diabetes who were overweight or obese at diagnosis, as compared with their normal-weight counterparts, or of an obesity paradox.

Namely, the greater the BMI the greater the chance of death. On the other hand amongst those who did not smoke there was the interesting anomaly that mortality increased at BMI below 22.5. One often wonders what this is due to and it is common across other morbidities.

The authors continue:

Our findings with respect to the relationship between BMI and mortality due to specific causes are consistent with those of prior studies conducted in the general population. Among participants who had never smoked, the relationship of BMI to both cardiovascular mortality and cancer mortality appeared to be monotonic and linear. No significant association was observed between any BMI category and the risk of death from cardiovascular disease among participants who had ever smoked; however, participants in the lowest BMI category who had ever smoked had a significantly elevated risk of death from cancer.

Proposed biologic mechanisms of the alleged obesity paradox include an increased genetic influence and more severe diabetes among normal-weight persons with diabetes or the effect of a "metabolically obese normal weight" phenotype. However, normal-weight participants in our cohort were no more likely to report diabetes symptoms or coexisting chronic diseases or to require insulin than were overweight or obese participants. In contrast, normal- weight participants were more likely to be smokers and to have lost weight before a diagnosis of diabetes. Comparisons with this heterogeneous normal-weight group may therefore underestimate the risk of death among the overweight and obese.

Smoking is a co-morbidity state. However the overall impact of lifestyle choices must be considered more extensively amongst insurance providers. Obesity is not a pre-existing condition nor is being a smoker. They are life style choices. As such they should be assigned related risks.

Reference

Tobias, D., et al, Body-Mass Index and Mortality among Adults with Incident Type 2 Diabetes, NEJM, 370; 3, Jan 2014. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1304501

Labels: Diabetes, Health Care

WHEN WATCHFUL WAITING WON'T WORK

Recent research regarding the "watchful waiting" or as they call it "active surveillance" has indicated that often what has been suspected to be a rational and efficacious effort has feet of sand. In a recent piece in Health Imaging the writer summarizes a recent study[94][1]:

Results revealed that men treated with RP (radical prostatectomy) were significantly younger, had smaller prostates, lower prostate specific antigen (PSA), fewer comorbidities, more sampled biopsy cores, and more positive cores. The median total biopsy length was 140 mm and the extent of cancer was six mm. Eighty-six percent of the men had a ratio of cancer extent that was less than 15 percent. Half of the study group (2,235 patients) had adverse pathology at RP. Predictors of adverse pathology were older age, higher PSA, PSA density greater than 0.15 ng/ml/cm 3 and palpable disease and extent of cancer greater than four mm on biopsy. Adverse pathology was evident in 33 to 45 percent of the men who met the study inclusion criteria of six different AS protocols.

Namely the adverse results on a RP were often quite higher than they had suspected. That means specifically two things. First, prostate biopsies are notoriously weak in determining the Gleason grade. We know that all too often they dramatically underestimate the extent and grade. This is not surprising since they are often sextant biopsies and at best can garner some adequate cellular samples to determine the presence of PCa. In many cases where PCa is present, even multiple biopsies may miss it if it is somewhat confined.

Now the paper states[95][2]:

Many studies have demonstrated the frequent disparity between Gleason scores reported on prostate biopsy and at radical prostatectomy. In a recent review Epstein et al reported that about a third of cases with a biopsy Gleason score of 5-6 were upgraded at RP.

Thus as they note, and as we have commented, even with a good set of core samples, PCa may be identified but its grade is often underestimated. They continue:

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[94][1] http://www.healthimaging.com/topics/oncology-imaging/prostate-cancer-active-surveillance-criteria-needs-expansion

[95][2] http://www.jurology.com/article/S0022-5347%2813%2905475-X/fulltext

This issue is particularly germane to men with presumed low risk prostate cancer considering active surveillance, for whom accurate pretreatment risk stratification is paramount. As reviewed by Dall'Era et al, in most AS programs candidates are chosen based on GS (Gleason Score), clinical stage and PSA based parameters. Depending on the particular inclusion criteria 4% to 82% of men were eligible for AS, and conversion to active treatment was reported in 11% to 33% of men on AS, with changes in tumor histology as the most common reason for discontinuing AS.

Namely the methods to select for watchful waiting are subject to substantial error and underestimation. Note that there has been no consideration in this study of the many available genomic tests currently being developed. It would have been useful if they had also pursued a parallel study using a selection of the genomic studies we have discussed here. They continue:

A recent consensus conference concluded that AS is underused. However, the limitations of current clinical staging and disparities in selection criteria among current protocols are important in evaluating obstacles for expanding the use of AS.

The claim of underuse is essentially a claim for excess costs. Many Government controlled Health Care plans would like to shift the costs of surgery to the patient's mortality and morbidity. In the US we see this coming with the development of CCE, Comparative Clinical Effectiveness[96[3]]. They continue:

These results have important implications for the optimization of AS in the future. Most AS programs consider PSA and clinical stage for patient selection, and we confirmed that there is a greater risk of misclassification in men with a higher PSA and/or palpable disease. Despite recent controversy over the usefulness of digital rectal examination in PCa screening, these results suggest that it continues to have a role in staging.

Meanwhile we identified 2 other predictors of adverse pathology that are not currently used by many AS programs and should be considered in the future.

One predictor was PSA density, which was independently associated with adverse pathology in all subsets evaluated, yet is currently only used by a minority of AS programs. Our results concur with those of Sfoungaristos and Perimenis, who reported that PSAD was a stronger predictor of adverse pathology than PSA or biopsy Gleason score. Although Sfoungaristos and Perimenis suggested a PSAD cutoff of 0.20 ng/ml/cm3, the threshold currently used by the PRIAS protocol, we found that men with PSAD greater than 0.15 ng/ml/cm3 had a significantly greater risk of adverse pathology. The Johns Hopkins AS program has shown that PSAD is an important predictor of progression and uses a threshold of 0.15 ng/ml/cm3 for inclusion. In our population 21% of men had a PSAD between 0.15 and 0.20 ng/ml/cm3, demonstrating that this distinction affects a considerable proportion of men with otherwise low risk disease. Overall

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96[3] See Saver, R., Health Care Reform's Wild Card: The Uncertain Effectiveness of Comparative Effectiveness Research, 159 U. PA. L. REV. 2147 (2011).

PSAD is useful as it takes prostate volume into consideration when evaluating PSA, as we also showed that lower prostate volume is associated with a greater risk of adverse pathology.

We have argued for PSAD extensively in our studies. It is a logical measure and normalizes for prostate volume. However we have also argued for temporal analyses of PSAD, % PSA, PSA, and PSA Velocity. We have demonstrated that use of these temporal studies can be exceedingly helpful in even ascertaining between PCa and BPH for example. Moreover, no matter what we look at, genomics studies most likely will be the sine qua non for ascertaining results from biopsy studies.

The authors continue:

Older age was also positively associated with adverse pathology as previously reported. Although older men have traditionally been targeted for conservative management, they are more likely to have disease under staged, but they also have higher mortality from competing causes.

Overall there is clearly still room for improvement in PCa staging, including the biopsy protocol itself. Although 10 to 14 cores are often sampled on initial biopsy, sampling error remains problematic. Ruijter et al found an exact correlation between biopsy and prostatectomy grading in only 43% of cases, and less than 1 point difference in 77%. For men undertaking AS these issues become more critical, suggesting a role for saturation biopsies or early repeat biopsy to reduce misclassification. PSA density and cancer extent on biopsy should be considered as inclusion criteria for active surveillance.

The core issue is always a debatable issue. In larger volume prostates it seems logical that more cores are required. A baseline of 20 or more cores will yield substantially better results. Yet, no matter how many reasonable number of cores, we always face the risk of not detecting specific lesions.

Thus this study highlights the weaknesses of watchful waiting. The concern is that entities like PCORI which was established under the ACA will focus their CCE efforts on the perceived patient morbidity and failed to understand mortality. PCORI us dramatically unlike the FDA, where the FDA is Government controlled and reportable to Congress, and follows well established clinical trial protocols of substantial scientific validity. PCORI was set up to be extra any Congressional oversight as a non-governmental entity and thus can dictate whatever its management so desires with no recourse to the voters and the patients.

References

Vellekoop, A., et al, Population Based Study of Predictors of Adverse Pathology among Candidates for Active Surveillance with Gleason 6 Prostate Cancer, The Journal of Urology, Volume 191, Issue 2 , Pages 350-357, February 2014


Labels: Cancer, Health Care

SATURDAY, JANUARY 18, 2014

FOLLOW THE BOUNCING BALL

The Hill has a piece on the NSA issue which states:

"It's just the irony of this whole debate," said Rep. Mike Rogers (R-Mich.), the chairman of the House Intelligence Committee and a prominent defender of the NSA.

"I mean it's unbelievable what private companies collect from individuals and how they track them and track what their shopping habits are and where they may or may not be and how they shop," he said. "All of that is collected. The NSA doesn't do anything like that at all."

Now let us examine the logic a bit. A consumer buys something from Amazon. The chose to freely give Amazon information as part of the transaction. A user goes to Google for a search. There is a tacit agreement that they give Google the search info in return for performing the search. In either case the consumer can withhold the information by not buying from Amazon or not going to Google. The NSA data collection has no such agreement on the part of the consumer nor did the consumer even have an inkling. In addition the NSA search is a Government search. The Amazon is private. The Amazon search is part of any transaction. The NSA search is not, in fact there is a Constitutional issue which protects us from intrusion by the Government, not by private companies.

Thus is there a difference? The answer is year, and not the type as indicated in the quote above. Logic and facts seems to be clouded in this debate, a debate perhaps we should not even be having.


Labels: Commentary, Cyber Warfare, Government

THURSDAY, JANUARY 16, 2014

NEW YORK ABOVE THE CLOUDS

Great photo from my son of New York skyline from New Jersey side. Thought I would share it with those from beyond the sea.

Labels: Commentary

SUNDAY, JANUARY 12, 2014

SPANGLISH

My Spanish is good enough for Taxi cabs and some of our locals. I picked it up from my Puerto Rican friends decades ago, one fellow was a lifeguard with us and he was in Med School at the time. Thus it may not be the greatest accent. It is like my Russian learned from Jimmy Bula, a Ukrainian, who taught me as we sat on the lifeguard stand in New York. Now my French is not bad but I would never try it in Paris, and I once tried to write a Term Sheet and was laughed out of the room.

Thus when I needed Czech, Thai, Korean, I found someone who was fluent.

Now it comes to the ACA web site in Spanish. Modern Health Care states:

The site, CuidadoDeSalud.gov, launched more than two months late. A Web page with Spanish instructions linked users to an English form. And the translations were so clunky and full of grammatical mistakes that critics say they must have been computer-generated — the name of the site itself can literally be read "for the caution of health." "When you get into the details of the plans, it's not all written in Spanish. It's written in Spanglish, so we end up having to translate it for them," said xxxx, a healthcare navigator who helps with enrollment in Miami.

Now why they did not get someone fluent in Spanish I do not know, but it is the Government.

Labels: Health Care

THOUGHTS ON "FAIR WAGES"

In 1918 John Ryan a Catholic priest at Catholic University in DC wrote a book entitled Distributive Justice (MacMillan, New York). I believe it is worth going back to some of the remarks of Ryan and try to understand some of the issues today in the context of a century ago. Let us begin with some of his definitions:

DISTRIBUTIVE justice is primarily a problem of incomes rather than of possessions. It is not immediately concerned with John Brown's railway stock, John White's house, or John Smith's automobile. It deals with the morality of such possessions only indirectly and under one aspect; that is, in so far as they have been acquired through income. Moreover, it deals only with those incomes that are derived from participation in the process of production. For example; it considers the laborer's wages, but not the subsidies that he may receive through charity or friendship. Its province is not the distribution of all the goods of the country among all the people of the country, but only the distribution of the products of industry among the classes that have taken part in the making of these products.

These classes are four, designated as landowners, capitalists, undertakers or business men, and laborers or wage earners. The individual member of each class is an agent *of production, while the instrument or energy that he owns and contributes is a* factor *of production. Thus, the land-owner is an agent of production because he contributes to the productive process the factor known as land, and the capitalist is an agent of production because he contributes the factor known as capital; while the business man and the laborer are agents not only in the sense that they contribute factors to the process, but in the very special sense that their contributions involve the continuous expenditure of human energy. ...*

Moreover, there is the more fundamental ethical question concerning the titles of distribution: whether mere ownership of a factor of production gives a just claim upon the product, as in the case of the landowner and the capitalist; whether such a claim, assuming it to be valid, is as good as that of the laborer and the business man, who expend human energy m the productive process.Productive activity should be rewarded at different rates; in what proportion. Why should the capitalist receive six percent, rather than two percent, or sixteen percent? Why should the locomotive engineer receive more than the trackman? Why should not all persons be compensated equally? Should all or any of the benefits of industrial improvements go to the consumer? Such are typical questions in the study of distributive justice. They are sufficient to give some idea of the magnitude and difficulty of the problem.

To Ryan then and to the Progressives now Distributive Justice is allocation by some mechanism other than the Free Market of profits, and land and wealth in general. He accepts that individual ownership is not acceptable as it stood at that time and one would suspect now as well. He continues:

...that individuals are morally justified in becoming and remaining landowners. May we take a further step, and assert that private landownership is a natural right of the individual? If it is, the abolition of it by the State even with compensation to the owners, would be an act of injustice. The doctrine of natural rights is so prominent in the arguments of both the advocates

and the opponents of private landownership that it deserves specific treatment Moreover, the claim that private landownership is a natural right rests upon precisely the same basis as the similar claim with regard to the individual ownership of capital; and the conclusions pertinent to the former will be especially applicable to the latter. A Natural right is a right derived from the nature of the individual, and existing for his welfare. Hence it differs from a civil right, which is derived from society or the State and is intended for a social or civil purpose. Such, for example, is the right to vote or the right to hold a public office. Since a natural right neither proceeds from Z *is primarily designed for a civil end, it cannot be annulled and it may not be ignored, by the State, for example, the right to life and the right to liberty are so sacred to the individual, so necessary to his welfare, that the State cannot rightfully kill an innocent man, nor punish him by a term in prison.*

Thus he does attribute a right to land and property. But he does so through a principle of a Civil rather than a natural right. This is a twisting of Thomistic Theory. Now he moves to a Fair Wage. He states:

ALTHOUGH the principle of needs is somewhat prominent among the theories of wage justice, it received only incidental mention in the last chapter. Considered as a comprehensive rule, this principle has been defended with less energy and definiteness than most of the other canons. Considered as a partial rule, it is sound and fundamental, and therefore could not have been classed among theories that are unacceptable.

The Principle of Needs: Many of the early French Socialists of the Utopian school advanced this formula of distribution: "From each according to his powers; to each according to his needs."...The difficulties confronting it are so great and so obvious that they would defer the introduction of it to a time when the operation of their system will, they hope, have eradicated the historical human qualities of laziness and selfishness. To adopt needs as the sole rule of distribution would mean, of course, that each person should be rewarded in proportion to his wants and desires, regardless of his efforts or of the amount that he had produced. The mere statement of the proposal is sufficient to refute it as regards the men and women of whom we have any knowledge. In addition to this objection, there is the insuperable difficulty of measuring fairly or accurately the relative needs of any group composed of men, women, and children. ... Indeed, the standard of needs should be regarded as a canon of Communism rather than of Socialism; for it implies a large measure of common life as well as of common ownership, and paternalistic supervision of consumption as well as collectivist management of production.

The Right to a Decent Livelihood: Every man who is willing to work has, therefore, an inborn right to sustenance from the earth on reasonable terms or conditions. This cannot mean that all persons have a right to equal amounts of sustenance or income; for we have seen on a preceding page that men's needs, the primary title to property, are not equal, and that other canons and factors of distribution have to be allowed some weight in determining the division of goods and opportunities. Nevertheless, there is a certain minimum of goods to which every worker is entitled by reason of his inherent right of access to the earth. He has a right to at least a decent *livelihood. That is; he has a right to so much of the requisites of sustenance as will enable him to live in a manner worthy of a human being. The elements of a decent livelihood may be summarily described as: food, clothing, and housing sufficient in quantity and quality to maintain the*

worker in normal health, in elementary comfort, and in an environment suitable to the protection of morality and religion; sufficient provision for the future to bring elementary contentment, and security against sickness, accident, and invalidity; and sufficient opportunities of recreation, social intercourse, education, and church-membership to conserve health and strength, and to render possible in some degree the exercise of the higher faculties.

These rights are thus not only to a salary but to all other things as he describes them. The list above is significant because it was presented in 1918 and not last week! He then goes on to describe what he calls the Principal Canons of Distributive Justice:

BEFORE taking up the question of the morality of profits, it will be helpful, if not necessary, to consider the chief rules of justice that have been or might be adopted in distributing the product of industry among those who participate actively in the productive process. ...The canons of distribution applicable to our present study are mainly six in number: arithmetical equality; proportional needs; efforts and sacrifices; comparative productivity; relative scarcity; and human welfare. (1) The Canon of Equality: According to the rule of arithmetical equality, all persons who contribute to the product should receive the same amount of remuneration. ... It is unjust because it would treat unequals equally... (2) The Canon of Needs: The second conceivable rule is that of proportional needs. It would require each person to be rewarded in accordance with his capacity to use goods reasonably. If the task of distribution were entirely independent of the process of production, this rule would be ideal; for it would treat men as equal in those respects ...Like the rule of arithmetical equality, the rule of proportional needs is not only incomplete ethically but impossible socially. ...Moreover, any attempt to distribute rewards on this basis alone would be injurious to social welfare. It would lead to a great diminution in the productivity of the more honest, the more energetic, and the more efficient among the agents of production. (3) The Canon of Efforts and Sacrifice: The third canon of distribution that of efforts and sacrifices, would be ideally just if we could ignore the questions of needs and productivity. But we cannot think it just to reward equally two men who have expended the same quantity of painful exertion, but who differ in their needs and in their capacities of self-development. To do so would be to treat them unequally in the matter of welfare, ... (4) The Canon of Productivity: According to this rule, men should be rewarded in proportion to their contributions to the product. It is open to the obvious objection that it ignores the moral claims of needs and efforts. ... When men of equal productive power are performing the same kind of labour, superior amounts of product do represent superior amounts of effort; when the tasks differ in irksomeness or disagreeableness, the larger product may be brought into being with a smaller expenditure of painful exertion. If men are unequal in productive power their products are obviously not in proportion to their efforts. ... (5)The Canon of Scarcity: It frequently happens that men attribute their larger rewards to larger productivity, when the true determining element is scarcity. The immediate reason why the engine driver receives more than the track repairer, the general manager more than the section foreman, the floorwalker more than the salesgirl, lies in the fact that the former kinds of labour are not so plentiful as the latter. ...As between two men performing different tasks, superior skill receives superior compensation simply because it can command the greater compensation; and it is able to do this because it is scarce. ...(6) The Canon of Human Welfare: We say "human" welfare rather than "social" welfare, in order to make clear the fact that this canon considers the well-being of men not only

as a social group, but also as individuals. It includes and summarizes all that is ethically and socially feasible in the five canons already reviewed. It takes account of equality, inasmuch as it regards all men as persons, as subjects of rights; and of needs, inasmuch as it awards to all the necessary participants in the industrial system at least that amount of remuneration which will meet the elementary demands of decent living and self-development. ... Owing to the exceptional hazards and sacrifices of their occupation, a combination of producers might be justified in exacting larger compensation than would be accorded them ...

Ryan leaves the reader somewhat with the old adage, "on the one hand, on the other hand". He does however demand a living wage, yet it is left undefined, only that it must cover all the factors he outlined. Finally with regard to Profits Ryan states:

The Question of Indefinitely Large Profits: As a general rule, business men who face conditions of active competition have a right to all the profits that they can get, so long as they use fair business methods. This means not merely fair and honest conduct toward competitors, and buyers and sellers, but also just and humane treatment of labour in all the conditions of employment, especially in the matter of wages. When these conditions are fulfilled, the freedom to take indefinitely large profits is justified by the canon of human welfare. The great majority of business men in competitive industries do not receive incomes in excess of their reasonable needs. Their profits do not notably exceed the salaries that they could command as hired managers, and generally are not more than sufficient to reimburse them for the cost of education and business training, and to enable them to live in reasonable conformity with the standard of living to which they have become accustomed. Efforts and sacrifices are reflected to some extent in the different amounts of profits received by different business men. When all due allowance is made for chance, productivity, and scarcity, a considerable proportion of profits is attributable to harder labour, greater risk and worry, and larger sacrifices. Like the principle of needs, that of efforts and sacrifices is a partial justification of the business man's remuneration. Those profits which cannot be justified by either of the titles just mentioned, are ethically warranted by the principles of productivity and scarcity. This is particularly true of those exceptionally large profits which can be traced specifically to that unusual ability which is exemplified in the invention and adoption of new methods and processes in progressive industries. The receivers of these large rewards have produced them in competition with less efficient business men.

The question as to the above is who makes all these decisions? Government? Well a century later we see what has transpired. But let us read Timothy 5(16)

If any of the faithful have widows, let him minister to them, and let not the church be charged: that there may be sufficient for them that are widows indeed.

This is Paul stating the Individual responsibility, not the Church or the State. One wonders how this conflict is resolved.

Labels: Commentary, Economics, Religion

DREAM MERCHANTS

A good entrepreneur is also a good "Dream Merchant". Not a Huckster, not some creature from Hollywood's distortion of reality, but a person who has a dream, has embodied it in some form, and sees where it can go where others cannot yet see it.

I will give an example. In 1980 I went to Warner Cable. The Chairman at the time wanted me to develop a business using video on demand and extend it well beyond home shopping and banking. I took that dream and embodied it in reality and then brought in companies like Bell Atlantic, Bank of America, GTE and DEC. Each did their due diligence and the like. The problem with many dreams is exogenous factors often interfere, Warner rand upon hard times with Atari, and also we were a bit too early, say thirty years too early. But the Dream had legs, it was an Amazon before perhaps many today at Amazon could read. But that is at best a foot note to history.

At the other end there were executives at our partner, who would say that this home shopping would never work. They went on to head major banks and computer companies. They were right in the short run but well off the mark of the march of history. Yet in business timing is everything. Dream Merchants are only as good as the timeliness of their dream.

Now to a piece in the New Yorker. It says:

The greatest business icon of our era, Steve Jobs, was legendary for his "reality-distortion field," which allowed him to convince people that improbable outcomes were not just possible but certain. Jobs's endless rehearsals for his public presentations and his scripting of every moment for maximum effect—these are all straight from the con artist's playbook. So, too, is the sense of conviction he projected. In Weinberg's words, "Before you sell a deal you have to live the deal. You have to believe in it, because, if you don't believe in it, you can't sell it."Of course, the fundamental difference between entrepreneurs and con artists is that con artists ultimately know that the fantasies they're selling are lies. Steve Jobs, often enough, could make those fantasies come true. Still, that unquantifiable mélange of risk, hope, and hype provides both the capitalist's formula for transforming the world and the con artist's stratagem for turning your money into his money. Maybe there's a reason we talk about the American Dream.

I knew Jobs at a distance from my Atari days. At Atari they saw Apple as the competition, and even had Apple decals lining the urinals, some Silicon Valley humor I guess. But Jobs was a Dream Merchant, but one who always believed that he could achieve the dreams. He was not a con man, for the most part almost all entrepreneurs are Dream Merchants and not con men. The article's nexus is not only unfair but a distortion of reality. I have seen con men, they stand out like sore thumbs. I have seen them in Russia, Poland, Korea, New York and yes California. They have no substance behind their pitches. Jobs had reality.

Dreams and Dream Merchants as entrepreneurs are essential to our culture. They "burn their boats" and set out forward towards their dream. Without them we would have a very different world. Jobs had to have certainty, after all he is setting out on a journey from which there is only one goal, success, achievement of what he predicted. Then again, like Warner, he may have a

great product but at the wrong time, look at Lisa. Yet in the long run he set a standard that few can beat.

The author in my opinion totally misunderstand the entrepreneur. The entrepreneur is no con man, the entrepreneur is what makes America. We have con men everywhere. We need to honor and cherish and nurture our entrepreneurs, not defame them out of ignorance.

Labels: Commentary, Press

SATURDAY, JANUARY 11, 2014

HEALTH CARE AND LOGIC

I am always amazed at the gaps in logic from the defenders of the ACA. Let us take as an example one MIT Professor who states:

"I am totally biased", xxx quipped about his advocacy of the Massachusetts program. "Nonetheless, if you look at the facts, I think it's been, by the objective facts, a success." He noted that about two-thirds of formerly uninsured residents are now covered, while premiums for individual insurance have dropped by about 50 percent.

First, yes he is biased. That in itself is not what an academic should be. One should seek the facts. It is like having dedicated dyed in the wool Marxists teaching in the Economics Departments. One would hardly expect a fair hearing. I believe he is speaking of Massachusetts. Yet the new insured are often under Medicaid and as such have very limited access to physicians. He continues:

xxx also emphasized that states' adoption of Medicaid expansion is an important facet of the plan to monitor. The Affordable Care Act offers full federal funding of Medicaid (an expense that is normally split 50-50 between the federal government and the states) for three years, an amount that declines to about 90 percent thereafter. Yet governors in 26 states have declined to accept the funding, a stance made possible by a 2012 Supreme Court ruling — and one xxx labeled as "political malpractice."

"There is no citizen in a state like Florida that is worse off if they expand Medicaid," xxx suggested. "None. All of the [uninsured] get health insurance. Everyone else gets enormous federal stimulus injected into their economy." He added: "That's another thing to keep an eye on: How long are states going to hold out?"

Now the logic fails as follows. If they expand Medicaid in Florida, or any state, the costs must be picked up somewhere. That means increased taxes or fees. That means that those who do not get Medicaid will see increased Government confiscation and thus an imputed harm. One then assumes that they are thus not better off but worse off.

In fact, as Medicaid is expanded, it is essentially "free" to the new subscribers but "paid" for by the limited Middle Class which is further squeezed. I have argued this for over fiver years now since the current Administration started this process.

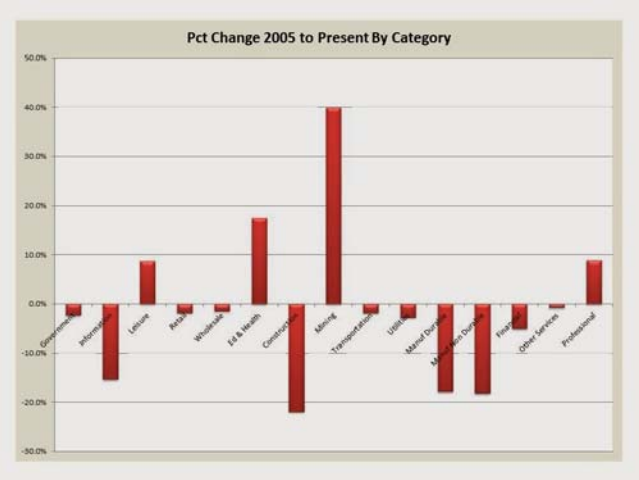
Labels: Health Care

FRIDAY, JANUARY 10, 2014

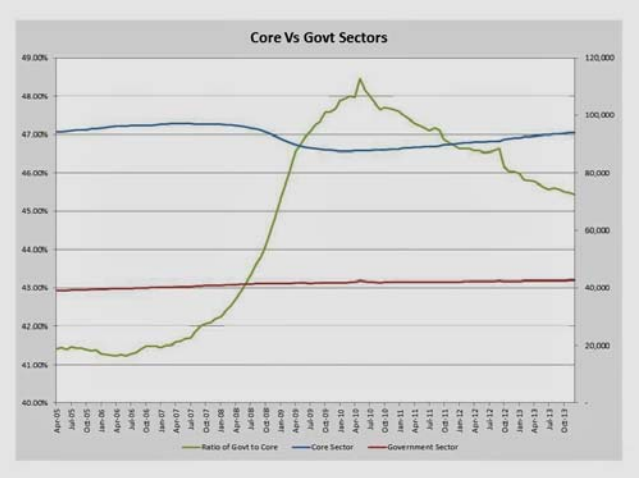
MORE ON EMPLOYMENT

It is worth looking a bit deeper into the employment numbers.

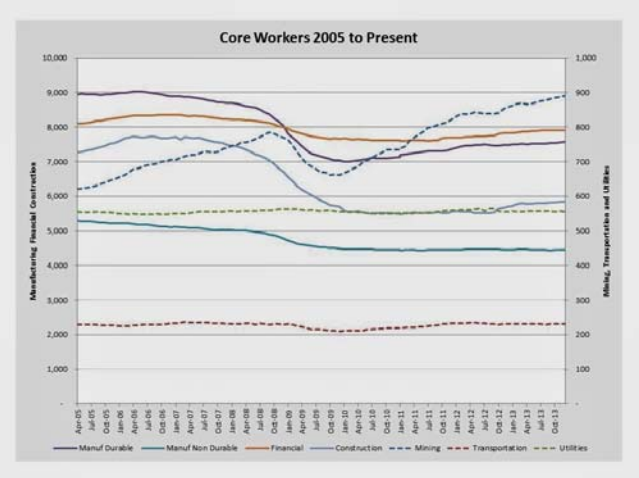
Look at the three services oriented businesses above. There has been a consistent growth in professional, and slower growth in financial.



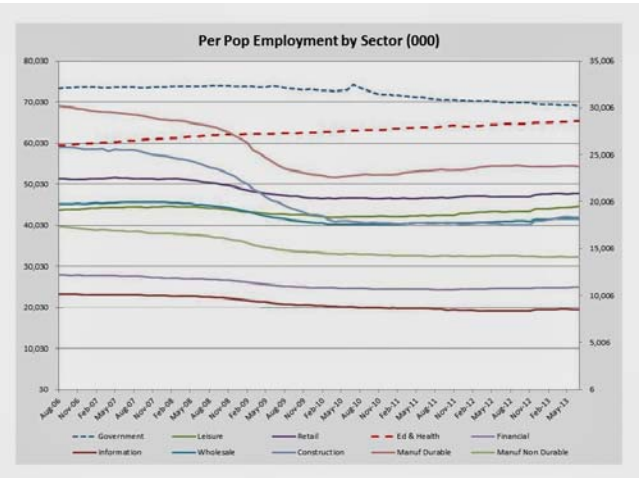
Then if we look at 2005 and December 2013 we see the changes above. Mining has increased but it is small. Manufacturing is down almost 20% in both sectors. This is a major concern. Construction is down almost 25%. Even Government is down. However Ed and Health is up almost 20%.



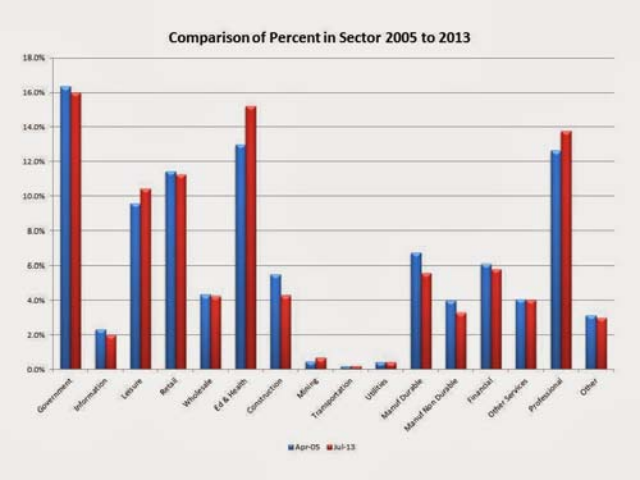
The above is the Government and related sectors as compared to the core non Government sectors. We see the ratio has increased but is still quite higher than 2005.



The above is the core worker numbers. The Manufacturing are down but with a slight recovery. Construction is also flat.



We present a similar set of stats below but on a per PoP basis.



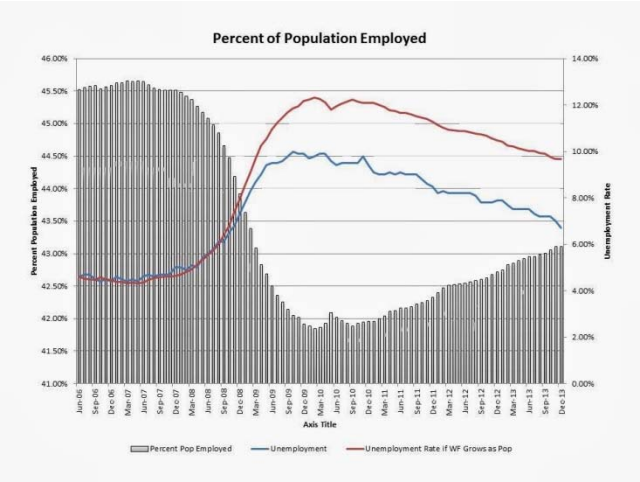
Finally we show the percent by sector in mid 2005 and December 2013. Leisure, Ed & Health and Professional have increased as a percent. Almost everything else has decreased

Overall this does not bode well for any recovery increasing in 2014.

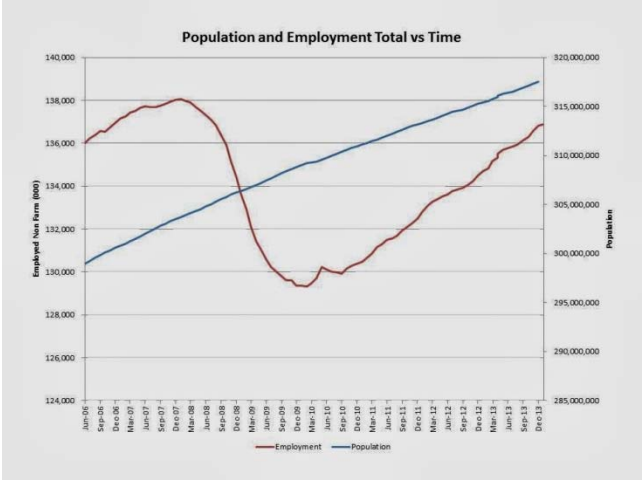
Labels: Economy

EMPLOYMENT: NOT GOOD NEWS

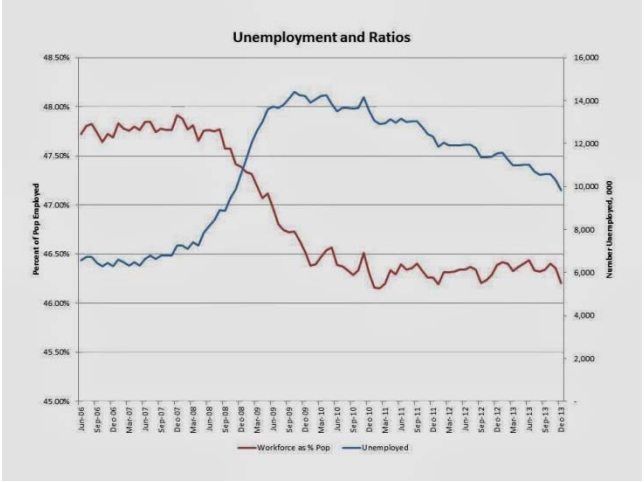
Whenever you can change the denominator you can make up whatever number you want. Thus goes the employment numbers. The economy demands just by growth of people alone well over 100,000 new hires net per month. We got 75,000 and the unemployment rate goes down. Only in Economics can you have totally counter factual numbers.



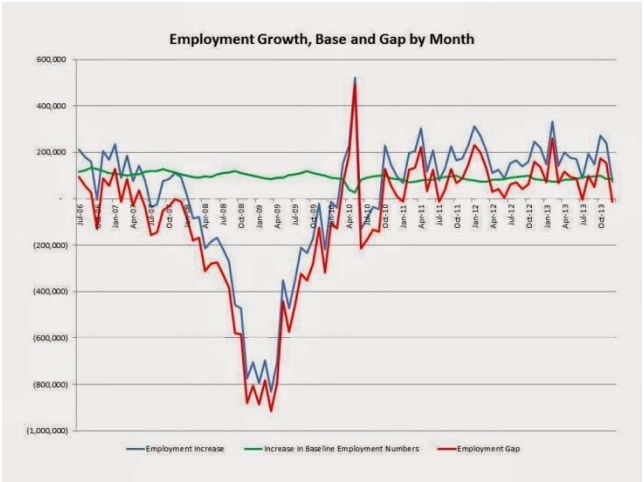
First the population percent employed. In June 2006 we had over 45.5% Now we are at 43%. That means that the gap are permanently unemployed, not generating GDP and not producing taxes, and worse requiring unemployment payments and other benefits.



This shows the population increase and the non farm seasonally adjusted employment. Yes it is increasing, except for a drop last month. The gap is closing, which may be some good news.



But when you look above at the workforce percent it has dropped again this month which accounts for most of the decrease in unemployment! In fact the unemployed has gone up if we consider the 2006 numbers.



The above details some of these numbers. Bottom line, we are still getting worse, despite the Government's saying otherwise.


Labels: Economics

MONDAY, JANUARY 6, 2014

YOU CAN'T MAKE THIS UP!

To anyone familiar with the alleged "English Constitution" one knows that it cannot be found anywhere, it just exists. Furthermore, at its core, is the division of England into three parts; the Crown, the Aristocracy, and the Common Folk.

Now in line with that the Guardian announces that the hairdresser of the PM has gotten an MBE from the Crown for his service in hairdressing. Really! They state:

David Cameron's barber was awarded an MBE in the New Year honours list for "services to hairdressing", it has emerged.

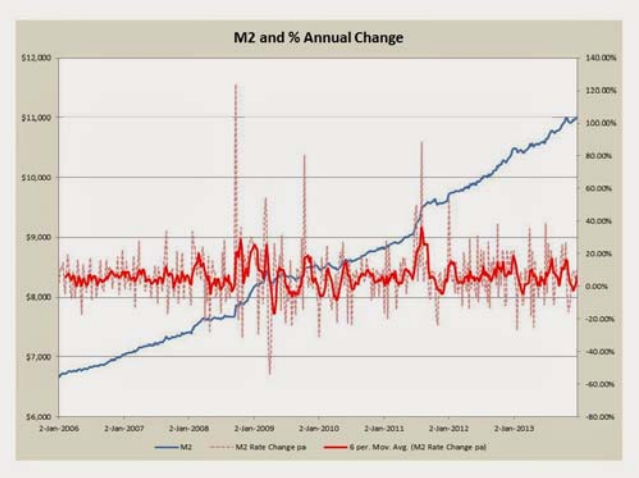
This is England, awards, honors, class etc. It reminds me of Admiral King during WW II who hated the British Navy for being a bunch of snobs. King thus demanded that wearing one's medals on a regular uniform was prohibited. All one needed was rank. Keep the chest clear. British officers were burdened down with their medals, many "awarded" for the least of things. Unfortunately we see today that US General officers come to Congress with shelves of ribbons, many for just having shown up. King would not be happy.

King would never have imagine how far the Brits would go however. Yet we do have our Hollywood awards, self promotion for a segment of society which contributes not a not to productivity, and in fact, often send the worst of message of our society to others.

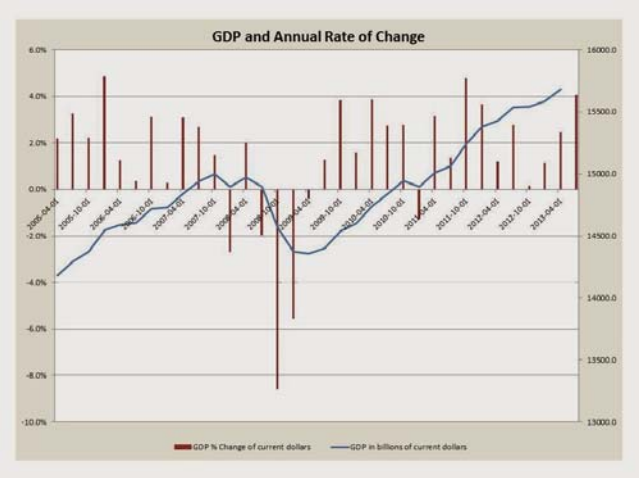

Labels: Commentary

INFLATION FOR 2014?

One has been concerned about inflation with the massive expansion of the FEDs Balance Sheet. We have been following that now for some five years plus. But alas the money is printed but is still not going anywhere. Let us examine some of the details.

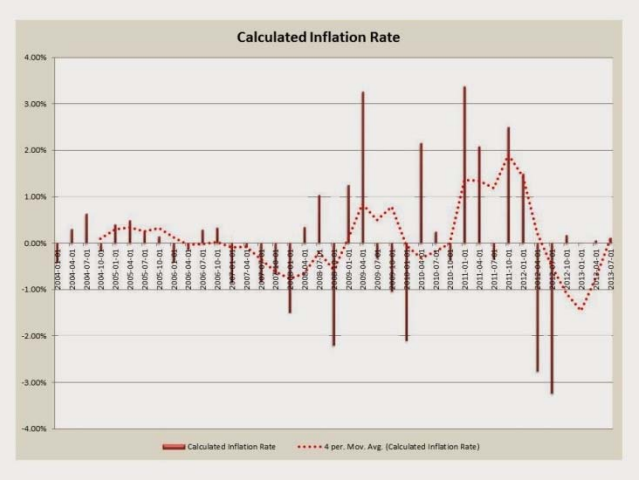


First M2 and its annualized change as above. M2 is increasing at a fairly good clip. It has gone from $ 6.7T to $11 T in the past seven years. That frankly is a massive increase. It should spur inflation, but it has not.

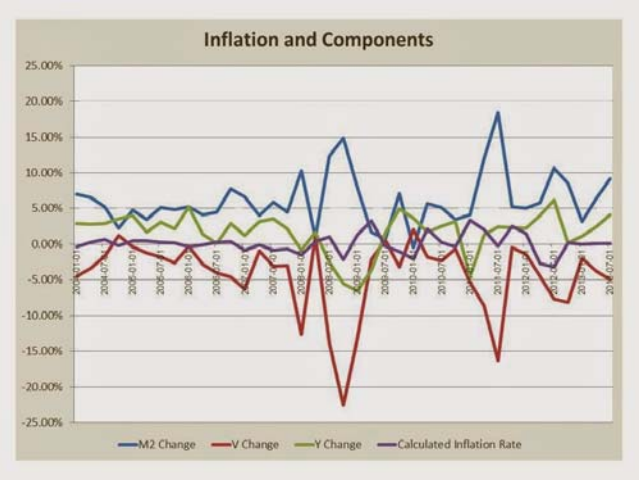


Here is most likely why. No GDP growth. The money is printed, it is out there but people are not getting it to spend.

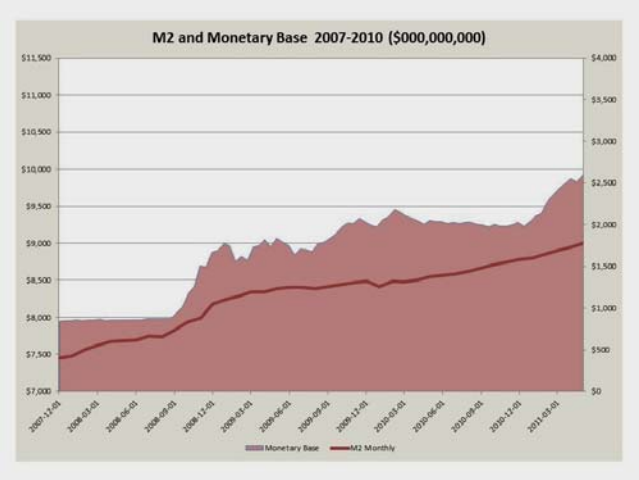
Now look at the Monetary Base. Some five years ago we wrote a piece on the Monetary Base suggesting what would happen. And it has happened.



Thus when we look at the calculated inflation rate it is near zero. Things are going no where. The money is staying with the Banks, they are using it to make more money and it is hidden from the economy.



The above shows the details. The velocity is low, money is not changing hands, except in the banks themselves, which makes them money but leaves the rest of society broke. This is a FED artifact. It also seems to be a hidden fact.



Is we look at M2 and the Monetary Base we see what is happening. Money printed by the FED, flows into the Banks and stays there. The question is; how do we break this log jam, and what is the cost in inflation when it does break.

Labels: Economy

SUNDAY, JANUARY 5, 2014

UNDERSTANDING BAYES, AND ECONOMICS

In a recent NY Times piece the Fellow from the South had a discussion on Bayes analysis. Now I wrote a book on that in the late 1960s so let me refresh your memory. Bayes said that if you took into account the data up to the present that reflected information on the data you were trying to estimate then you could get better estimates than if you just used what was available a priori. Let me make this a bit simpler.

Assume you have some system with variable x which is a dynamic system you know follows some law of nature but may be perturbed by some random process. Namely let:

$dx(t)/dt = a\ x(t) + w(t)$

and that you have some measurement of y(t) which relates to x(t) but may also have noise:

$y(t) = b\ x(t) + n(t)$

Here we assume that w(t) and n(t) are random processes and further we assume they are Wiener processes. Most likely they are not in reality, but who cares, this is an academic problem. Now we want the best possible estimator in a mean square sense of x(t) give that we have y(t) over some interval (s,t).

The answer is a Bayes least mean square estimator gotten by determining the conditional probability density, p(x,t|y; (s,t)). That approach was initially proposed by Kolmogorov and Wiener and then by Kalman. The nonlinear version was done by Stratonovich and, you guessed it, me.

The essence of a Bayesian world is that we are desiring to estimate some variable, say x, and we have a set of observations, say y over some time period, and, this is key, we know both the relationship between y the observation and x the system plus we know how the "noise" disturbs things.

The conditional probability described above is the Bayesian methodology. Now there is another way to consider this problem and also to add complexity, namely it is to allow for the Rowe Conjecture. Now Nick Rowe proposed this conjecture about four years ago as a simple premise. Namely, if one looks at some "Economics Law", in his case the Efficient Market Theory, one knows that this may or may not hold in reality. Thus there is a random process related to the law itself being extant. Also inherent to the EMT or Hypothesis, there is randomness to it being true or not. In addition, for Rowe both nature, namely the Economics law, and the people themselves may be random. This means people may "believe" that the EMT applies or does not apply. The people may be in one state or another and that means the people may act differently based upon their belief no matter which law is in action. Thus the combined system of law and people as a system description is itself totally random. It would be like us saying above that the system, as the EFT, is:

$$dx(t)/dt = a\ x(t) + w(t)$$

or

$$dx(t)/dt = d\ x(t) + w(t)$$

where we may or may not know a and d and further we may have (for the people):

$$y(t) = b\ x(t) + n(t)$$

or

$$y(t) = e\ x(t) + n(t)$$

It actually may be even more complex. But we will not consider that here.

Now we all know gravity does not work that way, nor does thermodynamics, nor even bridge design, but somehow it works in Economics, just look at the Nobel Prizes. Second, as Rowe conjectured, people act either believing this law holds or not believing it holds, and some fraction of the population may hold one view and some another. There is a whole lot of literature on this type of a world as well and even another Nobel Prize in this area.

Thus, using the Rowe Conjecture, we have cycles developed where the law may or may not hold and people may or may not believe in it. This then is one way to explain the Business Cycle, in part. Now there is no Nobel Prize in this statement. But its does provide insight into human behavior and the lack or consistency in economic "theory".

Along comes the Fellow from the South and presents his theory and this is what he says:

It seems to me that xxx position – he only said it was a danger, not that it would happen at any particular time, so it signifies nothing if it doesn't happen even after four years have passed – is just untenable in its strong form. If saying that something is a danger carries no implications for the likelihood that it will actually occur, what is the point of saying it? You might as well stand up there and say "Nice day for weather" or sing "Mary had a little lamb."

No, clearly talking about the danger of inflation was some kind of statement about probabilities – in particular, a statement that the probability of inflation is, according to the speaker's model of the world, higher than it is in other peoples' models of the world. And that means that actual events do or at least should matter – they may not prove that one model is wrong and another is right, but they should certainly affect your assessment of which model is more likely to be right.

In short, it's a Bayesian thing.

Well not really. It is a Rowe Conjecture "thing" I believe. A Bayes "thing" is purely probabilistic about a well structured world. A Rowe Conjecture "thing" is a probabilistic structure about a probabilistic world. You see, the theory is just that a theory, and the "theory" has the tendency to change. Furthermore people may or may not believe the theory, especially after the past five years of ranting amongst Economists.

Labels: Academy, Economics

FRIDAY, JANUARY 3, 2014

CHOOSING THE HIGH COST OPTION

In a study of the Oregon lottery Medicaid program the authors noted in Science that the Medicaid recipients as compared to others used the ER at a dramatically higher rate. They conclude:

These limitations to generalizability notwithstanding, our study is able to make use of a randomized design that is rarely available in the evaluation of social insurance programs to estimate the causal effects of Medicaid on emergency department care. We find that expanding Medicaid coverage increases emergency department use across a broad range of visit types, including visits that may be most readily treatable in other outpatient settings. These findings speak to one cost of expanding Medicaid, as well as its net effect on the efficiency of care delivered, and may thus be a useful input for informed decision-making balancing the costs and benefits of expanding Medicaid.

Namely those with Medicaid did not, as expected, find physicians to deal with their ailments, but just fell back into the old pattern of the ER but now at a substantially higher rate. This does not bode well to the ACA cost controls. In fact nothing seems to be helping! Told you all so!

Labels: Health Care

FRIDAY, JANUARY 3, 2014

BURKE AND PAINE

The book by Levin, The Great Debate, is an excellent contribution to the studies of Burke versus Paine. Although their debates are over two centuries ago, they ring true today as well. The questions explored by Levin center around the "conservatism" of Burke and the "progressivism" of Paine. Although this alignment is attempted, that is much of the text deals with trying to understand both authors in a context interpretable today, in many ways there is a bit of current day "conservatism" and "progressivism" in both Burke and Paine. There is not a one to one alignment.

Levin presents his arguments in an exceptionally clear and concise manner. The book is quite readable and the structure of his argument is built in sections presented in each chapter. One does not have to dig to any depth to see where he wants to take the reader. Levin clearly understands Burke and also has a good grasp of Paine.

Burke was the conservative, born in Ireland and raised in the Church of England and a Member of Parliament. His career was highlighted by his writings as compared to any Legislative prowess. Paine was class wise a step or two below Burke, leaving England and starting anew in what was to become the United States. His skill as a pamphleteer was extraordinary and in so doing he absorbed and even created the sense of his times. Paine personally paid for his major work, Common Sense, which in many ways ignited the Revolution.

Levin begins by providing a brief overview of the lives of the two men. It is well done but it in some ways fails to dig deeper and understand what may have made a Paine and a Burke. Paine was in a sense an entrepreneur, he abandoned England and his "place in that society" to travel to American where he could create the person he became. Paine was the risk taker, seeing the need for change, albeit with risk, and taking the chance. Burke in total contrast knew his places and sought ways to maximize the best as possible his position in that place. Burke not only accepted the system as is but proselytized that system as the sine qua non of how things should be. Paine rejected that system and saw in the individual the path to change.

The reader should have some knowledge of the times to best understand some of the content. Let me provide a first example. On p 31 in discussing Burke there is the statement "Praising the gradualism of the English constitution …" First, there is no document in existence which one can call the English Constitution. Second, when one looks for the English constitution one starts with the Magna Carta and then proceeds forward with an amalgam of Laws, Parliamentary proceedings and the rulings from Common Law courts, namely precedents. In addition the English constitution assumes that English society is built around three classes; the Crown, the Aristocracy, and the Commons. Namely, one always knew one's place, and one must act accordingly. It was this theme which flows throughout the book and also was essential to Burke's thought. In contrast in America one could be whatever one wanted, and class was essentially non-existent, thanks in many ways in which the English ruled.

There is a second theme that flows throughout the book, individualism. Levin comment on p 29 as follows: "Burke laid out an argument against radical individualism," A major issue which needs clarification is; what is the definition of individualism? This terms in in Burke and it returns a few decades later in de Tocqueville as a major characteristic of America in the early 19th century. Individualism was in many ways a rejection of the Burkean conservatism, namely of a society with an immutable class system, a society of strict structure. On p 36 the author states the core set of points upon which the battle between Burke and Paine rested, namely;

"…what makes a government legitimate, what the individual's place is in the larger society, and how each government should think about those who came before and those who will come after."

This question then flows throughout the book. Levin does a splendid job and going back and forth from Burke to Paine and exploring the details of the answers thereto.

Chapter 2 presents the two varying views of Nature that each had. These world views become the platforms upon which they build their ideas of government and society. To Burke there is formality and structure. Burke was a traditionalist, a royalist. On p 61 Levin presents the famous quote from Burke's Reflections where he states:

"We fear God; we look up with awe to kings; with affection to parliaments; with duty to magistrates; with reverence to priests; and with respect to nobility."

This as Levin note is the totality of Burke's world view. The irony is that Burke, as an Irishman by birth, with a Catholic mother, see reverence to priests of the English Church but death to the priests of the Catholic or Irish Church. Again one must read de Tocqueville's comparative journey through Ireland in the mid-19th Century to best understand this comparison. The question is; is this conservatism or a dogmatic slavish following akin to Stalinism?

In contrast Levin ascribes a "radical liberal thinker" to Paine (p 57) and these types of thinkers, says Levin, "leave the human sentiments and role of the imagination out of the understanding of human nature". This was an Enlightenment battle between reason and custom.

In Chapter 3 the author begins a discussion of Justice and Order. He states on p 69, “For Paine, the appeal to nature is primarily an appeal to justice.” One must ask; what definition of justice do we use here? On p 71 Levin presents an excellent discussion of the integration in Burke’s conservatism of utilitarian ideas, a “procedural conservative” mind.

Chapter 4 is a key chapter wherein the issue of individual choice and obligations (duties) are discussed. This chapter alone is worth reading. As Levin states on p 92; “The idea of rights sits at the core of Thomas Paine’s political philosophy. Rights are the organizing principle of his thought and the prime concern of all his writings about government.” But what is most important is that rights refer to the individual, each individual, qua individual, has the rights. The rights are not group rights; they are rights to the person. Burke vied society as an amalgam, he rejected the individual qua individual. Burke believed in classes, groups, because English society was so structured. Paine understood most clearly as a result of the discussion of the Bill of Rights that they accrued to the person, each and every person. In contrast Levin speaks of Burke on p 101 where he states: “As Burke sees it, each man is in society not by choice but by birth. And the facts of his birth – the family, the station, and the nation he is born into – exert inescapable demands on him, while also granting him some privileges and protection …” One need go no further to understand the difference. To Paine the individual is unbounded in potential, to Burke the individual is molded by eons of history and genetics. England had its Aristocracy, a core element in its English constitution; America had the individual, and the Bill of Rights.

Chapter 5 the author discusses Reason and Prescription. Reason is the core to the Enlightenment, namely by reason we can come to truth. Prescription is term defined by Levin on p 1`40 as; “The term prescription originated in Roman property law, where it referred to ownership by virtue of long-term use, rather than by formal deed.” Simply put, the battle between Reason and Prescription is the battle between what we think NOW is best as compared to what tradition had determined as best. It arguably is what many think is the contrast between liberal and conservative in current day America. I would argue that perhaps that is not the case and that the battle is truly between the individual versus the group. But here in two adjoining chapters Levin lays out the principles as advocated by Burke and Paine, and as battled today.

There is an undercurrent discussion in Chapter 5 as well, the discussion on equality. On p 151 there is a discussion of equality and the individual. For Paine one should be allowed to open the discussion up on the laws at least in every generation, for Burke he sees a slow representative government. The issue is the individual and equality. This theme comes again when Paine enters the fray of the French Revolution. The Liberty, Equality, Fraternity motto was focused on Liberty in the Americas and Equality in France. One can see Paine struggling with this issue. Whereas Liberty is consonant with Individualism, Equality may be taken to an extreme and destroy the individual. The resolution is left unsaid.

On p 153 the author makes a most important observation; “”He (Paine) argues that every individual is capable of employing his own reason to discern the truth or falsehood of a political question … Paine believes that every individual has the capacity to begin from scratch, rather than beginning where others left off.”

In the Conclusion the author makes the following statement on p 237:

"The fundamental utopian goal at the core of Paine's thinking – the goal of liberating the individual from the constraints of the obligations imposed upon him by his time, his place, and his relations to others – remains essential to the left in America."

I would argue that Paine placed power in the individual and not the group and that the left empowers the group often against the individual. Progressive ideas are ideas of group culture and are often opposed to individual culture. Paine I would argue is the champion of the individual and it is Burke who empowers the group. But Levin does a superb job in bringing these issues to the fore. His book is an essential read for anyone who wants to understand the differences in our present day culture and more importantly the bases from which they sprung. What makes a conservative or a progressive? This book helps one think through that process better than any other.

Labels: Books, Commentary, Political Analysis

THURSDAY, JANUARY 2, 2014

STUCK IN A DITCH

Science has a piece on the changes occurring to the Clean Water Act controls. As Science states:

The confl ict is rooted in the Clean Water Act of 1972, which requires anyone wanting to dredge or fi ll a stream or wetland to get a permit from the federal government. (Many agricultural activities are exempt.) For decades, U.S. offi cials and the courts held that the law applied not just to the "navigable waters" mentioned in the act, but also to all the smaller streams, wetlands, and ponds connected to them in a variety of ways. Numerous groups challenged that interpretation, however, and in the 2000s the U.S. Supreme Court dealt the government several setbacks. In a 2006 split decision, for instance, it ruled that EPA could not regulate any waters unless it demonstrated that they had a "signifi cant nexus" with downstream navigable waters, such as affecting their physical, chemical, or biological integrity. Since then, confusion has reigned over the legal status of ephemeral streams and isolated wetlands. In 2010, EPA began to try to clarify matters by writing the new rule. It calls for the Clean Water Act to cover all tributaries, headwater streams, and "adjacent" wetlands.

Namely we now see ditches becoming part of navigable waters. That is "dry" ditches. It is not even clear how deep a ditch has to be. The actions of the EPA will make it illegal for anyone anywhere altering in anyway a run-off area without prior EPA authorization. This clearly affects hills, slopes, gulleys, and almost any and every piece of land everywhere.

Admittedly there are agricultural carve outs but the new regulation, yes regulations written without a new law are now laws, the new regulation delimits plowing of a field, setting up a home garden, and yes folks watering your lawn.

Labels: Government

WEDNESDAY, JANUARY 1, 2014

HAPPY NEW YEAR!

We are starting a new year here and it is most interesting to see what has transpired since 2008 when we began this effort. Many of the Blogs that I had been following then have faded away. I guess it takes a bit of work to continue one over such a period, or perhaps you just run out of rants. Fortunately we have had the fine fortune to continually interact with folks who throw up new and enticing thoughts, thoughts to be rolled around and refined.

On the other hand I have seen the left wing blogs seem to continue their screaming-out their protests of injustice, inequality, and only God knows what. In addition they just continue to be nasty, rather rank in their dealing with people and topics. But it is a new year and it brings many challenges. Let me outline a few that should be of interest:

1. Middle East is Exploding: This is in the worst mess since I can remember. It is not just Israel and the Palestinians this time. It is the rest of the mess. The US does not seem to understand what is happening, revolutions are afoot and we seem to have not a clue.

2. Energy: This is a strange once since we no longer depend on foreign oil. Wind mills still turn but they have not been brought to a point of being a true contributor. Unlike the 70s we now can sustain an energy crisis elsewhere unless of course Washington makes it worse. Then again given what brainpower we have there it highly likely that we will see it messed up no matter what.

3. Health Care is a Debacle: One expects as this rolls out that there are so many cooks in the kitchen, and for those employed by the Government rather dullard types, that we can expect people doing the most foolish things. Just think how easy this would have been if we did it like auto insurance. Individual, no Government intervention, and portable. Just make it so it is required by all, no preexisting conditions bias, rates by age, penalties based on life style choices such as smoking and obesity. It plays into what we do in auto insurance. But no, we had to have Government control. Just watch.

4. Employment and Productivity: Productivity still increases driving out labor. The labor content of produced goods is dropping dramatically and will accelerate. What that means is that the strategic advantage of cheap labor will disappear and market location will be selected more on tax, regulation, and political stability. Perhaps this may be a God send for Ireland.

5. Nuclear Threat: I lived through the Soviet-US nuclear threats, they were real, but the parties were fundamentally rational. Mutual Assured Destruction was clear, do not go there. The current crop of crazies are not the Russians. The Russians have a culture, a love of their children, and the desire to survive an thrive. Not the same can be said for some of the current crop. This is a clear and present danger.

6. Data and Personal Security: The biggest political debate I believe will be over the heavy handed actions by the US Security apparatus. Not only do they intercept outside of the country but now they appear to be invading our very homes. One could not envision a more brutal attack

on our fundamental Constitutional Rights. Many in Congress are turning a blind eye to the effort. I have been aware of the actions of some of these folks for decades, but in the old days it was done outside the US. Now, we have seen the reverse. I continue to say that terrorists are not that dumb, they can find ways to keep below the radar. That leaves the rest of us vulnerable. This may very well become the debate of the decade.

Let us see how 2014 plays out, Happy New Year.

Labels: Commentary