2/5/2014

The Squirrel's Nest 2013

Terrence McGarty

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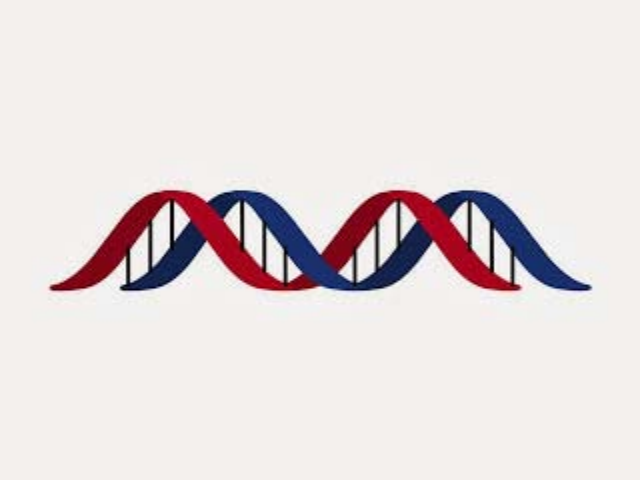
THE SQUIRREL'S NEST

MONDAY, DECEMBER 30, 2013

EVOLUTION AND FAITH



The Pew Research Group, an entity that I have had the chance to interact with and have found them quite left of center and in my opinion a bit biased, has issued a report on Creationism and Religion. The bottom line is:

According to a new Pew Research Center analysis, six-in-ten Americans (60%) say that "humans and other living things have evolved over time," while a third (33%) reject the idea of evolution, saying that "humans and other living things have existed in their present form since the beginning of time."

Then they go on to state:

A majority of white evangelical Protestants (64%) and half of black Protestants (50%) say that humans have existed in their present form since the beginning of time.

Now I remember my first year in secondary school we had biology and we spent time on evolution. That was a Catholic school and there was not even a peep otherwise. The other half of the class was genetics and DNA, and that was 1957. Our Instructor had just finished his PhD in Biochemistry and was all aghast about Watson and Crick. We may very well have been one of the few classes in New York at the time with a glimmer of what DNA even was.

Furthermore being trained amongst other things as a Botanist, I play around with DNA all the time, albeit rather roughly via hybridizing. Thus the idea of evolution is not only believable but there can be no other explanation given the wealth of facts.

Thus when one sees 2/3rds of the population of one class, a class which I perhaps am not exposed to, believing in something which is so against the facts, I am amazed. But here is the

catch from Pew:

Roughly two-thirds of Democrats (67%) and independents (65%) say that humans have evolved over time, compared with less than half of Republicans (43%).

Why am I not surprised. I just wonder where all these folks are? Or is this something that one would like to believe? Just asking, seems too convenient.
Labels: Politics, Religion

HOW FAST IS FAST?

The complaints about broadband continue. I was amazed to see the piece today in the NY Times. I guess it is a slow week.

Now let us discuss a few facts. You see, I know Lativia, I have been to Riga and it is one of those old Hanseatic League countries. Then again it is also home to may Soviets transplants and in my experience is not necessarily a great place. It also is tiny, there is not much there with the exception of the Baltic Sea.

As for broadband in Lativia, I negotiated that for my company in 2001. I did all of Central Europe and even Russia. It was easy. Then I thought that I could come back to the US and do the same. Wrong. Why? Franchises and the local Boards.

I tried some 35 towns in Vermont, New Hampshire and Massachusetts. There are, except for Vermont, Cable Boards in each and every hamlet. Composed of what appeared to be people who have nothing else to do except delay and demand exorbitant add ons for free. The Barrier to Entry in the US are the very people who complain. They want everything for free! No wonder we have a health care mess. Free just does not exist, at least in this current world.

Now the Times states:

There is ample evidence that faster broadband spurs economic growth. The White House cites a study of 33 of the largest national economies worldwide, which found that from 2008 to 2010,

doubling a country's broadband speed increased gross domestic product by 0.3 percent. In its report, "Four Years of Broadband Growth," the Obama administration says that since 2002, Internet access has contributed an average of $34 billion a year to the economy, or 0.26 percent of G.D.P. growth.

The problem is that the Government also spent some $8 Billion on Stimulus Grants, that is free money, or as we on the right say, more debt, and thus the $34 B putative gain must be offset by that $8 Billion at the very least. How much of that $8 Billion is accounted for? Is there any public record of what has been done? I have gone back to USDA and DoC, NTIA, sites and they are vague at the very best. You see very little was done, Billions just flew out the window.

Let us examine some of the Times statements:

But those speeds can come at a very high price. In Chattanooga, Internet service of 1 gigabit a second costs a consumer $70. But in Lafayette, the same speed costs nearly $1,000 a month. In Seoul, it's about $31 — a result of government subsidies to encourage Internet use.

First, 1 Gbps is awfully fast for a residence. Just what are you doing with that, running a cloud service from your garage! Second, to get a Gbps one only needs a single strand of fiber, as is in most FTTH builds. Yet, and this is a critical yet, that is 1 Gbps to a hub, at which point you mix with all the other 1 Gbps folks dramatically dropping your speed! Does that author have any clue about what he is saying? 1 Gbps at the home is meaningless, it is the backbone network. You do NOT have a strand supporting 1 Gbps to everyone else. It is a network for God's sake! Thus neither need nor reality drives any 1 Gbps demand.
Labels: Broadband

SUNDAY, DECEMBER 29, 2013

WORDS MEAN SOMETHING

Words really mean something. If you have even been deposed, cross examined at a trial, or written an expert report, you should have a somewhat sharpened sense of words. In the NY Times today as they discussed the Libya disaster the Times states:

Months of investigation by The New York Times, centered on extensive interviews with Libyans in Benghazi who had direct knowledge of the attack there and its context, turned up no evidence that Al Qaeda or other international terrorist groups had any role in the assault.

Now read this carefully. They say that the Times could not turn up any evidence, NOT that the allegation was false. All they could say was that they could not say one way or the other, that is what *turned up no evidence* means in plain English. Now I do not want to take a position one way or the other but I do want to deal with the use of English. Words mean something. Thus there must have been dozens of edits of this sentence. Just look at how convolved it is, except the four words they use are clear. Whether they did a good job or bad, they could not find anything.

Yet again why would anyone even suspect that they could. They are New York reporters trying to gather information in a war zone amongst people who not only hate Americans but I suspect

do not like the Times either.

Yet reporters, or "news readers", on the media have stated that the Times unequivocally said there was no relationship. That is not what these words mean. This is the very definition of equivocation.

One wonders if anyone can read in today's world.
Labels: Politics

FRIDAY, DECEMBER 27, 2013

MOVE OVER GPS

China Daily reports that China is launching the equivalent of GPS satellites and will provide the service free. They state:

The world can expect to use China's "reliable" global positioning and navigation services for free by 2020, the director of the country's satellite navigation office said on Friday. "The Beidou Navigation Satellite System is committed to providing services to the whole world — currently for the Asia-Pacific — for free," said Ran Chengqi, director of the China Satellite Navigation Office. The office released two documents to specify China's homegrown navigation system's open service performance standard and to facilitate research and development of various terminals for global users. After deploying 16 satellites since 2000, the country will begin launching newer navigation satellites near the end of 2014, Ran said at a news conference. In six to eight years, the number of satellites that will be launched is expected to grow to 40 to form a constellation as coverage expands globally, according to a statement from Ran's office. These satellites, with enhanced functions, will have a lifespan of up to 15 years. The satellites currently in use work for about eight years.

Interesting competition or threat? And there is as of yet no reports in the Western Press.
Labels: China

WHOSE PROPERTY?

John Locke introduced the arguments for individual property rights at the end of the 17th century. Succinctly if you pay for it you own it. Now let us examine telephone service. I have spent a few years there, last one at Verizon/NYNEX as SVP and COO and billing was under me amongst other things. We charged the customer for the service, all the service, and that included the bill. In a Lockean sense therefore the customer "owned" the bill. We protected the data since we were at best a common carrier and part of that duty under common carriage law was protection of the entire package.

I entrust a common carrier with my package, the entire package. Under common carrier law they are responsible for the package and its integrity but if lost their liability is limited to the cost of transport not the value of the package. The law gives them this break so we can entrust them with the ability to conduct commerce. We trust a common carrier and their reward to honoring the trust is elimination of total liability. If they break that trust then what?

Now does the same apply to the Post Office? Not really since we know the post office is a Government entity and thus we have no expectation of privacy. In addition the address is in plain sight, and it cannot be protected. However telephone call records are secure, encrypted, protected, and thus an expectation of privacy is apparent.

Now with the NY Judge and the NSA. The NY Times reports:

Judge Pauley said that protections under the Fourth Amendment do not apply to records held by third parties, like phone companies. "This blunt tool only works because it collects everything," Judge Pauley said in the ruling."While robust discussions are underway across the nation, in Congress and at the White House, the question for this court is whether the government's bulk telephony metadata program is lawful. This court finds it is," he added.A spokesman for the Justice Department said, "We are pleased the court found the N.S.A.'s bulk telephony metadata collection program to be lawful." He declined to comment further.

Now whose property is is. Did the Telco pay for it out of their profits? No way! The consumer paid for the collection and processing and never waived their rights. At best the Telco has a duty to protect the customer. This is a classic case of Common Carriage protection. It dates back to Elizabeth I around 1602. Somehow all the wonderful protections we had obtained in the past centuries are slipping away, perhaps because of a poor pleading, perhaps because of a nefarious government.

Now I had written several papers a while back worth recounting:

Privacy In this paper I discuss privacy rights in an Internet world.

Internet Hubbing In this paper I discuss using a hub in Europe to protect privacy on Internet traffic. This was 2002! It was clear then that Echelon was snooping all wireless traffic.

Network Neutrality Internet Neutrality also means Internet privacy. In this paper I noticed the loss of ownership under common carriage.

I believe that there is a fundamental right of ownership that the Telcos are denying and that the Government is destroying. NSA for many years spied on foreign traffic. As a military entity one wonders what rights they have to function in the country. Posse Comitatus notwithstanding.
Labels: Government

MORE ON THE FACEBOOK VALUE PROPOSITION

Having been a very early adopter of Facebook and then gone years ago I never really understood the value proposition. Today almost every web page is filled with advertising trash, it pops up, slides around, blinks, makes noises, dumps cookies, and keeps attaching itself to every other page you examine. In addition you see silly comments by people you have no knowledge and then your name gets connected to data as if these were your interests. So what is the value proposition again?

In today;s Telegraph they state:

A study of how older teenagers use social media has found that Facebook is "not just on the slide, it is basically dead and buried" and is being replaced by simpler social networks such as Twitter and Snapchat. Young people now see the site as "uncool" and keep their profiles live purely to stay in touch with older relatives, among whom it remains popular.

So what is the value proposition again? It appears as if they are "losing" subs and morphing into a billboard system. Having users is not the same as booking revenue.
Labels: Commentary

INCOME REDISTRIBUTION

In an article in the NY Times the following is stated:

ESPN is hardly needy. With nearly 100 million households paying about $5.54 a month for ESPN, regardless of whether they watch it, the network takes in more than $6 billion a year in subscriber fees alone. Still, ESPN has received about $260 million in state tax breaks and credits over the past 12 years, according to a New York Times analysis of public records. That includes $84.7 million in development tax credits because of a film and digital media program, as well as savings of about $15 million a year since the network successfully lobbied the state for a tax code change in 2000.

Now I have never seen a football or basketball game and I have only seen Red Sox World Series games, my wonderful wife is from Boston. So why am I paying some $70 per year for something I neither use or want? Where is Congress on this or the FCC? In New Jersey it should be the PUC or equivalent but I gather they are pure political appointees who are in my experience clueless.

Imagine a $6 Billion Income Transfer from the poor to the rich. Where is the outcry? It makes for extreme pay to the players of these sports, almost all of whom seem to end up in legal trouble one way or the other. Thus the externality costs could easily double this obscene transfer.

Thus for a cause for 2014 perhaps we can solve this Pirate like taking from those who see no benefit but pay for the costs.
Labels: Economy, FCC

THURSDAY, DECEMBER 26, 2013

HEALTH CARE COSTS: FACT VS FICTION

In a recent NEJM paper some of the creators of the current ACA system comment on Health Care costs.They discuss what they see as the current trends and then they comment on the reduction in costs and reduction in demand.

As to costs they state:

In an analysis of inflation-adjusted ("real") spending, the major factor in cost growth during the past 50 years has been the development and diffusion of new medical technology. The specific innovations have varied over time — from cardiac procedures to prescription drugs to advances in imaging — but the importance of technology as a whole has not. Estimates suggest that about half the annual increase in U.S. health care spending has resulted from new technology.

Namely, it appears that one blames the technology. True, there is a great deal more technology but also true, it is oftentimes quite effective. When I first studied there was no CAT scans available and one would look carefully at shadows in plain film to try to determine what was the problem. This was of little use in the case of strokes as one tried to ascertain a block or a bleed. The result was high mortality and lower follow up costs. Thus technology has substantially prolonged life, at a cost, and has reduced some morbidities, while frankly increasing others, but then reducing mortality. It is not as simple as we would have hoped.

As to demand they state:

Some authors have suggested that slow cost growth may result from a reduced need for care, since trends in rates of obesity have flattened. Such changes are small as compared with overall medical spending, however. During the 2000s, rates of obesity increased by 3.8% annually, leading to projected spending growth of 0.3% annually; between 2009 and 2010, this increase was cut in half, implying a slowdown of 0.1% in growth annually...

On the demand side, many people are now facing very high cost sharing, and this discourages the use of health services.A total of 20% of Americans with employer-sponsored coverage have high-deductible plans Percentage of Covered Workers Enrolled in a High-Deductible Health Plan or Medical Savings Account (MSA), 2006–2013.), and the typical plan deductible exceeds the typical family's available savings. In addition, many consumers have insurance policies that reward them financially for using lower-cost services.

Here they argue two points. First the demand decreased due to a reduction in comorbidity proclivities. Second a demand reduction due to costs. Frankly we have reduced smoking in men greatly and tus the reduction in smoking related disease but we have seen an explosion in obesity and the comorbidities there. The advantage of lung cancer is rapid death, the disadvantage of the sequellae to obesity if a long life at a high societal cost.

The arguments are a bit loose and are still hand waving in presentation. The conclusions are somewhat useful but frankly they do not relate in any way yet to the ACA. The results they present are somewhat hopeful in the long run.
Labels: Health Care

WISDOM AT THE FCC

I noticed a piece from the FCC by Commissioner Pai speaking of the 100th anniversary of the Kingsbury Decision of 1913. Simply, the Kingsbury Decision was an inside deal with the Justice Department that gave AT&T the exclusive monopolistic control of all telecommunications. This was in the Wilson term and Wilson was at the same time attacking all other monopolies.

As Pai states:

What should a new Kingsbury Commitment look like? At the risk of being an impolite guest, I'd like to dispute the premise of that question. To me, the Kingsbury Commitment is not a model to be emulated. Instead, it's a cautionary tale about the dangers of regulatory capture and the folly of attempting to manage competition. A comforting mythology has long existed in many quarters about the development of our nation's telephone system. We are often told that the telephone industry was a natural monopoly. The rise of Ma Bell, or something like it, was inevitable. And it follows that the proper role for government was—and, by implication, still is—to regulate that monopoly and ensure that it served socially productive goals. As AT&T's slogan in the early part of the 20th century put it, "One System, One Policy, Universal Service." But there's a tiny problem with this view of history. As Adam Thierer and others have explained, it doesn't comport with the facts. To be sure, in the earliest days of the telephone industry, there was little competition. But that's because of patents obtained by Alexander Graham Bell. Once those patents began to expire in 1893, things began to change—dramatically. By 1894, eighty competitors had entered local telephone markets. Less than ten years later, there were over 3,000. As a result, AT&T's market share fell from 95 percent in 1894 to 49 percent in 1907.

This is a brilliant and quite true observation. This was an inside deal to destroy competition and establish a monopoly. It was a monopoly that was to hinder telecommunications development for another seventy years.

Pai continues:

Here are three of the lessons we should draw.

First, the government should not try to manage competition. The Kingsbury Commitment is a prime example of regulators attempting to do so and failing miserably. No regulatory scheme, no theoretical formula for competition, no matter how finely crafted, can replace actual competition, with all its unmanageable imperfections.

Second, the government should not confuse the goal of protecting competitors with the objective of promoting competition. One could argue that the Kingsbury Commitment served the interests of both AT&T and its rivals. For AT&T, the compact ended an antitrust challenge to its domination of the longdistance market. For independents, the compact ensured their survival in some form. The real losers were the American public, who lost the benefits of actual competition. Similarly, our goal today should not be to preserve the position of any particular company in the marketplace or to help one segment of the industry gain regulatory advantages over its rivals. In a competitive marketplace, we must understand that there will be winners and losers. It is not the government's job to tilt the playing field by punishing the winners or helping the losers.

Third, beware of businesses bearing commitments. Companies do not offer commitments out of the goodness of their hearts. Instead, as in the case of the Kingsbury Commitment, these commitments are generally designed to serve a company's self-interest. This is entirely understandable, of course. Butwe regulators must keep it in mind when companies come to our

door. Is a company trying to use a voluntary commitment that sounds good on paper to obtain a regulatory leg up on a competitor? What is couched as an attempt to serve the public interest is often in reality an attempt to further private interests and raise rivals' costs of doing business.

I would never have expected such a statement from the FCC. This is a brilliant analysis of Kingsbury and worth a read by all. Pai in my opinion stands out as a brilliant star whose insight may be highly productive at the FCC, long in need of such understanding.
Labels: FCC

WEDNESDAY, DECEMBER 25, 2013

HOW OLD IS TYPE 2 DIABETES?

In a recent Nature paper the authors examine Mexican and Latin Americans for genetic markers of those afflicted with Type 2 Diabetes. The found that the genetic marker related to control of Triglycerides was one originating from Neanderthal ancestors, prevalent in this class but not so in Asians, Europeans or Africans. They state:

The risk haplotype carries four amino acid substitutions, all in SLC16A11; it is present at 50%frequency in NativeAmerican samples and 10%in eastAsian, but is rare in European andAfrican samples. Analysis of an archaic genome sequence indicated that the risk haplotype introgressed intomodern humans via admixture with Neanderthals.

It is interesting to see this but then again there is the basic issue that obesity is a major driver, although there may be an aggravating genetic issue as well. One often sees populations where for generations there were poor nutritional basics and then they have excess food that Type 2 Diabetes accompanies obesity, the Irish being a classic example.

Dr. Lewis on PLOS has an excellent analysis of this paper. Lewis is a highly perceptive and articulate analyst of these topics and she is always worth reading. The sad part is the first comment is an accusation of racism which appears to be based on the Neanderthal comment. Sad to think that people just jump on something that perhaps they have no knowledge of what they speak.

But back to the results. I have read through many of the GWAS studies and fell the same way as Lewis. Yet I would take it a bit further because the driving element is obesity and not necessarily the genetic effects. I suspect the genetic effects may exacerbate the problem but if the BMI were driven below 22.5 one almost always sees the HgA1b driven below 5.0.

Notwithstanding this is a well done paper and worth following.
Labels: Diabetes

THOUGHTS FROM THOMAS PAINE

I often visit the only memorial to Thomas Paine here in Morristown. A short distance from where Washington spent a good deal of his time and a short distance from several Winter encampments. When it comes to Paine and Burke, despite Burke's "conservative" mindset I all too often fall with Paine.

From the opening of Common Sense he states:

SOME writers have so confounded society with government, as to leave little or no distinction between them; whereas they are not only different, but have different origins. Society is produced by our wants, and government by our wickedness; the former promotes our happiness positively by uniting our affections, the latter negatively by restraining our vices. The one encourages intercourse, the other creates distinctions. The first is a patron, the last a punisher.

Society in every state is a blessing, but government even in its best state is but a necessary evil; in its worst state an intolerable one; for when we suffer, or are exposed to the same miseries by a government, which we might expect in a country without government, our calamities is heightened by reflecting that we furnish the means by which we suffer. Government, like dress, is the badge of lost innocence; the palaces of kings are built on the ruins of the bowers of paradise. For were the impulses of conscience clear, uniform, and irresistibly obeyed, man would need no other lawgiver; but that not being the case, he finds it necessary to surrender up a part of his property to furnish means for the protection of the rest; and this he is induced to do by the same prudence which in every other case advises him out of two evils to choose the least. Wherefore, security being the true design and end of government, it unanswerably follows that whatever form thereof appears most likely to ensure it to us, with the least expense and greatest benefit, is preferable to all others.

Somehow the Progressives, and with Paine oftimes being the First Progressive, take the anti-Paine view, a love and trust in Government and none in people themselves. Paine saw what extremes Government could go, despite his blind spot in the French Revolution, in many ways a result of his view to overthrow the evils of the French monarchy.

So as we enter the New Year one must at time hark back to Paine and his words, truer now than when they were first written. Merry Christmas, and yes, I will visit Tom.
Labels: Government

TUESDAY, DECEMBER 24, 2013

MOOCS AND DISCUSSION FORA

As I begin to better understand MOOCs as an educational vehicle I am still confused as to the usefulness of the Discussion Fora. I believe it is a generational thing. Coursera appears to be giving the option to pay to belong to a TA interactive Forum. Perhaps there is value in such for some.

But I have made a few observations:

1. It is cultural. There is a class of participants who appear to like to "hear" themselves on such a vehicle by posting everywhere and commenting on everything. It is not clear that they are even taking the course.

2. Some questions are purely administrative or are of the type that a reasonable Professor would just blow off. It is a student who has no judgment or experience and is asking ceaseless trivia.

3. Some seem to be professing how well they are doing. Just why I want to know that so and so got a 95 is uncertain.

The list could go on. A recent study has indicated that perhaps there is a bigger problem. They conclude:

The larger goal behind our two main research questions is to improve the quality of learning via the online discussion forums, namely by (1) sustaining forum activities and (2) enhancing the personalized learning experience. This paper makes a step towards achieving these end-goals by relying on an extensive empirical dataset that allows us to understand current user behavior as well as factors that could potentially change the current user behavior. We showed, for example, that the teaching sta 's active participation in the discussion increases the discussion volume but does not slow down the decline in participation. We also presented two proof-of-concept algorithms for keyword extraction and relevance-ranking to remedy the information overload problem, both of which are demonstrated to be e ffective. Devising eff ective strategies to reduce the decline of participation in the online discussion forums is the main open problem to be addressed next.

Specifically usage of Discussion groups seems to collapse. My view is that they seem to linger with just a few making any comments except the classes as above. The problem is the structure of the way it is done. I do not have any suggestion other than to say that what is done now just does not work.
Labels: Education

MERRY CHRISTMAS TO ALL

1. FACTUM EST AUTEM IN DIEBUS ILLIS EXIIT EDICTUM A CAESARE AUGUSTO UT DESCRIBERETUR UNIVERSUS ORBIS
2. HAEC DESCRIPTIO PRIMA FACTA EST PRAESIDE SYRIAE CYRINO

3. ET IBANT OMNES UT PROFITERENTUR SINGULI IN SUAM CIVITATEM
4. ASCENDIT AUTEM ET IOSEPH A GALILAEA DE CIVITATE NAZARETH IN IUDAEAM CIVITATEM DAVID QUAE VOCATUR BETHLEEM EO QUOD ESSET DE DOMO ET FAMILIA DAVID
5. UT PROFITERETUR CUM MARIA DESPONSATA SIBI UXORE PRAEGNATE
6. FACTUM EST AUTEM CUM ESSENT IBI IMPLETI SUNT DIES UT PARERET
7. ET PEPERIT FILIUM SUUM PRIMOGENITUM ET PANNIS EUM INVOLVIT ET RECLINAVIT EUM IN PRAESEPIO QUIA NON ERAT EIS LOCUS IN DIVERSORIO
8. ET PASTORES ERANT IN REGIONE EADEM VIGILANTES ET CUSTODIENTES VIGILIAS NOCTIS SUPRA GREGEM SUUM
9. ET ECCE ANGELUS DOMINI STETIT IUXTA ILLOS ET CLARITAS DEI CIRCUMFULSIT ILLOS ET TIMUERUNT TIMORE MAGNO
10. ET DIXIT ILLIS ANGELUS NOLITE TIMERE ECCE ENIM EVANGELIZO VOBIS GAUDIUM MAGNUM QUOD ERIT OMNI POPULO
11. QUIA NATUS EST VOBIS HODIE SALVATOR QUI EST CHRISTUS DOMINUS IN CIVITATE DAVID
12. ET HOC VOBIS SIGNUM INVENIETIS INFANTEM PANNIS INVOLUTUM ET POSITUM IN PRAESEPIO
13. ET SUBITO FACTA EST CUM ANGELO MULTITUDO MILITIAE CAELESTIS LAUDANTIUM DEUM ET DICENTIUM
14. GLORIA IN ALTISSIMIS DEO ET IN TERRA PAX IN HOMINIBUS BONAE VOLUNTATIS
15. ET FACTUM EST UT DISCESSERUNT AB EIS ANGELI IN CAELUM PASTORES LOQUEBANTUR AD INVICEM TRANSEAMUS USQUE BETHLEEM ET VIDEAMUS HOC VERBUM QUOD FACTUM EST QUOD FECIT DOMINUS ET OSTENDIT NOBIS
16. ET VENERUNT FESTINANTES ET INVENERUNT MARIAM ET IOSEPH ET INFANTEM POSITUM IN PRAESEPIO
17. VIDENTES AUTEM COGNOVERUNT DE VERBO QUOD DICTUM ERAT ILLIS DE PUERO HOC
18. ET OMNES QUI AUDIERUNT MIRATI SUNT ET DE HIS QUAE DICTA ERANT A PASTORIBUS AD IPSOS
19. MARIA AUTEM CONSERVABAT OMNIA VERBA HAEC CONFERENS IN CORDE SUO
20. ET REVERSI SUNT PASTORES GLORIFICANTES ET LAUDANTES DEUM IN OMNIBUS QUAE AUDIERANT ET VIDERANT SICUT DICTUM EST AD ILLOS

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

1 وَفِي ذلِكَ الزَّمَانِ، أَصْدَرَ الْقَيْصَرُ أُغُسْطُسُ مَرْسُوماً يَقْضِي بِإِحْصَاءِ سُكَّانِ الإِمْبِرَاطُورِيَّةِ.
2 وَقَدْ تَمَّ هَذَا الإِحْصَاءُ الأَوَّلُ عِنْدَمَا كَانَ كِيرِينِيُوسُ حَاكِماً لِسُورِيَّةَ.
3 فَذَهَبَ الْجَمِيعُ لِيُسَجَّلُوا، كُلٌّ وَاحِدٍ إِلَى بَلْدَتِهِ.
4 وَصَعِدَ يُوسُفُ أَيْضاً مِنْ مَدِينَةِ النَّاصِرَةِ بِمِنْطَقَةِ الْجَلِيلِ إِلَى مَدِينَةِ دَاوُدَ الْمَدْعُوَّةِ بَيْتَ لَحْمٍ بِمِنْطَقَةِ الْيَهُودِيَّةِ، لأَنَّهُ كَانَ مِنْ بَيْتِ دَاوُدَ وَعَشِيرَتِهِ،
5 لِيَتَسَجَّلَ هُنَاكَ مَعَ مَرْيَمَ الْمَخْطُوبَةِ لَهُ، وَهِيَ حُبْلَى.
6 وَبَيْنَمَا كَانَا هُنَاكَ، تَمَّ زَمَانُهَا لِتَلِدَ،
7 فَوَلَدَتِ ابْنَهَا الْبِكْرَ، وَلَفَّتْهُ بِقِمَاطٍ، وَأَنَامَتْهُ فِي مِذْوَدٍ، إِذْ لَمْ يَكُنْ لَهُمَا مُتَّسَعٌ فِي الْمَنْزِلِ.
8 وَكَانَ فِي تِلْكَ الْمِنْطَقَةِ رُعَاةٌ يَبِيتُونَ فِي الْعَرَاءِ، يَتَنَاوَبُونَ حِرَاسَةَ قَطِيعِهِمْ فِي اللَّيْلِ.
9 وَإِذَا مَلاَكٌ مِنْ عِنْدِ الرَّبِّ قَدْ ظَهَرَ لَهُمْ، وَمَجْدُ الرَّبِّ أَضَاءَ حَوْلَهُمْ، فَخَافُوا أَشَدَّ الْخَوْفِ.
10 فَقَالَ لَهُمُ الْمَلاَكُ: «لاَ تَخَافُوا! فَهَا أَنَا أُبَشِّرُكُمْ بِفَرَحٍ عَظِيمٍ يَعُمُّ الشَّعْبَ كُلَّهُ:
11 فَقَدْ وُلِدَ لَكُمُ الْيَوْمَ فِي مَدِينَةِ دَاوُدَ مُخَلِّصٌ هُوَ الْمَسِيحُ الرَّبُّ.
12 وَهَذِهِ هِيَ الْعَلاَمَةُ لَكُمْ. تَجِدُونَ طِفْلاً مَلْفُوفاً بِقِمَاطٍ وَنَائِماً فِي مِذْوَدٍ».
13 وَفَجْأَةً ظَهَرَ مَعَ الْمَلاَكِ جُمْهُورٌ مِنَ الْجُنْدِ السَّمَاوِيِّ، يُسَبِّحُونَ اللهَ قَائِلِينَ:
14 «الْمَجْدُ لِلهِ فِي الأَعَالِي، وَعَلَى الأَرْضِ السَّلاَمُ؛ وَبِالنَّاسِ الْمَسَرَّةُ! »
15 وَلَمَّا انْصَرَفَ الْمَلاَئِكَةُ عَنِ الرُّعَاةِ إِلَى السَّمَاءِ، قَالَ بَعْضُهُمْ لِبَعْضٍ: «لِنَذْهَبْ إِذَنْ إِلَى بَيْتِ لَحْمٍ، وَنَنْظُرْ هَذَا الأَمْرَ الَّذِي حَدَثَ وَقَدْ أَعْلَمَنَا بِهِ الرَّبُّ!»
16 وَجَاءُوا مُسْرِعِينَ، فَوَجَدُوا مَرْيَمَ وَيُوسُفَ، وَالطِّفْلَ نَائِماً فِي الْمِذْوَدِ.
17 فَلَمَّا رَأَوْا ذلِكَ، أَخَذُوا يُخْبِرُونَ بِمَا قِيلَ لَهُمْ بِخُصُوصِ هَذَا الطِّفْلِ.
18 وَجَمِيعُ الَّذِينَ سَمِعُوا بِذلِكَ دُهِشُوا مِمَّا قَالَهُ لَهُمُ الرُّعَاةُ.
19 وَأَمَّا مَرْيَمُ، فَكَانَتْ تَحْفَظُ هَذِهِ الأُمُورَ جَمِيعاً، وَتَتَأَمَّلُهَا فِي قَلْبِهَا.

Labels: Commentary

TUESDAY, DECEMBER 24, 2013

MARX AND POLITICS

Upon rereading Marx and Engles, always an interesting thing to do on Christmas Eve, they state their ten point plan:

1. Abolition of property in land and application of all rents of land to public purposes.

2. A heavy progressive or graduated income tax.

3. Abolition of all right of inheritance.

4. Confiscation of the property of all emigrants and rebels.

5. Centralization of credit in the hands of the State, by means of a national bank with State capital and an exclusive monopoly.

6. Centralization of the means of communication and transport in the hands of the State.

7. Extension of factories and instruments of production owned by the State; the bringing into cultivation of wastelands, and the improvement of the soil generally in accordance with a common plan.

8. Equal liability of all to labour. Establishment of industrial armies, especially for agriculture.

9. Combination of agriculture with manufacturing industries; gradual abolition of the distinction between town and country, by a more equable distribution of the population over the country.

10. Free education for all children m public schools. Abolition of children's factory labour in its present form. Combination of education with industrial production.

Well we are not there yet but perhaps we can judge the progress by examining the actions of our Politicians but more importantly of our Government Administrators.

Just a few of the above:

Centralizing Credit and Banks, well we are on our way there.

Centralizing means of communications, well the NSA has really helped out there.

Cultivation of Wastelands, that has been the EPA, Marx never asked for productive "cultivation"

Mao tried the "all to agriculture" thing in the "Great Leap Forward". I find it interesting that perhaps we could get all those folks in DC out in the fields working crops. Just a thought as we move towards a new year.
Labels: Government

ALAN TURING

The Queen has given a rare Royal Pardon to Alan Turing for his alleged personal practices. As the BBC reports:

"Turing deserves to be remembered and recognised for his fantastic contribution to the war effort and his legacy to science. A pardon from the Queen is a fitting tribute to an exceptional man."
The pardon comes into effect on 24 December.

Turing died in June 1954 from cyanide poisoning and an inquest decided that he had committed suicide. However, biographers, friends and other students of his life dispute the finding and suggest his death was an accident.

Although Turing was known for his seminal ideas on computers and his work on code breaking, my personal appreciation was his work on tessellation and flower coloring. This essentially was the development of the understanding of inter-cellular communications which only now is being fully understood. I often wonder what would have happened if Turing had lived and had the

chance to understand what Watson and Crick had done just up the road a piece from where he was at the time.
Labels: Commentary

THE PHONE SYSTEM

The NY Times has an Editorial regarding what they term the "phasing out of the phone system". The say that what we have now we have had since Bell. Not even close guys. I love it when people who know nothing of what they speak on a specific topic prognosticate, especially on the Editorial pages of the Times. It appears all too often that lawyers and journalists are all too prone to do this, and yes, economists as well.

There has been a revolution in telephone architectures since 1984 with the official breakup of AT&T. Competition and market forces, fettered at times by the FCC, opened the market. To some degree wireless would not be what it is today if we still had Bell Labs and vertical integration. Steve Jobs would have been in prison for violating Federal Law. And most likely we would have more people in AT&T than employed by the Federal Government.

As of now the US does not have a single telephone switch manufacturer left. They have moved elsewhere, including China. What we have a a high capacity wireless network along with extremely clever end user devices working on an IP based network.

As the Times states:

Some telecommunications companies like AT&T argue that the country needs to begin moving away from the traditional system, in which copper wires connect phones to big machines known as switches, to a more efficient Internet-based system that work over wireless or fiber-optic technologies.

The F.C.C. is expected to authorize AT&T and other phone companies to replace conventional telephone wires with wireless or fiber-optic connections in certain neighborhoods or a large rural area to see how such a change would work in practice.

Frankly what right does the FCC have to tell companies how to offer their service. It arguably is the authority Congress gave them for Universal Service. Now the Times in its brilliance states:

Phone companies maintain backup batteries and electricity generators at their central offices to make sure service is uninterrupted during blackouts. But consumers have to plug in devices to use cellphones and Internet-based services, which means there's a risk of losing service if the electricity goes out.

As the F.C.C. deals with new technology, it needs to keep in place safeguards that have long ensured that the phone system serves everyone. Today, Americans who cannot afford regular phone service can get a subsidized wired or wireless connection. That should continue even if the underlying technology changes.

Batteries in COs are all too often environmental hazards. Just look at 140 West Street, the basement was filled with batteries, then flooded and now being rented out as upscale condos. Perhaps because they cannot tear it down due to the battery deposits. Just a thought.

But must we keep "horse stables" when we have automobiles, must we keep the buggy whips factories going when we have the same new means of transportation. Cell phone have batteries, they battery lasts a long time unless you are using it excessively. Thus I am really aghast as to the Times demanding we keep all those toxic battery vaults so the "poor" can use their cell phones and Internets during a temporary power outage. Just to let the Times know, most people get Internet via a wireless or Cable feed and not over copper! Those Hayes modems just do not do a great job anymore.

The last paragraph is truly amazing for its Luddite tones:

America has a long history of telecommunications innovation since Bell made the first call to Watson nearly 140 years ago. The issue is not whether the phone system needs to be upgraded. It's how.

First, the US telecom technology was suppressed until the breakup of AT&T. Bell Labs designed capital intensive systems since its profit was a return on investment. The motivation for cost effectiveness was non-existent. The change started with McGowan and MCI and took hold only in 1984. Secondly, technology moves at its own pace. Once started the Times and the FCC can only be temporary roadblocks. So for those "poor" with their free Government supplied, taxpayer supported, phones and Internet, try charging it before the storm! Let technology evolve naturally, not the way our elite wants it to.
Labels: FCC

MONDAY, DECEMBER 23, 2013

PCA GENETIC TESTS: DO THEY MAKE ANY SENSE?

The recent report on such a cancer prognostic model such as Oncotype DX by Knezvic et al is a putatively prognostic method used in prostate cancer. Fundamentally what they do is examine cancer cells for the expression of various genes and examine three sets; baseline expressions, excess expressions and reduced expression. They use the baseline to set levels for excess and reduced. They then use the excess or reduced in a one dimension expression to determine a prognostic measure. This seems to be in contrast with work we reported on a few months ago[1[1]].

Like PSA measures, CA125, CEA, and the like, they try to reduce everything to a single number. We argue here that such an approach is problematic at best. Furthermore they fail totally to demonstrate any internal pathway influence. There is no predictive basis for their approach predicated upon the actual dynamics of the cell. It is purely correlative and there may be substantial confounders involved. This approach is an example of what we fell to be the poorer aspects of genomics applied to cancer prognostics.

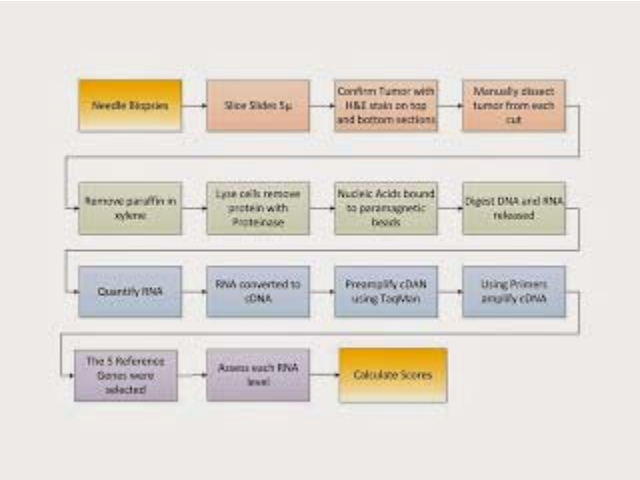
[1[1]] See http://www.telmarc.com/Documents/White%20Papers/98%20CCP.pdf Note that this study was based upon a different vendor with different genes.

In a recent study the authors develop a score called the GPS score which is based upon know malignant PCs cells and then argue that then score has significant prognostic value. The authors state:
The Oncotype DX Prostate Cancer Assay has been clinically validated, demonstrating that the GPS, assessed in diagnostic biopsy tissue, can predict the likelihood of the presence of adverse pathology (high-grade and/or high-stage disease), and that it complements existing pre-treatment risk assessment tools such as PSA levels, Gleason Score, and clinical stage. The assay is intended to help guide treatment decisions in early-stage prostate cancer, including the decision between immediate therapy and active surveillance. As evidence that the analytical assay was designed well for its intended use to test RNA from small biopsies, in a clinical validation study, valid GPS results were generated for more than 95% of samples requiring 1 mm and 30 microns of tumor tissue…

They continue:

Optimization of the Oncotype DX platform has enabled the development and analytical validation of the Oncotype DX Prostate Cancer Assay for use with prostate biopsy specimens. This RT-PCR assay has been clinically validated to predict the risk of high grade and/or non-organ confined disease at radical prostatectomy using biopsy samples containing as little as 1 mm of tumor tissue. The Oncotype DX Prostate Cancer Assay complements traditional clinical and pathologic diagnostic features and will assist clinicians to discriminate patients with indolent prostate cancer from aggressive prostate cancer to help make the most appropriate treatment decisions.

The approach is as follows as shown in the Figure below. Basically take the malignant cells and measure the expression of certain genes via their RNA using a baseline reference gene expression level.



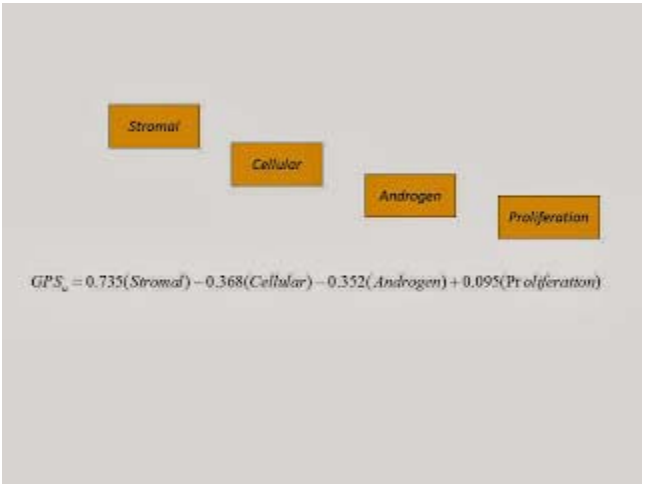
Now the genes they have selected are categorized as follows. They have four categories related to PCa and one category for the purpose of setting a reference level.

Stromal Gene	*Cellular Organization Group*	*Androgen Group*	*Proliferation Group*	*Reference Genes*
BGN	FLNC	FAM13C	TPX2	ARF1
COL1A1	GSN	KLK2		ATP5E
SFRP4	TPM2	AZGP1		CLTC
	GSTM2	SRD5A2		GPSI
				PGK1

Now based upon the levels of expression of these genes against the gene reference level they have proposed a metric which they term the GPS metric which is a measure of prognostic value related to the aggressiveness of the cancer. The GPS metric is given by:

$$GPS = \begin{cases} 0 & if\ 13.4(GPS_u - 10.5) < 0 \\ 100 & if\ 13.4(GPS_u - 10.5) > 100 \\ 13.4(GPS_u - 10.5) & otherwise \end{cases}$$

The higher the GPS measure the arguably the greater the virulence of the cancer. The internal value above is given by:



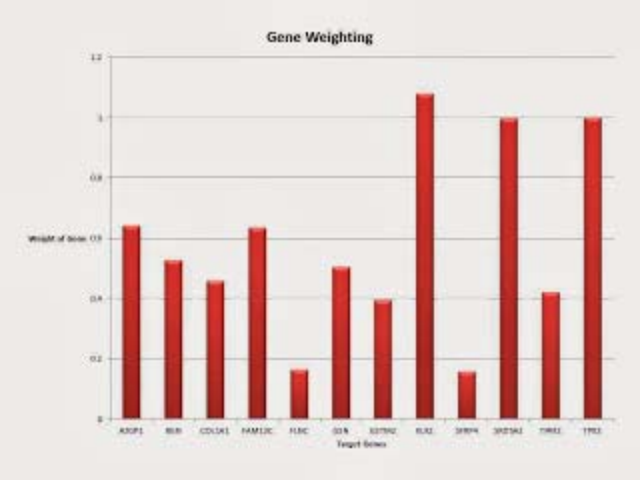
Finally the specific value calculations by class are given by:

$$Stromal = 0.527BGN + 0.457COL1A1 + 0.156SFRP4$$
$$Cellular = 0.163FLNC + 0.504GSN + 0.421TPM2 + 0.394GSTM2$$
$$Androgen = 0.634FAM13C + 1.079KLK2 + 0.642AZGP1 + 0.997SRD5A2^{*}$$
$$\text{Proliferation} = TPX2^{*}$$
where
$$SRD5A2^{*} = \begin{cases} 5.5 & \text{if SRD5A2} < 5.5 \\ SRD5A2 & \text{otherwise} \end{cases}$$
$$TPX2^{*} = \begin{cases} 5.0 & \text{if TPX2} < 5.0 \\ TPX2 & \text{otherwise} \end{cases}$$

We summarize this below:

Group	Genes	Weight
Stromal Gene		
	BGN	*0.527*
	COL1A1	*0.457*
	SFRP4	*0.156*
Cellular Organization Group		
	FLNC	*0.163*
	GSN	*0.504*
	TPM2	*0.421*
	GSTM2	*0.394*
Androgen Group		
	FAM13C	*0.634*
	KLK2	*1.079*
	AZGP1	*0.642*
	SRD5A2	*0.997*
Proliferation Group		
	TPX2	*1.00*
Reference Genes		
	ARF1	
	ATP5E	
	CLTC	
	GPSI	
	PGK1	

We present graphically below thevalues as shown above, namely the weights:



From an earlier Press Release there was reported the results of a study stating[2][2]:

Results showed that the test, developed in collaboration with UCSF and Cleveland Clinic, strongly predicted disease aggressiveness (p=0.002) offering information beyond currently available clinical factors, such as PSA and biopsy Gleason Score, to help physicians and their prostate cancer patients confidently choose the most appropriate treatment based on an individualized risk assessment.

Furthermore, 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.

"The results of our study showed that the individual biological information from the Oncotype DX prostate cancer test tripled the number of patients who can more confidently consider active surveillance and avoid unnecessary treatment and its potential side effects. The test also identified a smaller number of patients who, despite seemingly low-risk clinical factors, had more aggressive disease and, would suggest that they consider immediate treatment," said Peter Carroll, M.D., MPH, professor and chair, Department of Urology, UCSF and principal investigator of this validation study.

"With these new study results, I believe we may be able to significantly increase the use of active surveillance, which has been limited to some extent by the absence of a validated genomic tool to more accurately distinguish low and high risk disease at the time of biopsy." Active surveillance is a treatment plan that employs careful and consistent monitoring of the cancer in a man's prostate without removing it. Under active surveillance, patients have regular check-ups and periodic PSA blood tests, clinical exams and potential biopsies to closely monitor for signs of prostate cancer progression.

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

[2][2] http://investor.genomichealth.com/releaseDetail.cfm?releaseID=762874

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.

Now there are many significant issues in this analysis.

1. The weights are arguably chosen to maximize the risk of missing an aggressive PCa. However I have not yet seen adequate clinical evidence to that effect.

2. Prior proposed genes and the ones included herein are shown below, one from the study currently in discussion and the other from a prior study of a Myriad genetic profile:

Target Genes Oncotype DX	***Housekeeping Genes Oncotype DX***	*Target Gene Myriad*	*Housekeeping Gene Myriad*
AZGP1	**ARF1**	**ASF1B**	**CLTC**
BGN	**ATP5E**	**ASPM**	**MMADHC**
COL1A1	**CLTC**	**BIRC5**	**MRFAP1**
FAM13C	**GPSI**	**BUB1B**	**PPP2CA**
FLNC	**PGK1**	**C18orf24**	**PSMA1**
GSN		**CDC2**	**PSMC1**
GSTM2		**CDC20**	**RPL13A;LOC728658**
KLK2		**CDCA3**	**RPL37**
SFRP4		**CDCA8**	**RPL38**
SRD5A2		**CDKN3**	**RPL4**
TPM2		**CENPF**	**RPL8**

Target Genes Oncotype DX	*Housekeeping Genes Oncotype DX*	*Target Gene Myriad*	*Housekeeping Gene Myriad*
TPX2		**CENPM**	**RPS29**
		CEP55	**SLC25A3**
		DLGAP5	**TXNL1**
		DTL	**UBA52**
		FOXM1	
		KIAA0101	
		KIF11	
		KIF20A	
		MCM10	
		NUSAP1	
		ORC6L	
		PBK	
		PLK1	
		PRC1	
		PTTG1	
		RAD51	
		RAD54L	
		RRM2	
		TK1	
		TOP2A	

It should be obvious that these two tests are dramatically different. Yet they claim similar results. The question is; what genetic expression has gone astray? Why, for example, do we see such a massive disparity? Frankly, other than CLTC we see no other commonality. What causes these disparate expressions? The answers are left hanging. At least with PSA we have some clear cause and effect. Here, at best, we have some correlative values.

With such disparate sets of genes one wonders why and how can these tests be compared if at all. Or, are these results just suggestive and are neither causative or resulting from the lesions.

3. In the current test under discussion the cells used for extraction are arguably from the prostate biopsy. The Myriad appear to be more wide spread.

4. Are these tests worth anything? Furthermore, groups are offering tests to assess risks based upon genetic profiles. As stated[3][3]:

Myriad also rolled out new tests. In September, the company launched its myRisk Hereditary Cancer™ test, a 25-gene panel covering eight major cancers (breast, colorectal, endometrial, gastric, melanoma, ovarian, pancreatic, and prostate) at an average selling price of $3,700. In

[3][3] http://www.genengnews.com/insight-and-intelligence/the-10-biggest-events-of-2013/77899986/

October the company introduced myPlan Lung Cancer, which carries a $3,400 list price; followed in November by myPath Melanoma, which has an average selling price of $1,500. By 2015, Myriad has said, it expects to discontinue several current tests, including the BRACAnalysis test at the center of the Supreme Court case.

Just because some genetic profile may have some correlative relationship the genetic profile is not causative. Tests like these can be costly and of yet to be fully justified clinical value. Take a melanoma, if one has a suspect pigmented lesion then a simple excision and competent path study should suffice. That is an order of magnitude less than the genetic profile. In fact if one were to do a profile it should be of the melanocytes and not of the cells in general.

References

Knezvic, D., et al, Analytical validation of the Oncotype DX prostate cancer assay – a clinical RT-CR assay optimized for prostate needle biopsies, BMC Genomics 2013, 14:690.

http://www.telmarc.com/Documents/White%20Papers/98%20CCP.pdf

Labels: Cancer

SUNDAY, DECEMBER 22, 2013

AND THEY WANT TO CONTROL HEALTH CARE!

I ordered a package of no great note a few weeks ago and I thought I would let you know how our US Postal Service has thus far handled it.

It was to go here in New Jersey. It went on to Maryland and now in North Carolina. You really cannot make this up. Imagine if it were your gall bladder, you would have had a lobotomy by now! This was to be an expedited delivery.

How it is getting passed around only befuddles me but they are Government workers after all.

20 Dec 2013 21:00	Package processed by local post office	GREENSBORO, NC
19 Dec 2013 11:03	Package processed by local post office	CAPITOL HEIGHTS, MD
18 Dec 2013 13:09	Shipment Info Received by Post Office	WHIPPANY, NJ

Date	Description	Location
Dec 18 2013	Package transferred to Post Office	DV DANIELS, NJ
Dec 18 2013	Ready for post office entry	Logan Township, NJ
Dec 18 2013	Package received by dest MI facility	Logan Township, NJ

Dec 17 2013	Package transferred to dest MI facility	Bensenville, IL
Dec 17 2013	Package processed by Mail Innovations	Bensenville, IL
Dec 16 2013	Package received for processing	Bensenville, IL

Labels: Government

FRIDAY, DECEMBER 20, 2013

HAPPY 5TH BIRTHDAY

It has been five years since I began this Blog. After some 1.25 million words on various topics I look back and see what I intended and what I did.

The main reason why in late 2008 I decided to write this Blog was that it was clear that with the incoming Administration that there would be upheavals of the type we had not seen in this Country for quite a while. I also was reading what others were saying, especially economists, and saw that they were clueless. Thus an intent to examine issues and present an alternative view.

I have had over 100,000 visitors from almost 150 countries and 45% are from outside the US. My focus was a bit idiosyncratic, covering topics from one area to another but with a nexus on how they would reflect on our lives here in the US. Let me proceed through how we got to where we are now:

1. Macroeconomics: For any somewhat familiar with this Blog you can sense that I have a low opinion of macroeconomists. They are a snarky crowd who believe individually they are correct but when one compares any random selection there is never any agreement. I know no other collection of humans who have such a high self esteem but hold their peers in such opprobrium. My first cut was the analysis of the Romer curves. Here is a case of a Head of the CEA who said what unemployment would be with the dispersal of $1Trillion and then as her predictions never even came close would only appear to dig her heels in ever so deeper.

2. Health Care: I was opposed to Government Health Care as started by Hillary and even more so by the current crowd, even more so. I went line by line over the Bills as they progressed and indicated what we are now seeing. No surprise, it is a true disaster and will get even worse. Ironically we had the same cast of characters. Macroeconomists. My result was a Draft Book on Health Care economics and Policy. I focused on one area initially, Obesity and Type 2 Diabetes and wrote a Draft Book there also. There has been over 100,000 downloads of that Book! Amazing. I developed an alternative Health Care Plan with numbers. I believe in universal Health Care but provided in the free market, and requiring only catastrophic coverage. I do not want some woman telling me what to do with my prostate. Especially some Government employee, one who know nothing.

3. Genomics: As an offshoot of the Health Care debate it became clear that reducing costs through the obesity path was important and also that genomics in cancer was to have a major impact. I then returned to Medicine in detail and examined and tracked genomics and cancer. From this cam my Draft Books on Melanoma and Prostate Cancer. I find the development here amazing and attempt to analyze them as they are produced. I have also tried to develop a broader

system theory of cancer focusing on specific malignancies.

4. Political Philosophy: What was also clear as I followed the political debate was that an understanding of a Political Philosophy for our age was missing. Progressives had reared their ugly heads again saying that the Government, whoever that may be, would always know better and could take care of us since we cannot. Nonsense. Thus I examined Individualism and write a Draft Book on Progressivism and Individualism. My understanding of Individualism is not that of ignoring others but of respecting the person. I continue this effort.

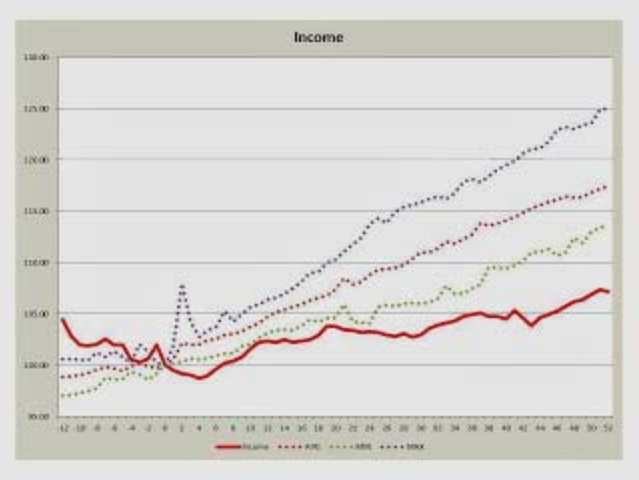
These have been the major threads I have examined over the past five years. I anticipate continuing the process and look forward to where this may take us. The next three years will be a continuing challenge. My initial concerns have proven correct. My concerns for the next three years are just more of the same, but I suspect an ever so more a stumbling effort.

To those who have read this, I hope I have provided a modicum of insight. I have tried not to be too critical but when needed I am. Many thanks and let us see what happens next.
Labels: Commentary

WEDNESDAY, DECEMBER 18, 2013

UPDATED RECESSION STATS 2013

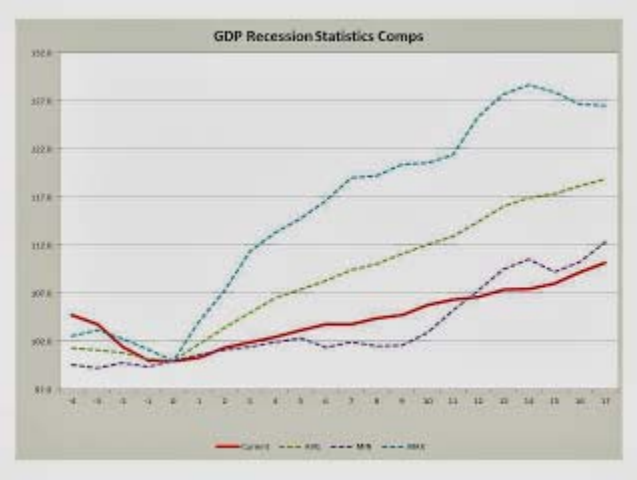
From time to time we review the Recession Stats from the St Louis FED. Today seemed like a good day give what the FOMC decided. The first above is Industrial Production. Now this does not appear that bad. Not great but not bad. We are producing at about normal for this time in a recovery. But remember this is 52 Quarters, 156 Months after the nadir!



The above is Personal Income growth. This is the worst recovery ever for this factor. Personal Income, other than for Bankers and Sports Folks, is horrible. That is the engine for any growth and we see none. How do we reconcile that with employment? We don't since the employment numbers are all rigged as we have been showing for five years.

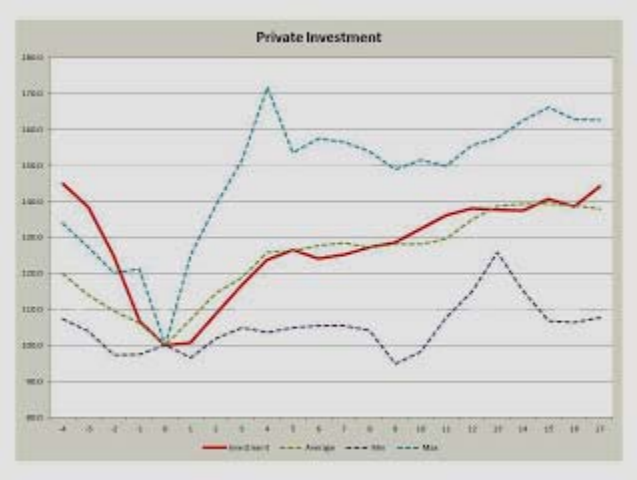
The above is Employment. It also is at the bottom or nearly so. The Employment numbers are deplorable and will not change much in the months to come.

Yet for some reason Retail Sales has remained on a norm. It in fact is getting a bit above average. If unemployment is high and salaries are low then what one wonders is driving this?

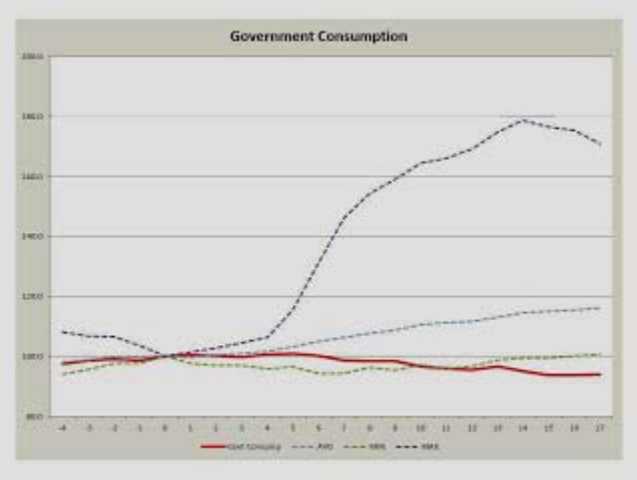


The GDP growth is above. It is below the lowest for any prior Recession and is getting worse. It is clear that we are no where out of any Recession, not with this number.

Personal Consumption as an element of GDP is low and a drag. In fact this almost single-handedly is holding it back.

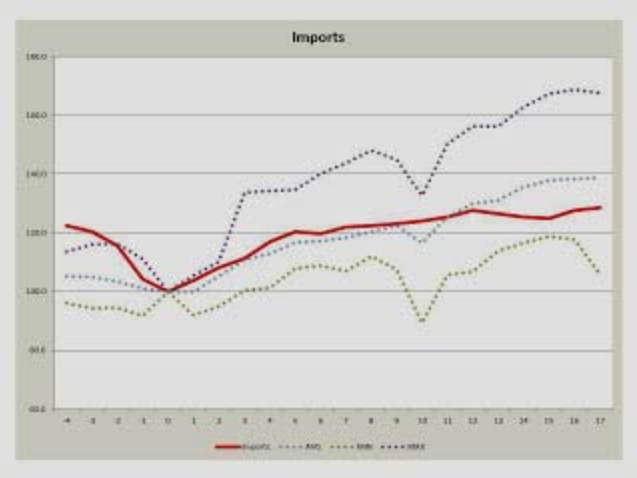


Private Investment returned quickly and has regained an average level. Thus people with money are doing well but people with jobs are sinking slowly.



Government Consumption has been level and is not a driver for any growth despite all the concerns. In fact the Stimulus was just wasted money incompetently allocated, so what else is new.

The following are Exports and Imports.



Nothing really new here although we seem to have a beneficial run up on Exports.

In summary this is the weakest recovery ever.
Labels: Economy

SATURDAY, DECEMBER 14, 2013

MORE THOUGHTS ON MOOCS

One should never dismiss a bad idea. It may eventually get fixed. MOOCs are an example. When I first explored this a year or so ago, when EdX started, it was less than a band leader. The software just did not work and the materials at lecture were, well just pompous. Having finished Lander's Biology at EdX I found it had many moments of excellence. After all it is Lander and he is both smart and a great showman. The weakness was less in the software than the English.

I had gone through this before when I was an Instructor. Back in the late 60s I sent a class home; it was Random Process Theory, 6.573, at Christmas with a Take Home Quiz. But I made a mistake, or it may have been our secretary but I take the blame. I asked the class to prove an inequality and I put the inequality backwards. Thus it was impossible to prove it. Now all, but one student, proved the wrong inequality. One guy, I forget who, caught my mistake and proved it the right way! I often wonder where he went. His approach was that there was a right answer and he found it and the other class members were just silly for not getting the right answer.

But the lesson was plain. Never send a class out with not lifeline and an exam with possible errors. I apologized but I found out how many hours people spent trying to solve the unsolvable. No one ever questioned that I may have been wrong.

The second lesson is to try to understand how others will read your question. Wording counts. In some of the 7.00X questions one wondered just what they were asking. In addition it often took longer to read the question then to answer it. Why? I suspect it was the attempt to set the question up to be answered using the computer interface. The technique has yet to be mastered. I can write questions that require a written answer. I would find it more challenging to get the student to answer a computer solved question. Ambiguity reigns. In addition by trying to be a bit tricky in answers to challenge the student one further increases the ambiguity level.

The third observation is that one should not try to answer the questions the way I may have done so say 60 years ago. Namely do not try to be fast and try to get close; there is no close in computer graded answers. The grader has no sense that you got it but just left out a hyphen. After all why put those hyphens in anyhow. But alas, read the directions. Last time they did not want hyphens and this time they do. They are not testing course materials but reading skills. That to me is one of the problems with the MOOCs and computer grading.

The other observation I made was that in the Discussion sections the students seem to have that computer age chatter urge. Nothing is thought out just typed in half-baked and expecting responses. They are never disappointed; there are always others who will respond. The net result, however, is that the Discussions are useless.

Finally, Lander was truly professional for where the state of the art is today, but in another Harvard Med course they had the wrong answers and then tried to patch it up. Prior planning prevents poor performance. This is the risk of MOOCs; it is like my old MIT days, but multiplies it by thousands. You have to be not only clear but correct. There is little room for corrections.

Thus after almost two years looking at these are they getting better? Yes, some more than others. But I still believe that have a way to go.

In a recent NY Times piece the write points out[4[1]]:

And perhaps the most publicized MOOC experiment, at San Jose State University, has turned into a flop. It was a partnership announced with great fanfare at a January news conference featuring Gov. Jerry Brown of California, a strong backer of online education. San Jose State and Udacity, a Silicon Valley company co-founded by a Stanford artificial-intelligence professor, ..., would work together to offer three low-cost online introductory courses for college credit.

Mr. ..., who had been unhappy with the low completion rates in free MOOCs, hoped to increase them by hiring online mentors to help students stick with the classes. And the university, in the heart of Silicon Valley, hoped to show its leadership in online learning, and to reach more students.

But the pilot classes, of about 100 people each, failed. Despite access to the Udacity mentors, the online students last spring — including many from a charter high school in Oakland — did

[4[1]] http://www.nytimes.com/2013/12/11/us/after-setbacks-online-courses-are-rethought.html

worse than those who took the classes on campus. In the algebra class, fewer than a quarter of the students — and only 12 percent of the high school students — earned a passing grade.

One may ask why? I think that the explosion of courses has been useful but the platforms need fine tuning, and in some case a total overhaul. The Lander 7.00X course is a brilliant example of how to get there. The lectures are classic MIT. The Problem Sets are also classic. You learn more from the sets than from the lectures, but that in no way demeans the lectures. The Exams are a bit different and the problem again was classic MIT. Problem sets are NOT Exams, so be careful. But like the old days, there is always a Hidden Curriculum in MIT classes and once you discover it is all downhill from there. The key is finding the Hidden Curriculum, the way the Prof thinks and what he wants.

I would not like to see this abandoned, just the expectations balanced. There could be an asset here, just not a goldmine yet.

Labels: Academy

SATURDAY, DECEMBER 7, 2013

REMEMBERING PEARL HARBOR

Some 72 years ago today the Japanese attacked Peal Harbor. The above was take on the USS Albert W Grant (DD-649) in 1945 when it came to Japan after its travails during the long war. It is always good to remember the good and bad. Many thanks to the men and women who saved the day then.
Labels: Commentary

MONDAY, DECEMBER 2, 2013

CHOPPED LIVER?

Stanford Researchers have completed a Study which shows that technical people are just adept if not more so in start ups. The summary is:

New research on entrepreneurship shows that diverse business skills are not always the secret to success in the world of tech start-ups. While different strengths matter sometimes, researchers found that a tech-focused founding team is almost always best. ...

The research revealed that a technically focused team can more quickly reach market milestones, from design and prototype completion – all the way to product launch. On the other hand, more diverse founding teams are better prepared to compete against mature companies, which similarly have well-established diverse skills in areas like marketing, operations, sales, engineering and other skills.

It is good that this is now known to the Business School Academics. After all, if one looks outside the Stanford Campus there lies Silicon Valley.

But wait, my sarcasm may be not on point. Again I am reminded of my students a few years ago remarking after a dinner with a MIT PhD CEO that they did not know that a MIT PhD could start and run his own company. They believed they needed to get a Harvard Law or Business person. My response was, "What do I look like, chopped liver?"

That also may have been a bit much, since I have no idea how that transliterates to Mandarin. Now the issue of competing against large mature companies may also be best done by technical entrepreneurs. Evidence also demonstrates this as well. The Business types will develop strategies whereas the Technical types will just attack at the weakest points.

The problem is that all too often the Technical types get too entrenched and secure and/or the Business types take over. The classic example of both happening was DEC. A great company but it just grew mold.
Labels: Commentary

MONDAY, DECEMBER 2, 2013

SCIENCE: PRINCIPLES OR COOK BOOK?

There is a recent paper by Prof. Dougherty from Texas A&M which bemoans the state of some parts of science in the current environment[5][1]. As Dougherty so clearly states:

[5][1] http://bsb.eurasipjournals.com/content/2013/1/15

...science concerns relations between measurable variables and it is these relations that constitute the subject matter of science, scientific knowledge ipso facto is mathematically constituted…

Let me give a couple of examples of how this applies.

First, let us look at the world of genomics which I have been discussing herein for a while. The introduction of the microarray has allowed an explosion of data that has then allowed scientists to putatively argue some relationship between genes and cancers. Namely they go about examining say 9,000 prostate cancer patients and using microarrays primed for say 500 genes they conclude that say some 50 of these gene are seen in prostate cancer. They then allege that there is some actionable clinical relationship between the presence of the gene and the cancer. There is no underlying system model identifying this, just a microarray demonstrating that "oftentimes" these genes are under or over expressed.

Second, let us look at the BRAF V600 melanoma cases. Here unlike the above we have a case where one knows the RAF pathway and that loss of control of certain elements of that pathway lead to gene instabilities and thus a malignant expression. Therefore one targets the mutated RAF gene, the BRAF V600, and it results in a suppression of the malignancy, for a while. Then we had squamous cell carcinomas, but since the full pathway was known, go down one step and there was MEK and controlling it controlled the sequella. In this case there was a model, a system, and by logically following the system one found what the next step should be.

The above are two examples of how "science" is being done today in the area of gene related results. The second example is a Dougherty like science, namely it connects data to an underlying model which is predictable, and by using that the cancer is controllable, at least until another instability results. The first model, data collecting, is not really science as we accept it today. It is more akin to 19th century Botany, at best, where one goes out and collects specimens of plants and then tries to sew together a quilt of understanding to explain nature.

What Dougherty is focusing on is the Why question. When I recall Medical School, one is taught What and How. What disease is it and How do I treat it. In contrast Engineering is first Why and then How. There is a strong dissonance when an Engineer is studying Medicine. At least forty years ago. An Engineer all too often keeps asking Why, what is the underlying set of basic scientific principles that explain the phenomenon and how can I express them in a manner in which they can be used on a predictable basis. Why would drive many a Medical Professor to apoplexy. Medicine was for a long while the transfer down of "facts" and not validatable principles. The old adage at graduation that fifty percent of what one had just learned in Medical School was now invalid was a bit of a joke but sadly it was also true.

But as we move to Genomics we sadly see this trait arise again. There is a tension between those who want to have basic repeatable principles to build upon and those who believe that collecting data is the sine qua non. Let me give an example of a recent experience. Prof Lander at MIT is teaching an EdX course on Biology. Now Lander is brilliant and his style of teaching is in many ways classic MIT. Namely he highlights the basic principles, and then the student works through the Problem Sets developing the details for themselves. So far so good. His first two three

fourths of the course was fantastic. Then I noticed a subtle change, a change that, unless you were prepared to recognize would have slipped through the cracks. He slowly started giving a mixture or core predictable principles and cook book recipes. For example, we know that we can denature DNA because the base pair bonds are Hydrogen bonds, relatively weak, and the backbone Phosphate bonds are strong because they are ionic. Thus by heating the molecule we break the Hydrogen bonds first and then before we break the ionic bonds we can do our complementary additions, thus PCR works well.

On the other hand as he progressed to a discussion of Knock Out genes there were a collection of "tricks" or cook book recipes that were used. Why, for example did one get the modified DNA into the denatured gene the way he said? Well it just happens. Well nothing just happens. Fortunately bench Biologists have developed many "tricks", like alchemists, and as a result they have become a bit too comfortable with this unexplained bevy of tools, albeit indispensable, but in the long run self-defeating.

As Dougherty states when he examines data mining as an example of the Biologist's flair for data at all costs:

Data mining and Copernicus share a lack of experimental design; however, in contradistinction to data mining, Copernicus thought about unplanned data and changed the world, the key word being 'thought.' Copernicus was not an algorithm numerically crunching data until some stopping point, very often with no adequate theory of convergence or accuracy. Copernicus had a mind and ideas. William Barrett writes, 'The absence of an intelligent idea in the grasp of a problem cannot be redeemed by the elaborateness of the machinery one subsequently employs'. Or as M. L. Bittner and I have asked, 'Does anyone really believe that data mining could produce the general theory of relativity'? Data mining represents a regression from the achievements of three and a half centuries of epistemological progress to a radical empiricism, in regard to which Reichenbach writes, 'A mere report of relations observed in the past cannot be called knowledge. If knowledge is to reveal objective relations of physical objects, it must include reliable predictions. A radical empiricism, therefore, denies the possibility of knowledge'. A collection of measurements together with statements about the measurements is not scientific knowledge, unless those statements are tied to verifiable predictions concerning the phenomena to which the measurements pertain.

What is Dougherty getting at? Simply, to reiterate the first quote: Science demands a marriage between data and models, to be true science it must be predictable and predictable based upon an embodiment in an abstraction.

Let me now apply this to genomics. Consider prostate cancer. The question is complex but can be asked; what is the first set of steps that lead to prostate cancer? Let us examine what we know:

First, we know many of the pathways. We know that the AKT pathway is critical, we know that c-MYC is a critical control element, we know that PTEN is often mutated, and we know that AR (Androgen Receptors) ultimately get mutated and we have metastatic growth. We pathways, we have relationships; we can demonstrate causality and results. Thus a modicum of a basis in

reality exists. If one would use this pathway model and then search using microarrays matched against the model one arguable could iterate to improved models and improved predictability. The data without the model is useless and the model without the data is unverifiable.

Second, we can ask what sets the process off. Are all the changes due to mutations or more likely due to epigenetic insults? Thus when we look at MDS for example, we are looking at a hypermethylated set of blood stem cells. Something hypermethylated them and we know that since they are hypermethylated that the gene expression is repressed and thus cell proliferation of immature cells is a result. In prostate cancer, is the control mechanism lost because of a mutation, methylation, both, and in what order? Having a model allows one to validate and then iterate along a consistent trajectory of reality.

What does Dougherty have to say here?

While ignorance of basic scientific method is a serious problem, it is necessary to probe further than simply methodological ignorance to get at the full depth of the educational problem. Science does not stand alone, disjoint from the rest of culture. Science takes place within the general human intellectual condition. Biology cannot be divorced from physics, nor can either be divorced from mathematics and philosophy. One's total intellectual repertoire affects the direction of inquiry: the richer one's knowledge, the more questions that can be asked. Schrodinger comments, 'A selection has been made on which the present structure of science is built. That selection must have been influenced by circumstances that are other than purely scientific'

The point I believe he is making is that in the new world of Genomics, it is necessary to have a foundation that exceeds just the Laboratory and its tricks. One must understand that no matter what we think that every time we look at a cell, at an organism, we are looking at a system, at some stochastic dynamical process wherein things move forward, albeit randomly, but in a way controlled by principles. We must look at the world wherein data is used not as an end in itself but as an iterative process with our mathematical world view. Thus the tools needed to view this world are extensive yet available. Engineers are trained to use them daily. Perhaps Genomics will grow to appreciate their essential import.

Labels: Genetics

SO WHAT'S NEW?

In a recent piece in the NY Times by some Professor at some Midwest school he bemoans the state of Liberal Arts education.

Let us jump to his logic. He bemoans the fact that those who major in Liberal Arts, and he means it in the most narrow sense, earn less. He states:

Is the crisis rather one of harsh economic reality? Humanities majors on average start earning

$31,000 per year and move to an average of $50,000 in their middle years. (The figures for writers and performing artists are much lower.) By contrast, business majors start with salaries 26 percent higher than humanities majors and move to salaries 51 percent higher.

But this data does not show that business majors earn more because they majored in business. Business majors may well be more interested in earning money and so accept jobs that pay well even if they are not otherwise fulfilling, whereas people interested in the humanities and the arts may be willing to take more fulfilling but lower-paying jobs.

First, young people should go to college and find a major that will get them a job, unless they are already independently wealthy. If you end up $200,000 in debt you owe it to those of us funding the debt to get to some point at which you can pay it back. If you want to be a performance artist what good is college, go out on the street and perform. So you do not get paid, what is new?

Second, the Liberal Arts has substantial value. As an undergraduate I minored in Philosophy. Why, because it was interesting, a challenge, and it was fulfilling. Yet I knew that I could not get a job with that alone. Thus engineering, and a job. Yet engineering is also fulfilling, it is a profession, and has legs that last a lifetime as well, and it teaches a mental discipline that is essential in today's world.

Third, Liberal Arts is like a fine quality desert. It is wonderful, but you cannot live on deserts alone. One needs the protein of a sustainable diet. Thus balance in all things. Also one should not demand, expect, but be realistic.

Then the author really goes off the track. He states:

We could open up a large number of fulfilling jobs for humanists if we developed an elite, professional faculty in our K-12 schools. Provide good salaries and good working conditions, and many humanists would find teaching immensely rewarding. Meeting the needs of this part of the cultural middle class could, in fact, be the key to saving our schools. ...

Fair treatment for writers and artists is an even more difficult matter, which will ultimately require a major change in how we think about support for the arts. Fortunately, however, we already have an excellent model, in our support of athletics. Despite our general preference for capitalism, our support for sports is essentially socialist, with local and state governments providing enormous support for professional teams. To cite just one striking example, the Minnesota State Legislature recently appropriated over $500 million to help build the Vikings a new stadium. At the same time, the Minnesota Orchestra is close to financial disaster because it can't erase a $6 million deficit. If the Legislature had diverted only 10 percent of its support for football, it would have covered that deficit for the next eight years.

That's right, do not allow scientists or engineers to teach K-12, allow performance artists. That should really improve our scores on the world stage. Secondly, I have to admit I have never seen a football game, but my daughter went to WVU, but football pays, millions watch it, and also football and other sports have figured out how to get me to pay whether I watch it or not. They

have made me pay on my cable channels! Never watch it but ESPN gets a $10 a month fee from me. Thanks Washington! Let's try to get the Philosophy Departments to see if they can do this.

When I see articles like this I often wonder what world the author is living in. Students go to college to get a job. Later on in life one can expand themselves, based upon a lifetime of experience.

Then there is the arrogance of demanding special treatment. As if these folks are something special. They are not. Ultimately all decisions are economic decisions, and yes with a moral undertone. If one decides to be a Classical French Major then one is making the decision to either attempt to to be the best in the world and get one of those three to five job slots, like the best violin player at some major world class orchestra. There just are not that many slots. Nor I gather are there that many slots for Quarterbacks in the NFL.
Labels: Academy, Commentary

SUNDAY, DECEMBER 1, 2013

CHINA IS GOING TO THE MOON

China Daily announced the launch of the first moon rover on its way.

As they state:

Chang'e-3 is expected to land on the moon in mid-December to become China's first spacecraft to soft land on the surface of an extraterrestrial body.

It is also the first moon lander launched in the 21st century.

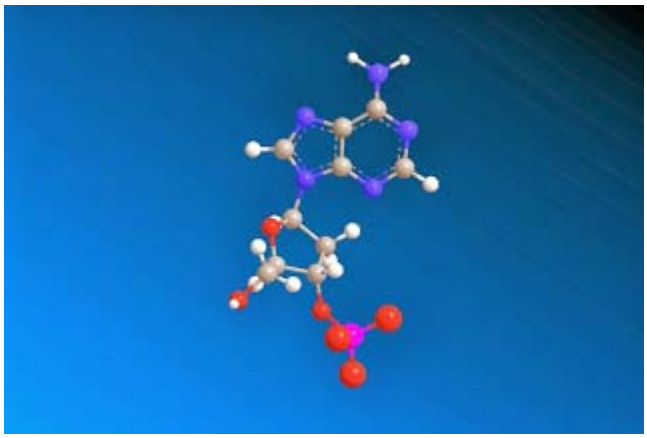
The probe entered the earth-moon transfer orbit as scheduled, with a perigee of 200 kilometers and apogee of 380,000 kilometers.

"The probe has already entered the designated orbit," said Zhang Zhenzhong, director of the launch center in Xichang. "I now announce the launch was successful."

This may very well be the first of many such steps. This is worth following as well.
Labels: China

SATURDAY, NOVEMBER 30, 2013

GREAT GENOMICS BOOK



The book by Dale, Von Schantz and Platt, From Genes to Genomes, is almost perfect. It is a 350 or so page exceptionally well written book describing all the introductory materials one would need to become current with genomes and genomics efforts. As with many of the other books I had around I first looked at this and at a glance set it aside. Then came the moment when I wanted to re-understand something and I opened this book up and I was hooked. It in a clean and clear manner takes the reader from basic DNA principles and through all of the key techniques used in genomic studies today. It avoids getting to complex into any one area and it reads in a straightforward and consistent manner. It is a superb asset for "catching up" and I suspect for first learning the materials.

Chapter 1 is the basic introduction to genes and genomes. It is DNA 101 but it contains little tidbits of essential materials that are all well integrated. One thus starts with a clear understanding where the authors are taking the reader.

Chapter 2 is the material on basic gene cloning. It uses the plasmid approach with bacteriophage and does so without burdening the reader with too much overhead and history. This Chapter discusses technique and technology and the reader is given a logical approach to the basics of cloning. Restriction enzymes are introduced and the material is adequate to have enough depth to see how they can be applied. There are, of course, a lot of implementation questions that are left hanging but that is typical of this study. There is a section on ligation and I would like to have seen this carried over a bit when discussing gene knock-outs. We can understand how the genes ligate but the question is how well does this carry-over the later processes.

Chapter 3 discusses DNA libraries. This is a wonderful summary of the concept. The graphics supplement the text without over powering it. One example of what I call the cook book facts is demonstrated in p 95 when discussing hybridization. Here is the curve showing how as temperature increases the DNA starts to break apart. This is the denaturing of DNA, a concept again used with the PCR analysis. This is less a theoretical or structure issue but one of those cook-book facts that have been added to the tool chest of the Genome builder.

Chapter 4 is the PCR process. Simply it is the separating of DNA, then tagging one end and the other end and going through a temperature sensitive denaturing and rebuilding until what is left is millions of copies of a desired DNA segment. My only complaint here is that the graphic, good, albeit it could be made a bit better with color.

Chapter 5 discusses sequencing and it gives a superb discussion of the Sanger approach. Namely ddNTPs are used with segments and then measured in a gel electrophoresis. I assume that the reader may have had some understanding of the physical details but overall it is clear and exceptionally useful.

The text continues developing other elements used in current day genomics. Chapter 9 is an attempt to provide an overview of microarrays, SNP, and even GWAS and phylogenetics. My problem here is that they are trying to stretch it a bit too far. These are reasonable summaries but to do microarrays justice it may take a bit more detail, and yes color, and the phylogenetics is much too much just a high level summary.

Finally the Glossary is fantastic and worth every page.

The strengths and weakness of the book are simple. On the strength side it covers all the key issues superbly. On the negative side, and this may be perhaps me, I find that almost like Organic Chemistry, in Gene manipulation there still are many cookbook rules that are scattered between the facts and logical constructs. If somehow there could be a clarification of the cook book rule and the well understood logical steps that would be a help.

Overall I would highly recommend this book for almost anyone, from beginner to professional. My focus is clinical and theoretical modelling and analysis, and I have avoided bench work as much as possible. But by reading this book I can see again how much work has been done over the past few decades.
Labels: Books, Genetics

SOCRATES MAY HELP ON THIS ONE

As a youth I studied in the Seminary in anticipation of becoming a Franciscan. I had yet to read Ockham nor did I yet have any appreciation for Aquinas, the Dominican. However my French Christian Brother Teachers would soon let me understand that of all the religious orders that one must always beware of, beware the Jesuits. As I later found out, many Jesuit educated students

ended up in the CIA, and one student became President, yes Clinton. John Paul II almost went as far as disbanding the Jesuits as a result of their extreme positions.

In my opinion, the self-assured arrogance of many of these Jesuits has brought forth new forms of "theology"; the kinds of theology we saw foment various revolutions in Latin America[6][1]. The Jesuits are in my opinion sophists of the first degree, capable of turning a phrase to benefit whatever argument they desire to hold forth.

Thus when we saw the first Jesuit Pope it was no surprise that this may be a bumpy ride, in fact it would make our own current president appear reactionary. Before commenting on the recent note by the current Bishop of Rome let me establish some basic facts.

Catholicism was initially, and had remained for many of the early centuries, a religion based upon the individual. The individual was judged based on what the individual did, not what the group did. Thus the whole concept of Distributed Justice, and here it is worth reading John Ryan, a Catholic Priest in the 19th Century, or as we now seems to call it Social Justice, was a reconstruction of post Constantinian Roman Justice. Namely it was the obligations of a group, and especially a group controlled by the local bishop.

The best example would be to examine Augustine, Bishop of Hippo, who controlled his throng, and their money, through what he knew as the basic principles of Roman law. Gregory I, the Bishop of Rome in the early 7th Century, was before becoming bishop basically the "Mayor" and "Proprietor" of the Roman properties, handed over to the Church, including the very City of Rome. The Church used the denigration of individual wealth as a means of control, a tactic consistent with classic Roman precepts. Furthermore, the post-Constantinian Church used these principles to centralize the "redistribution" into the hands of the local bishops. This allowed the bishop to take the wealth of the few and "redistribute" it in whatever manner they saw fit. It in effect eliminated individual responsibility.

Christianity was primarily seen in the early Church as duties ascribed to individuals and between individuals. What a person did or did not do was the basis for their redemption. Sacraments were not group exercises, but they were a relationship of the individual with God.The Ten Commandments were individual commandments. The Beatitudes were individual dicta, not what the group should do but what the individual should do. Salvation is not attained via the group, but by singular individual actions. Thus the view that groups, read that Governments, have duties to redistribute wealth, is fundamentally against the principals first ordained.

Charity is not the taking of funds from those who have and then get redistributing the wealth by third parties. Charity is the giving by an individual to others who are in need, and moreover, the helping of those individuals to help themselves and thus in turn to help others. True Charity is

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6[1] See G. Gutierrez, A Theology of Liberation, Orbis (Maryknoll, NY) 1988. This is one of the classic works which John Paul II was so concerned about regarding Liberation Theology, fundamentally a philosophy of Distributed Justice amongst the indigents in South America.

helping others succeed as we ourselves may have been fortunate enough to do so. It is an individual and personal obligation. Charity is a bilateral obligation. The giver assist the impoverished, yet the impoverished has a duty to make good, nor just make do, with the gift transferred, thus creating another link in the human chain.

The distortion of this into some third party collective was a Roman artifact, and was not part of the origins of Christianity. Peter Brown has examined and analyzed these transitions from individual to group in Christianity as Christianity was Romanized[7][2].

Let us consider one other quote[8][3] by Woodrow Wilson in 1912 before moving on to the Bishop:

We have come upon a very different age from any that preceded us. We have come upon an age when we do not do business in the way i n which we used to do business, when we do not carry on any of the operations of manufacture, sale, transportation, or communication as men used to carry them on. There is a sense in which in our day the individual has been submerged. In most parts of the country men work, not for themselves, not as partners in the old way in which they used to work, but generally as employees,-in a higher or lower grade, of great corporations .

There was a time when corporations played a very minor part in our business affairs, but now they play the chief part, and most men are the servants of the corporations . . . .

Yesterday, and ever since history began, men were related to one another as individuals . . . .

To-day, the everyday relationships of men are largely with great impersonal concerns, with organizations, not with other individual men. Now this is nothing short of a new social age, a new era of human relationships, a new stage-setting for the drama of life.

Now here Wilson is praising the individual and denigrating the corporation. Wilson is almost Jeffersonian in his seeking the old ways and seeing in the new some end point of a fatal state controlled by corporations. Yet it was Wilson who did the most to encumber the individual. Income Tax, the Draft, the War, the oppression of women, again he jailed my grandmother who sought a vote, and Wilson's other Progressive programs of institutionalization and rejection of fundamental individualism.

In reality this period opened up opportunity for all. The Carnegies, Rockefellers, and others, albeit controlling mass wealth for the time, themselves came from little and each in turn demonstrated that it could be done and that in doing so each gave back many fold. Every time I look across from the entrance of Sloan Kettering to Rockefeller I see that long line of giving, individual giving. These people came from nothing. They were not from aristocratic families as

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[7][2] See Peter Brown, Through the Eye of a Needle: Wealth, the Fall of Rome, and the Making of Christianity in the West, 350-550 AD, Princeton University Press, 2012.

[8][3] See Diner, S., A Very Different Age, Americans of the Progressive Era, Hill and Wang (New York) 1998. The Preface.

was the case in Europe. They demonstrated the ability of the individual to prosper. They were examples for entrepreneurs for decades to come.

The last half of the twentieth century was also a time of individual success and in turn individual giving. The Cornell Weill hospital is the benefactor of not just the named man but of many others, the NYU Langone is also the same donation of an individual. The research conducted in the centers with names on them, and those who were anonymous, are a true sign of that individualism of the entrepreneur. Wilson used the corporations as a means to seek political support and failed to understand the full temporal and social benefits. The U.S., unlike Britain where an aristocracy and Class Society exists, has no class. Anyone may have the chance at the gold ring, and those who get it all too often return it in kind, several fold.

Now let us examine but one paragraph in this recent letter from the current Bishop of Rome. In EVANGELII GAUDIUM the Bishop of Rome states[9][4]:

54. In this context, some people continue to defend trickle-down theories which assume that economic growth, encouraged by a free market, will inevitably succeed in bringing about greater justice and inclusiveness in the world.

This opinion, which has never been confirmed by the facts, expresses a crude and naïve trust in the goodness of those wielding economic power and in the sacralized workings of the prevailing economic system.

Meanwhile, the excluded are still waiting. To sustain a lifestyle which excludes others, or to sustain enthusiasm for that selfish ideal, a globalization of indifference has developed. Almost without being aware of it, we end up being incapable of feeling compassion at the outcry of the poor, weeping for other people's pain, and feeling a need to help them, as though all this were someone else's responsibility and not our own.

The culture of prosperity deadens us; we are thrilled if the market offers us something new to purchase. In the meantime all those lives stunted for lack of opportunity seem a mere spectacle; they fail to move us.

First, as many have already recognized the pejorative of "trickle down" is just that, a wonderful proof of the sophist at work. Only those opposed to free markets and capitalism would use the term. Thus, unlike the many Sophists battled by Socrates, such as in Gorgias and Protagoras, this Sophist comes, from the beginning of his argument, to establish his bona fides.

As Mankiw writes on this as well[10][5]:

[9][4] http://www.vatican.va/holy_father/francesco/apost_exhortations/documents/papa-francesco_esortazione-ap_20131124_evangelii-gaudium_en.pdf

[10][5] http://gregmankiw.blogspot.com/2013/11/the-popes-rhetoric.html

First, throughout history, free-market capitalism has been a great driver of economic growth, and as my colleague Ben Friedman has written, economic growth has been a great driver of a more moral society.

Second, "trickle-down" is not a theory but a pejorative used by those on the left to describe a viewpoint they oppose. It is equivalent to those on the right referring to the "soak-the-rich" theories of the left. It is sad to see the pope using a pejorative, rather than encouraging an open-minded discussion of opposing perspectives.

Mankiw is quite observant of the facts. Mankiw understand market capitalism, has examined it in detail, and he has personally participated in the process. Indeed Mankiw is correct in saying that the use of the term is a pejorative, meant as such or not, it reflects a mindset.

But let us examine this paragraph from the current bishop.

1. His criticism of "trickle down" is not based upon any fact or metric but upon some concept, not defined, of justice. This is the classic redistributionist's Distributive Justice model having evolved from the 19th century.

2. There is no assumption about the goodness of those wielding power. There is in Christian dogma the burden placed upon the individual, not the Government, to recognize and need and help remedy it. That means teaching someone how to earn a living, not just feeding them, by being an example for those who need guidance, not just once but for a life time, by seeing a need for money, if that is the case, and helping provide it and the other non-monetary needs as may be required. If one has and denies and denigrates those who are less advantaged, or worse oppresses them, then that is an individual sin. There is no real community sin; it is only an agglomeration of individual errors. Here the Bishop errs.

3. We do not see the cries of the sick, dying and oppressed? The Beatitudes were individual directives, they said we are to visit the sick, help them. If a person is ill, without support, then it is our individual responsibility to "nurse" them, to go out of our way to visit them and bring them from the brink. It is not, from a Christian perspective, for us to be taxed and then the Government hands out money in our stead. Again the Bishop errs.

4. Finally what drives humankind in many cases is the movement forward of civilization, of humanity. Those who work in cancer therapy may have some ego involvement, may be compensated, but in many of not almost all cases they are individual commitments to make mankind better. When one walks down York Avenue in New York one sees what many wealth have contributed to help others, not only short term help caring for the sick, but in establishing long term efforts to relieve the disease that plague mankind. In fact the statement the Bishop makes, "*we are thrilled if the market offers us something new to purchase. In the meantime all those lives stunted for lack of opportunity seem a mere spectacle",* reflects a total lack of knowledge what a few wealth individuals have done for millions. Even more so, there are thousands more who have financially given, individually and of their total free will, to that which those with a great deal more have set a foundation for. The Bishop not only errs, but he seems to

either be deliberately ignorant of this process or totally denies individual duties as the sole path of rectification.

Individualism is not a concept of individual isolationism. It is a principle of individual responsibility and duty, of the belief that all individuals are equal, have equal opportunities, and that given that opportunity that they can achieve whatever they can perforce of their individual efforts. There is no requirement for redistribution; there is in fact a denial of any Distributive Justice, if each individual has unfettered opportunity and balance.

One must attempt to deconstruct what the Bishop is saying, since he now is saying it for the world, not for those in Argentina.

Perhaps we need to have a Columbanus, an Irish monk who argued continuously with Gregory I over issue after issue. The Irish never had the hand of Rome controlling them and thus did not have the fear of Rome. They feared God but not man. Perhaps another such dialog is timely.

Labels: Commentary

MONDAY, NOVEMBER 25, 2013

PERSONAL GENOME

There has been an explosive growth in people wanting to get their genome analyzed. The FDA last Friday issued what in my opinion appears to be almost a cease and desist order, or as they phrase it:

must immediately discontinue marketing the PGS until such time as it receives FDA marketing authorization for the device.

Specifically the FDA claims:

This product is a device within the meaning of section 201(h) of the FD&C Act, 21 U.S.C. 321(h), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body. For example, your company's website at ... markets the PGS for providing "health reports on 254 diseases and conditions," including categories such as "carrier status," "health risks," and "drug response," and specifically as a "first step in prevention" that enables users to "take steps toward mitigating serious diseases" such as diabetes, coronary heart disease, and breast cancer. Most of the intended uses for PGS listed on your website, a list that has grown over time, are medical device uses under section 201(h) of the FD&C Act. Most of these uses have not been classified and thus require premarket approval or de novo classification, as FDA has explained to you on numerous occasions.

There always has been a set of concerns here. Most people have no clue what some of these readings mean. Also the reading may be at best reflective a a still questionable result. One should

ask even if most physicians have the ability to ascertain the results.

There is also the question of what rights have you lost by sending your DNA to some third party.

This has always been an issue and the FDA may very well have taken a proper and necessary step. It will be interesting to follow this.
Labels: Genetics

MONDAY, NOVEMBER 25, 2013

DIVERGENT TRANSCRIPTION: AN INTERESTING TALE!

In a recent paper by Wu and Sharp the authors discuss the concept of Divergent Transcription. Simply this is a study of all the transcription that generally goes nowhere but from time to time does go somewhere and in this case the development of new genes.

A few decades ago when we looked at the DNA world we thought of it in terms of the Dogma: DNA to RNA to Proteins. Then the proteins did things.

Then we found that we had about 3 Billion base pairs and only about 20,000 genes. That means that we used only about 1-2% of our bases and the other 98-99% were not really used, but not really. That unused DNA was actually used in bits and pieces. There was a ton on non-coding RNA floating all over.

Thus we might think that decades ago the cell was filled with some well-organized proteins, coming from a well-orchestrated RNA process of translation. It was like an airport in the US, with all the people, base pairs, and lining up with the TSA, the promoters, and moving thorough the scanners in order, each being read for proper ID, the scanner being the RNA polymerase and coming out as ticked passengers grouping at each waiting area for the assigned flight. Each waiting area was the proteins composed of the translated bases now nucleic acids. Organized, controlled, and no unverified interlopers.

But now we look again and it really appears like Penn Station in New York. Doors all over, no lining up, people going on Amtrak, LIRR, NJ Transit, subways, no waiting, no seats, no tickets, no security. Then there are vagrants checking out the trash bins, and dozens of other types just wandering and looking. Order may be there but not the type we see at say Newark. There are, if you will, big RNAs and little RNAs, RNAs destined to become proteins, namely passengers on some transport, but there are also just lots of little segments of RNA going nowhere. These are the equivalent of non-coding RNAs just wandering around, crowding up the floor, slowing down the passengers, and at time changing who goes where.

The Model

Wu and Sharp conclude:

we propose that divergent transcription at promoters and enhancers results in changes of the transcribed DNA sequences that over evolutionary time drive new gene origination in the transcribed regions. Although the models proposed here are consistent with significant available data, systematic tests of these models await further advances such as in-depth characterization of additional genomes and experiments designed to test specific hypothesis. Over evolutionary times, genes formed through divergent transcription can be shuffled to other locations losing their evolutionary context. We envision future studies will uncover more functional surprises from divergent transcription, and illuminate how intergenic transcription is integrated into the cellular transcriptome.

Divergent Transcription is transcription that follows a different path than the organized transcription that we think of in a highly organized structure. As Seila et al stated:

Transcription initiation by RNA polymerase II (RNAPII) is thought to occur unidirectionally from most genes. Here, we present evidence of widespread divergent transcription at protein-encoding gene promoters. Transcription start site–associated RNAs (TSSa-RNAs) nonrandomly flank active promoters, with peaks of antisense and sense short RNAs at 250 nucleotides upstream and 50 nucleotides downstream of TSSs, respectively. Northern analysis shows that TSSa-RNAs are subsets of an RNA population 20 to 90 nucleotides in length. Promoter-associated RNAPII and H3K4-trimethylated histones, transcription initiation hallmarks, colocalize at sense and antisense TSSa-RNA positions; however, H3K79-dimethylated histones, characteristic of elongating RNAPII, are only present downstream of TSSs. These results suggest that divergent transcription over short distances is common for active promoters and may help promoter regions maintain a state poised for subsequent regulation.

As Wu and Sharp recount the classic transcription we use their description:

In the textbook model of a eukaryotic promoter, the directionality is set by the arrangement of an upstream cis-element region followed by a core promoter. The cis-elements are bound by sequence-specific transcription factors, whereas the core promoter is bound by TATA-binding protein (TBP) and other factors that recruit the core transcription machinery.

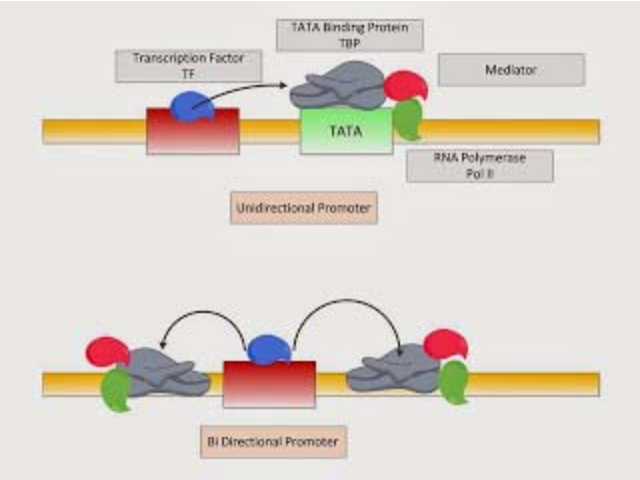
Most mammalian promoters lack a TATA element (TATA-less) and are CpG rich. For these promoters, TBP is recruited through sequence-specific transcription factors such as Sp1 that bind CpG-rich sequences and components of the TFIID complex that have little sequence specificity.

Thus, in the absence of strong TATA elements such as for CpG island promoters, TBP-complexes are recruited on both sides of the transcription factors to form preinitiation complexes in both orientations.

This model is supported by the observation that divergent transcription occurs at most promoters that are associated with CpG islands in mammals, whereas promoters with TATA elements in mammals and worm are associated with unidirectional transcription

We demonstrate the two concepts below using a modified graphic from Wu and Sharp. We show the TATA binding site on the gene and we show the TBP, the TATA binding protein and a mediator and ultimately the RNA Pol II. This is a classic unidirectional process moving across the exons and generating mRNA which is then cleaned and changed to a protein. The related cDNA do not show any of this underlying complexity.

Now below this is a second process, but now we show both forward and backward transcription. This requires a bi-directional promoter which Wu and Sharp discuss.



Wu and Sharp then argue that the model can be characterized by the system below. We have modified their graphic so that we may take a small step further. The Figure below depicts the four processes they consider:

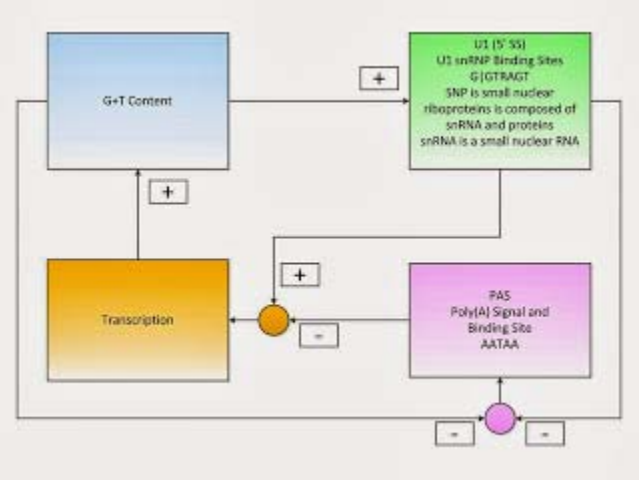
1. Transcription: This is the classic transcription process of taking DNA and changing it to RNA, usually an mRNA.

2. G+T Content: This is the G and T content of the intron and the propensity for mutations to occur in that area and thus setting up a region for the introduction of new gene type sequences.

3. U1 Process: There are small nuclear RNAs used to splice RNA segments together and these are called spliceosomes. One of them us the U1 snRNA. As the mRNA segments are produced they get spliced together by these nuclear RNA segments. They are powerful elements found in the nucleus.

4. PAS Process: The poly(A) is described as, from Baynes & Dominiczak, pp 430-432, as: *At the 3' end of all eukaryotic mRNAs (with the exception of histone mRNAs), a polyadenosine track is added, termed the polyA tail. The adenosine residues are not encoded by the DNA but instead are added by the action of poly(A) polymerase using ATP as a substrate. This polyA tail is frequently >250 nucleotides in length. Although it is still susceptible to the action of exo-RNases, the presence of the polyA tail significantly increases the lifetime of mRNA. The presence of the polyA tail has historically been used to isolate mRNA from eukaryotic cells.*

We now combine these elements into the Wu and Sharp dynamic, as modified, below:



We can then represent this model by the meta-equation below:

$$\frac{dGT(t)}{dt} = \alpha T(t)$$
$$\frac{dT(t)}{dt} = \beta U(t) - \eta PAS(t)$$
$$\frac{dU(t)}{dt} = \mu GT(t)$$
$$\frac{dPAS(t)}{dt} = -\theta GT(t) - \nu U(t)$$

or

$$\frac{dx(t)}{dt} = \begin{pmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{pmatrix} x(t)$$

Here we represent GT, T, U and PAS as some measure of each of the four processes represented in the diagram. Admittedly this is at best an ad hoc representation but it does demonstrate that indeed we have some form of dynamical system and in turn this system depending on whatever the constants are can become an unstable and ever growing process.

New Genes

Out of this process Wu and Sharp argue that new genes can be born. This is an ingenious and compelling argument. The time scale for such a development is not specified but perhaps it may be intuited. Also actual changes have yet to be fully observed from beginning to end. Yet the pieces are logically consistent and are all supported by the evidence.

First a brief summary of the splicesome (from Baynes and Dominiczak, pp 430-432)

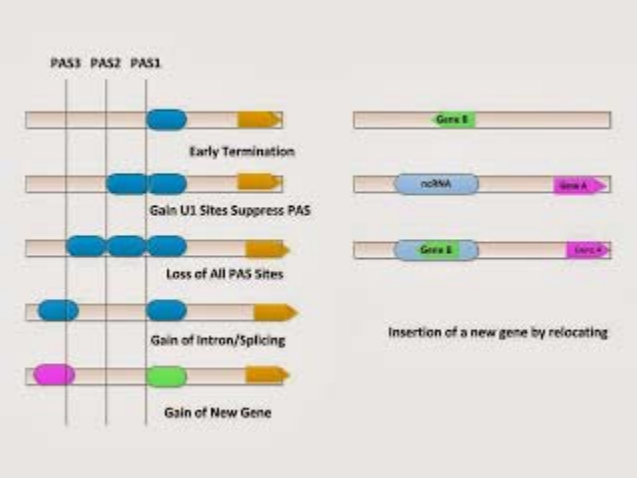
In the more complicated posttranscriptional processing of eukaryotic mRNAs, sequences called introns (intravening sequences) are removed from the primary transcript and the remaining segments, termed exons (expressed sequences), are ligated to form a functional RNA.

This process involves a large complex of proteins and auxiliary RNAs called small nuclear RNAs (snRNAs), which interact to form a spliceosome. The function of the five snRNAs (U1, U2, U4, U5, U6) in the spliceosome is to help position reacting groups within the substrate mRNA molecule, so that the introns can be removed and the appropriate exons can be spliced together precisely. The snRNAs accomplish this task by binding, through base-pairing interactions, with the sites on the mRNA that represent intron/exon boundaries. Accompanying protein factors are responsible for holding the reacting components together to facilitate the reaction.

We summarize the U below:

snRNA	*Size*	*Function*
U1	165 nt	Binds the 5' exon/intron boundary
U2	185 nt	Binds the branch site on the intron
U4	145 nt	Helps assemble the spliceosome
U5	116 nt	Binds the 3' intron/exon boundary
U6	106 nt	Displaces U1 after first rearrangement

We explain how this may work in the Figure below adapted from Wu and Sharp. There is on the left a progression of changes in a segment of DNA which would normally read left to right with the inclusion of a new segment from right to left. The PAS sites, three as shown in the Figure below, are covered by RNA segments ultimately allowing the creation of an Exon and Intron. The process is further elucidated on the right where are gene is putatively relocated from one chromosome to another or even just duplicated.



Let us use Wu and Sharp's text and go through the argument. They proceed as follows:

One consequence of transcription is that it can cause mutations, especially on the coding (nontranscribed) strand.

During transcription, transient R loops can be formed behind the transcribing RNA polymerase II, exposing the coding strand as single-stranded DNA, whereas the noncoding strand is base paired with and thus protected by the nascent RNA.

The lack of splicing signals in the divergent transcript also makes it more vulnerable to R loop formation, as splicing factors have been implicated in suppressing R loop formation.

In addition, divergent transcription generates negative supercoiling at promoters, which facilitates DNA unwinding and promotes R loop formation.

As a consequence of R loop formation, the single-stranded coding strand is vulnerable to mutagenic processes, such as cleavage, deamination, and depurination. Genomics studies have shown that during mammalian evolution, transcribed regions accumulate G and T bases on the coding strand, relative to the noncoding strand or nontranscribed regions.

Evidence suggests that such strand bias may result from passive effects of deamination, transcription-coupled repair, and somatic hypermutation pathways in germ cell-transcribed genes, in the absence of selection.

Accumulation of G and T content on the coding strand will strengthen the U1-PAS axis.

A-rich sequences such as PAS (AATAAA) are likely to be lost when the genomic DNA accumulates G and T.

In contrast, G+T-rich sequences, such as U1 snRNP-binding sites (e.g., resembling 50 splice sites, G|GTAAGT and G|GTGAGT), are likely to emerge in these regions. Since promoter-proximal PAS reduces transcriptional activity, the loss of PAS and gain of U1 sites should contribute to lengthening of the transcribed region as well as its more robust transcription.

The gain of U1 sites could also enhance transcription by recruiting basal transcription initiation factors or elongation factors.

Therefore a positive feedback loop is formed: active transcription causes the coding strand to accumulate sequence changes favoring higher transcription activity.

As noted above, strengthening of the U1-PAS axis also favors extension of the transcribed region. Being longer gives the transcript several advantages: by chance longer RNAs are more likely to contain additional splicing signals such as a 30 splice site to become spliced, or binding sites for splicing-independent nuclear export factors, thus escaping nuclear exosome degradation by packaging and exporting to cytoplasm .

Longer RNAs are also more likely to carry an open reading frame, either generated de novo or by incorporation of gene remnants.

Once in the cytoplasm, the RNA should at some frequency be translated into short polypeptides due to widespread translational activity.

Some of the polypeptides may provide advantage to the organism and become fixed in the population, thereby forming a new gene.

Thus we have seen a mechanism for new gene creation and insertion.

Observations

These are a very powerful set if insights and observations. They have significant conclusions as has been articulated by those in Sharp's Lab. The metaphor of a train station with wandering fragments of often "useless" RNA has certain merit. However all too often those fragments are not useless but have ways of interfering and disrupting the normal progress of cellular dynamics.

We now pose a few observation which may have some merit.

1. Somatic vs Germline: These changes seem to be mitotic in nature and thus are reflected in somatic cells. What is the impact in meiosis and germ line cells? Namely can these mutations be carried forward and be selected out in subsequent generations? Or is this process one almost exclusively found in somatic cells and thus may be causes for such diseases as the cancers? I could not find a clear path to follow here.

2. Causation: What causes some of these processes. Many if not most of the links are presented and explained but ultimate causality is missing.

3. Frequency: How frequently do these changes occur? Are they rare or common and at what rate do they occur? What are the overall temporal dynamics of these processes. Can we examine genomes and ascertain where they might occur. We all too often just skip over the Introns, focusing on the Exons and their resultant expression. There also are many regions of the Exons that are not expressed, and are they part of this phenomenon as well?

4. Reaction Dynamics: The actual reaction dynamics could possibly be explained and modelled. We have presented a meta model solely for the visualization of what may happen. It is expected that the model is most likely non-linear and more complex. In fact the actual metrics being measured and modelled are still in question. However not withstanding that we can envision a dynamic model exhibiting not only stability issues but also oscilliatory effects.

5. Methylation and Epigenetic Factors: Clearly the CpG islands play an important factor. Methylation has become a significant area of study over the past decade and the processes described herein rely on many of these CpG islands as well. Is methylation a competing process, an allied process, a controlling or mediating process?

6. What are all these RNA fragments doing?: Ultimately we find that a cell may have not only well understood Dogma based proteins and pathways but also a mass of disconnected non coding RNA spinning about in the nucleus and throughout the cell. Thus we ask; what do these snippets do? Are they just wanderers going nowhere and possibly just bumping into those going somewhere or are the truly entities which have predictable effects on pathways? Are they noise or an aberrant signal?

This is a very compelling paper and it presents in an elegant manner the results of the efforts to date. This effort demands to be followed and examined in detail as it progresses.

References

Baynes Dominiczak: Medical Biochemistry 3E, Mosby (New York) 2013.
Seila, A., et al, Divergent Transcription from Active Promoters, Science VOL 322 19 December 2008 1849.
Wu, X., P. Sharp, Divergent Transcription: A Driving Force for New Gene Origination? Cell 155, November 21, 2013.
Labels: Cancer

SATURDAY, NOVEMBER 23, 2013

THERE SEEMS TO BE A LOGICAL ISSUE HERE

In a recent NY Times piece by one of the Harvard economists, he states as follows:

Another clue to what's happening in the labor market is the vacancy rate. Although less widely followed than unemployment figures, this rate is its mirror image. To compile the unemployment rate, the Bureau of Labor Statistics surveys households to find workers without jobs. To compile the vacancy rate, the bureau surveys employers to identify jobs without workers. In short, the vacancy rate measures the percentage of available jobs that are currently unfilled.

Not surprisingly, the vacancy rate is highly cyclical. In recessions, when customers are hard to find, businesses post fewer new jobs. In addition, because the number of job seekers expands, the posted openings are filled quickly. As a result, the vacancy rate falls. Conversely, when the economy recovers, businesses start posting new openings, and jobs are harder to fill, so the vacancy rate rises.

The recent recession is a case in point. Seven years ago, the vacancy rate was a bit over 3 percent. It fell to a low of 1.6 percent in July 2009, a month after the official trough of the recession. The most recent reading puts it at 2.8 percent. So according to this measure of labor-market tightness, the economy is almost back to normal.

Let us examine the statements and numbers and let us see what may be wrong with this logic.

1. We know that the percent of the population employed has dropped precipitously. We have been noting that for five years now. Others seemed to ignore it for the first three years but since I am not an economist I deal with the facts, all the facts.

2. The percent unemployed is a floating and relative number. It helps get to the real number if and only if you know what the real number should be. To me it should be the percent of the population employed before the Recession adjusted for the increase in population.

3. Now the vacancy rate means nothing more than what industry demands. It is a meaningless number and reflective more of productivity than the ability of the economy at large to absorb workers. We may have a 20% vacancy rate if we had massive productivity gains and got rid of 40% of those employed and we may never fill it if the demand is for people who can do real things. Like engineers, electricians, even plumbers, but not fine art majors and not economists.

4. Thus to make any nexus between the total percent of the population employed, the employment vacancy rate, and the economy is specious at best. With the massive improvements in productivity we see less people required to be employed and those in demand have talents which are also in short supply. The work force is NOT homogeneous as one would assume if one were an old fashion economist who viewed the world of workers as factory types.

Thus the argument that we are improving because of an increased vacancy rate is at best wishful thinking. The percent of the total population is increasing, as we have noted, but barely. The economy is much more complex than as stated.
Labels: Economics, Economy

INDEPENDENT SCOTLAND

The BBC reports on an independent Scotland by March 2016. They state:

Scotland could be independent on 24 March, 2016, if voters back leaving the UK in the independence referendum, the Deputy First Minister has announced.

The date is included in the Scottish government's White Paper, described as a "blueprint" for independence.

Despite that a Catholic still cannot be the Prime Minister and Catholics still have limited rights in the Occupied Counties. They continue:

March 24 is also the anniversary of the Union of the Crowns in 1603.

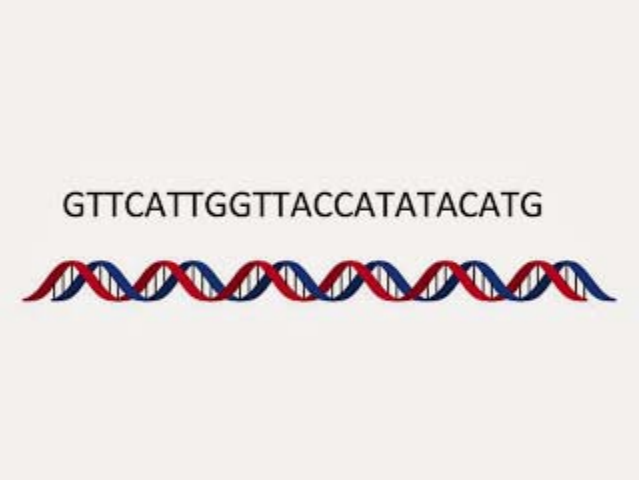
A Scotland Office spokesman said: "Naming the date of independence ahead of a referendum result would only weaken the Scottish government's negotiating position if Scotland voted to leave the UK.

"People in Scotland still don't know the full terms the Scottish government would try to negotiate but the 28 members of the EU, Nato and the rest of the UK would all know that for the Scottish

government the date is more important than the deal.

But Ireland has been dominated by the English since the Pope used the fraudulent Donation of Constantine to allow Henry II to donate it to his less than balanced son John.Good luck to the Scots!
Labels: Commentary

SISTER ROSITA AND THE MOOCS



In the Fifth Grade I had Sister Rosita for my teacher. Even though I was performing well, somehow I never got the spelling stuff quite right. My readers can amuse themselves reading the blogs wherein I have the right spelling but the wrong word. That is, spell check, not me, I just spell the right word wrong, not the wrong word right.

But what, you may ask; does this anecdote have to do with MOOcs? Simply, MOOCs use computers to grade. Computers do not offer partial credit. You are right or wrong. Over the years I mastered multiple choice tests, Board exams, and the like, not that they prove anything, they are required, but one learns a technique, not the reality of what one started learning in the first place.

But back to MOOCs. I have been taking Lander's MIT Biology, brilliant course, I know most of it but it is always good to gain a new perspective from one who really knows what they are doing. It is a typical MIT course in many ways, except it is a MOOC.

To explain, allow me again to digress back some almost fifty years when I was teaching at MIT. As a faculty member when we sat to do the final grades, say in 6.02, the required Electronics course, we had all the Teaching Assistants, Section Instructors, and myself, gather and look at each student. If the student got say a 95 average on all 12 Problem Sets but totally blew the Mid Terms we asked what we did wrong. Clearly the student knew something and each of us knew something of that student. We examined the exam. Frequently we could see that we had a set of problems that if one concept was misinterpreted then all that followed, albeit properly done, rely

on a correct first answer and thus was wrong. So what did we do, partial credit, regarded, and alas, the Final and Mid Terms went up. The person came out with the A.

But this is not at all possible with a MOOC. Now I am not after a grade. I have no idea what I would do with one. I am there to learn the material and the process.

Now back to Sister Rosita. Decades later I found that the problem was not my spelling but my particular kind of dyslexia. I can now look forward in the family and see it there and I guess if I could look backward I would see it also. But I can readily understand and inter-relate complex patterns, but somehow have a heck of a time differentiating “a” and “c” and “b” and “d”. But wait, I find that I have an even more challenging time with A, T, G, C! I get the idea but ask me to look at a sequence of five and then go and find the same five on another sheet of paper! Then present say 100 or so bases randomly presented and ask to find say six of a particular pattern, no way, ever. After all is that not why God created computers.

Now back to the MOOC. You see, in one of Lander’s Exams the TAs made you read the gene and you could not readily cut and paste it. I did finally remember how to do it but after the exam. Thus since this was the first part of some 65 point single question, miss that and you were sunk. No partial credit etc.

Now I did not worry but in examining the comments, I never comment on these things, but many students had the same if not similar problem. Thus what is the lesson MOOCs could learn?

Simply, not all students are the same. We all find ways to work around our handicaps, whatever they may be. But when administrators of sorts decide upon “rules” they believe to be correct, then it is incumbent upon them to understand the consequences. MOOCs will never look at every student the way we did half a century ago. Yet they can come close. They can and must become capable of understanding what a student is doing wrong, not just marking it wrong. One learns through one’s mistakes. One learns how to manage “blind spots”. Artificial walls should not be constructed because of the arrogance of some intermediary.
Labels: Academy

IS DIOGENES STILL SEARCHNG?

Is Diogenes still looking for truth? Does truth truly exist? Let's try truth in Health Care and especially the progress of the ACA.

According to the WaPo:

By mid-November, the 14 state-based marketplaces reported data showing enrollment has nearly doubled from last month, jumping to about 150,000 from 79,000, according to state and federal statistics. The nonprofit Commonwealth Fund, which has been tracking the data, called the most recent numbers "a November enrollment surge."

But one must look at the source of this good news. The source, the Fund so named above, is headed by one of the ACA principals, and brother of a Democrat Senator, and manager of the deployment of the EHRs that have somewhat in my opinion made chaos of every medical practice.

The question is; why is the Government not giving out the data? The answer may very lie with the fact they seem to have the tendency to distort it anyway, just look at the employment data. One wonders, in my opinion, why one would ever believe these politically well connected entities.

Truth has taken a real beating lately.
Labels: Health Care

FRIDAY, NOVEMBER 22, 2013

PCA, ONCOSOMES AND BLOOD BORNE MARKERS

Almost daily one can see new proposed markers for Prostate cancer and its potential metastatic growth. There simply are often too many to have true prognostic value. The major concern that we have expressed over the past few years is the lack of causative structure behind many of these

proposed markers. That is, the marker may be reflective of some more complex causative process and it is often that process, albeit unknown or not expressed, that we are seeking so that one may have the ability to develop targeted therapeutics against that target. For example we understand PSA as a marker reflective of an enlarging number of prostate cells but the driver may be any one of several things other than cancer.

(NOTE: The above is from *Grasso et al*. It is a powerful and current update of genetic profiles of PCa)

In this note we examine two specific areas. The first is recent reporting on exosomes, called Oncosomes in the discussed work. This work covered in a recent and several extensive previous papers examine encapsulated blood borne markers for aggressive PCa. In contrast we examine a second recent result, also a blood borne marker of aggressive behavior, an mRNA of a quite large gene. The second is another blood borne marker, an mRNA from a quite large gene, NAALADL2 or N-acetylated alpha-linked acidic dipeptidase-like 2, located at 3q26.31, a large gene with hundreds of introns[11][1].

An excellent paper by Grasso et al has discussed the genetic landscape of androgen resistant PCa[12][2]. The authors summarize their work as follows:

Characterization of the prostate cancer transcriptome and genome has identified chromosomal rearrangements and copy number gains and losses, including ETS gene family fusions, PTEN loss and androgen receptor (AR) amplification, which drive prostate cancer development and progression to lethal, metastatic castration resistant prostate cancer (CRPC). However, less is known about the role of mutations. Here we sequenced the exomes of 50 lethal, heavily pre-

[11][1] http://www.ncbi.nlm.nih.gov/gene/254827

[12][2] http://www.nature.com/nature/journal/v487/n7406/pdf/nature11125.pdf

treated metastatic CRPCs obtained at rapid autopsy (including three different foci from the same patient) and 11 treatment-naive, high-grade localized prostate cancers. We identified low overall mutation rates even in heavily treated CRPCs (2.00 per megabase) and confirmed the monoclonal origin of lethal CRPC. Integrating exome copy number analysis identified disruptions of CHD1 that define a subtype of ETS gene family fusion negative prostate cancer. Similarly, we demonstrate that ETS2, which is deleted in approximately one-third of CRPCs (commonly through TMPRSS2:ERG fusions), is also deregulated through mutation.

Furthermore, we identified recurrent mutations in multiple chromatin- and histone-modifying genes, including MLL2 (mutated in 8.6% of prostate cancers), and demonstrate interaction of the MLL complex with the AR, which is required for AR-mediated signalling. We also identified novel recurrent mutations in the AR collaborating factorFOXA1, which is mutated in 5 of 147 (3.4%) prostate cancers (both untreated localized prostate cancer and CRPC), and showed that mutatedFOXA1 represses androgen signalling and increases tumour growth. Proteins that physically interact with the AR, such as the ERG gene fusion product, FOXA1, MLL2, UTX (also known as KDM6A) and ASXL1 were found to be mutated in CRPC. In summary, we describe the mutational landscape of a heavily treated metastatic cancer, identify novel mechanisms of AR signalling deregulated in prostate cancer, and prioritize candidates for future study.

The Table that they present is quite useful in this study. The measures are primarily mutational in nature.

We have previously reported on the development of exosomes, small encapsulated particle ejected from cells, often carrying within them marker proteins reflective of the status of an organ. Exosomes have been used for first, a word on terminology. As Simpson and Mathivanan state:

The first problem relates to the terminologies used in naming eMVs. In the past, isolated eMVs were named based on the sample source from which they were derived. For example, exosomes isolated from dendritic cells were named dexosomes, while cancer cell derived exosomes were referred to as texosomes/oncosomes and prostate cancer cell derived exosomes as prostasomes. This sample material based vesicle naming customization has lead (sic) to different nomenclatures such as epididimosomes, argosomes, exosome-like vesicles, apoptotic blebs, microparticles, prominosomes, prostasomes, dexosomes, texosomes, dex, tex, exosomes, microparticles, nanoparticles, microvesicles, shedding microvesicles, ectosomes, archeosomes and oncosomes.

Note that a bleb is an outward protrusion from a cell. Recent work by Funkhouser et al has some interesting detailed analyses of this phenomenon.

Oncosomes

Let us begin by considering the Oncosome results. We use the term oncosome rather than the more encompassing exosome because that is what is done in the paper.

In that paper the authors make claims as regards to these "oncosomes" and they state the following[13][3]:

Prostate cancer cells release atypically large extracellular vesicles (EVs), termed large oncosomes, which may play a role in the tumor microenvironment by transporting bioactive molecules across tissue spaces and through the blood stream. In this study, we applied a novel method for selective isolation of large oncosomes applicable to human platelet-poor plasma, where the presence of caveolin-1-positive large oncosomes identified patients with metastatic disease. This procedure was also used to validate results of a miRNA array performed on heterogeneous populations of EVs isolated from tumorigenic RWPE-2 prostate cells and from isogenic non-tumorigenic RWPE-1 cells. The results showed that distinct classes of miRNAs are expressed at higher levels in EVs derived from the tumorigenic cells in comparison to their non-tumorigenic counterpart.

Large oncosomes enhanced migration of cancer-associated fibroblasts (CAFs), an effect that was increased by miR-1227, a miRNA abundant in large oncosomes produced by RWPE-2 cells. Our findings suggest that large oncosomes in the circulation report metastatic disease in patients with prostate cancer, and that this class of EV harbors functional molecules that may play a role in conditioning the tumor microenvironment.

Thus the description could best use the general term exosome but we shall remain with and use oncosome throughout. Before continuing it is worth examining some prior research in this area as well. In the 2009 paper the authors state:

Oncosomes are recently discovered membranous microvesicles that have been implicated in rapid intercellular transfer of oncogenic information from glioblastoma to indolent glioma cells. Although this process resembles paracrine signaling, it involves intercellular transfer of a membrane-bound micro-organelle rather than a soluble protein such as a growth factor or cytokine. In the present study, we show that PCa cells shed membrane-bound vesicles in response to signal transducers. These structures are fairly large (0.5 to f5 Am), originate from nonapoptotic blebs in response to signaling cues, and have biological activity in their free-floating state. We also identify the formin homology protein, DRF3/Dia2, as a protein that seems to functionally inhibit oncosome formation. We also provide the first evidence that chromosomal loss at the DRF3 locus (DIAPH3) is associated with metastatic PCa.

Note that DIAPH3, diaphanous-related formin 3, is a protein that "*this gene encodes a member of the diaphanous subfamily of the formin family. Members of this family are involved in actin remodeling and regulate cell movement and adhesion. Mutations in this gene are associated with autosomal dominant auditory neuropathy. Multiple transcript variants encoding different isoforms have been found for this gene*"[14][4]. The authors continue with a discussion of DRF3[15][5]

[13][3] Large oncosomes mediate intercellular transfer of functional microRNA, Matteo Morello, Valentina R Minciacchi, Paola de Candia, Julie Yang, Edwin Posadas, Hyung Kim, Duncan Griffiths, Neil Bhowmick, Leland WK Chung, Paolo Gandellini, Michael R Freeman, Francesca Demichelis, Dolores Di Vizio, Cell Cycle V 12 N 22 2013. also see https://www.landesbioscience.com/journals/cc/article/26539/

[14][4] http://www.ncbi.nlm.nih.gov/gene/81624

an actin facilitator gene:

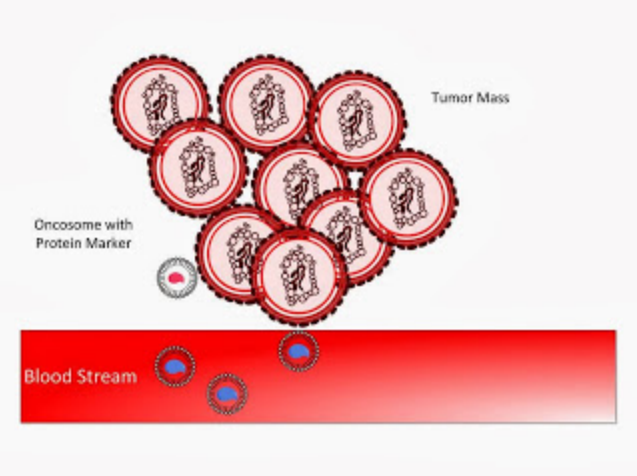
Our data indicate that the actin nucleator DRF3 is capable of inhibiting oncosome formation, because DRF3 knockdown by RNAi increased blebbing in DU145 cells, particularly in the presence of EGF. DRF3is expressed by LNCaP, DU145, and PC-3 human prostate cell lines. Formin homology proteins mediate cytoskeletal dynamics and, as a group, have been implicated in a wide range of cellular functions, including motility and vesicular trafficking. The formin FHOD1, which exhibits 45% sequence homology to DRF3, was recently implicated in Src-dependent plasma membrane blebbing.

It should be recalled that blebs are cell protrusions due to cytoskeleton breakdown and blebbing is the process of creating such nascent vesicles. The authors continue:

Human DRF3 is not well-studied, although analyses of the mouse homologue Drf3, and the close mouse paralog, Drf1/mDia1, indicate that DRF3likely mediates actin filament nucleation and elongation and microtubule stability Our experiments suggest that oncosome transfer between tumor cells, or between tumor and stroma, could play a role in propagation of aggressive behavior within the tumor microenvironment…… oncosome exchange is markedly different from paracrine effects induced by soluble ligands. However, this process could result in amplification of paracrine pathways through intercellular sharing of membrane-associated signaling complexes. Although our study focuses on PCa, a similar microvesicular transfer mechanism may operate in other tumor systems.

From the 2012 paper we have the following diagram which has been modified and simplified. The description is one of a tumor mass eluding encapsulated exosomes in which are specific proteins. It could possibly be equally likely that the exosomes may encapsulate mRNA as well which is a putative marker. This description also shows that any localization of the source is in question.

[15][5] http://www.kegg.jp/kegg-bin/highlight_pathway?scale=1.0&map=map04810&keyword=DRF3



The authors conclude in that paper:

Quantitation of circulating tumor cells (CTCs) is being evaluated to assess the risk of disease progression for prostate and other types of cancer. However, the clinical significance of CTCs remains to be established because of their extremely small number in peripheral blood compared with the number of blood cells. We have demonstrated that large oncosome-like structures can be separated from plasma in a manner that does not require the capture of CTCs or other cells. The molecular characterization of large oncosomes may potentially offer a more sensitive and specific liquid biopsy than CTCs for patient selection, monitoring of treatment efficacy, and assessment of drug resistance.

There seems to be a significant interest in various forms of circulating tumor cells, exosomes or otherwise. In a previous note we observed work done on extracting exosomes from urine as a way to assess PCa[16][6]. This approach was putatively a localized approach.

The observations of the press are oftentimes of use in understanding how these results are interpreted. Several comments are below[17][7]:

Investigators in the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute have made extensive progress in understanding the molecular mechanisms of disease progression. These results may help scientists better understand the prognosis of patients diagnosed with advanced prostate cancer. ..."One of the long-standing difficulties in treating men with advanced prostate cancer has been predicting the response to given therapies or treatments," said Di Vizio, associate professor in the Department of Surgery, Department of Pathology and Laboratory Medicine and Department of Biomedical Sciences. "These latest research findings provide tangible insight into the molecular and structural phenomena that result in prostate cancer metastases. They have the potential to create a new source of biomarkers and an innovative standard of care. These findings may also help distinguish individualized treatment plans best

[16][6] http://www.telmarc.com/Documents/White%20Papers/101%20Exosomes.pdf

[17][7] http://medicalxpress.com/news/2013-11-aggressive-prostate-cancer.html ; also one should compare this with the following: http://www.sciencecodex.com/novel_study_charts_aggressive_prostate_cancer-123155

suited for each patient." The new source of biomarkers is large oncosomes, which are vesicles released from aggressive prostate cancer cells with highly migratory features. These large oncosomes carry tumor molecules and have been shown in previous studies to contribute to tumor progression. This study demonstrates, for the first time in human samples, that identification of circulating large oncosomes can be an indicator of patients with more aggressive, treatment-resistant disease. Also notable, researchers found that large oncosomes contain microRNA, a molecule that regulates several biological processes now proven to influence tumor progression.

Another Marker

We now briefly examine another recent market for metastatic behavior. Specifically we discuss the NAALADL2 gene. The work of Whitaker et al has received some recent interest because it alleges to allow, upon biopsy, to ascertain if the lesion was of an aggressive nature. The authors also argue that this measure can be ascertained vial circulating mRNA related to the gene as well. Whether this circulating mRNA is exosome encapsulated is open for discussion.

From the paper by Whitaker et al[18][8]:

N-acetyl-L-aspartyl-L-glutamate peptidase-like 2 (NAALADL2) is a member of the glutamate carboxypeptidase II family, best characterized by prostate-specific membrane antigen (PSMA/NAALAD1). Using immunohistochemistry (IHC), we have shown overexpression of NAALADL2 in colon and prostate tumours when compared with benign tissue. In prostate cancer, NAALADL2 expression was associated with stage and Grade, as well as circulating mRNA levels of the NAALADL2 gene. Overexpression of NAALADL2 was shown to predict poor survival following radical prostatectomy. In contrast to PSMA/NAALAD1, NAALADL2 was localized at the basal cell surface where it promotes adhesion to extracellular matrix proteins. Using stable knockdown and overexpression cell lines, we have demonstrated NAALADL2-dependent changes in cell migration, invasion and colony-forming potential. Expression arrays of the knockdown and overexpression cell lines have identified nine genes that co-expressed with NAALADL2, which included membrane proteins and genes known to be androgen regulated, including the prostate cancer biomarkers AGR2 and SPON2. Androgen regulation was confirmed in a number of these genes, although NAALADL2 itself was not found to be androgen regulated.

NAALADL2 was also found to regulate levels of Ser133 phosphorylated C-AMP-binding protein (CREB), a master regulator of a number of cellular processes involved in cancer development and progression. In combination, these data suggest that changes in expression of NAALADL2

[18][8] http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013464a.html also see the discussion in http://www.newscientist.com/article/dn24628-prostate-cancer-tests-could-prevent-needless-surgery.html#.Uo9WfCetj0k also in PubMed they have http://www.ncbi.nlm.nih.gov/pubmedhealth/behindtheheadlines/news/2013-11-19-study-identifies-marker-for-high-risk-prostate-cancers/

can impact upon a number of pro-oncogenic pathways and processes, making it a useful biomarker for both diagnosis and prognosis.

Unfortunately the complete pathway models for NAALDL2 do not appear to be fully known. On the one hand the authors argue that it is androgen receptor independent, but that it plays a role in:

1. Cellular adhesion
2. Cell migration
3. Colony forming potential
4. Invasion

In the UK, this result has received considerable attention. For example, from the NHS report[19][9]:

"Prostate cancer patients could be screened to detect aggressive tumours after scientists identified a protein linked to severe forms of the disease," reports The Daily Telegraph. The news is based on the results of a complex laboratory study looking at a protein called NAALADL2. Scientists found that levels of NAALADL2 were high in prostate cancer when compared with healthy tissue, and levels were higher in more aggressive and more extensive prostate tumours. The level of the protein found in the tumours was also linked to whether men survived without recurrence of the cancer and overall survival after having radical prostatectomies (surgery to remove prostate cancer). This is exciting news as one of the biggest problems in helping men with prostate cancer is estimating the likely outcome. Some prostate cancers cause no or few symptoms and do not have any impact on life expectancy – doctors may tell you that "many men die with prostate cancer, not of prostate cancer". Other prostate cancers can be extremely aggressive. Around 10,000 men die of the disease in the UK per year. A test that could accurately identify high-risk cancers could potentially save lives and spare men with low-risk cancers unnecessary testing and treatment. So far this is early-stage research. The next hurdle is to see if the results of the lab research can be applied in the real world, and, most importantly, whether it can be used to help improve outcomes for men with prostate cancer. The researchers initially looked to see if the NAALADL2 protein was present in a range of normal and tumour tissues from different parts of the body.

The report, also in PubMed, then reports on the specific results regarding aggressive PCa. They state (as modified):

They then looked at whether the presence of NAALADL2 could differentiate between benign and cancerous tissue, and whether it could predict survival. Prostate tissue was taken from men who had radical prostatectomies (surgery to remove the prostate cancer) in Cambridge or Stockholm. The researchers then investigated the localisation of NAALADL2 within the cell, what cells making NAALADL2 can do, and which other genes are switched on (expressed) in combination with NAALADL2. What were the basic results? NAALADL2 was present at high levels in colon and prostate cancers. By measuring the amount of the protein, researchers were able to

[19][9] http://www.nhs.uk/news/2013/November/Pages/Study-identifies-marker-for-high-risk-prostate-cancers.aspx

distinguish between benign and cancerous prostate tissue with a relatively good level of accuracy. They found that in a group of samples from men in Cambridge:The level of sensitivity was 86% (sensitivity is the percentage of cancerous samples that were correctly given a positive result) , The level of specificity was also 86% (specificity is the percentage of benign samples correctly given a negative result) , Similar findings were seen in samples from a group of men from Stockholm.

Although this is a good value for sensitivity and specificity it is only for a small sample and only for ascertaining benign vs malignant. Aggressiveness may very well be another issue. They also continue as follows:

*Levels of NAALADL2 protein increased with the increasing aggressiveness of the prostate cancer, based on the microscopic appearance of the tissue (Gleason grade). Levels of NAALADL2 protein also increased with cancer stage (the extent and spread of the tumour), particularly between T2 (cancer confined to the prostate gland) and T3 (cancer that has begun to grow and spread outside the prostate into the seminal vesicles, the glands that produce the fluid component of semen). Levels of NAALADL2 RNA (*mRNA of NAALADL2 in the blood stream) *in the blood were found to be higher in men with biopsy-confirmed prostate cancer, compared with men who had raised prostate specific antigen (another protein associated with prostate cancer) but a negative biopsy.*

One of the concerns one would have here is that it is known that biopsies are often non-conclusive and require multiple tries. This is especially true with the older methodologies of sextant cores. With high density cores, 24 and higher, and with repeat biopsies at say 9 months, one can reduce but not eliminate this risk. Secondly, there is the issue of how the mRNA is obtained from the blood. We have been discussing exosomes but one suspects that the UK approach is not that but actual mRNA extraction. Blood extraction can be problematic because one does not know from whence it came. It could be prostate originated thus a local but aggressive disease or it could already have metastasized, having established itself in the bone. This is one of the major difficulties of blood borne markers.

The researchers then looked at whether levels of NAALADL2 protein could predict survival. One hundred and four men had radical prostatectomies in Cambridge, and 38 had recurrence of the cancer over a median follow-up period of 86 months.There was a trend that higher levels of NAALADL2 led to poorer outcomes, but this wasn't statistically significant. The researchers suggested that this might be because of the small number of men: the smaller the sample size, the less "statistical power" the results have. They then looked at data from Stockholm: in this cohort, there were 252 men, and 101 of them had recurrence over a median follow-up of 61 months. Of men with low levels of NAALADL2, 79.9% had no relapse at five years. Five-year recurrence-free survival was reduced to 72.5% for men with moderate levels of protein, and 65.3% for men with high levels of protein (hazard ratio 1.9). The result was still significant after adjusting for a number of factors, including the Gleason grade and cancer stage. Levels of NAALADL2 could also predict poor survival in low-risk patients (patients with low Gleason grades and cancer stage). Five-year survival was 93% in men with low levels of NAALADL2 and 45% in men with high levels of NAALADL2. The researchers found that NAALADL2 protein on the basal (base) cell surface, where it promotes cell adhesion, migration (movement) and

invasion (movement into tissue). They suggest that this could allow cells to escape the prostatic capsule and form tumours elsewhere. NAALADL2 was found to be expressed alongside androgen-related genes and prostate cancer biomarkers. How did the researchers interpret the results? The researchers conclude that, "NAALADL2 protein is expressed in a number of cancers, and highly expressed in prostate cancer, where it predicts for relapse following radical prostatectomy". They go on to say that, "These data suggest that changes in expression of NAALADL2 can impact upon a number of pathways [involved in cancer development], making it a useful biomarker for both diagnosis and prognosis."

The size of the samples is exceedingly small and thus although this result is compelling and of interest it is clearly not of clinical significance. Thousands of patients would have to be examined and one of the most confounding elements would be the type of biopsies and the way in which they were performed.

Now the work in this area has also led to a patent filing and issuance. From the Patent[20[10]]:

The invention features methods for detecting prostate cancer, especially hormone-refractory prostate cancer (HRPC) or castration-resistant prostate cancer (CRPC), by detecting over-expression of PKIB or NAALADL2 compared the normal organs. Also disclosed are methods of identifying compounds for treating and preventing prostate cancer including HRPC, based on the over-expression of PKIB or NAALADL2 in the prostate cancer, the cell proliferation function of PKIB or NAALADL2, the intracellular localization of PKIB or NAALADL2 or the interaction between PKIB and PKA-C. Also, provided are a method for treating prostate cancer by administering a double-stranded molecule against the PKIB or NAALADL2 gene. The invention also provides products, including the double-stranded molecules and vectors encoding them, as well as compositions comprising the molecules or vectors, useful in the provided methods. An isolated double-stranded molecule, which when introduced into a cell, inhibits in vivo expression of PKIB or NAALADL2 and cell proliferation, which double stranded molecule comprises a sense strand and an antisense strand complementary thereto, hybridized to each other to form the double-stranded molecule.

It is clear that the researchers have staked out their territory. But also have many others who have patented various other markers.

Observations

As one reads the current literature and discusses the issue of identifying what PCa is aggressive the general consensus is still that the problem has no simple solution. These two recent attempts identify new markers which may be useful. Blood borne markers, mRNAs or exosomes, have some improved predictive value in some limited trials. However there is not as of yet a true statistically significant set of such markers which we can rely upon.

[20[10]] http://www.faqs.org/patents/app/20120022128

The problem quite simply is as follows. The US Task Force has recently stated that there should be no PSA testing because most PCa are indolent. As we have argued again and again, the problem is that most is not all and that for that 5-10% who has this aggressive form that such a recommendation is most likely a death sentence.

The work in these two areas demonstrates two things. First, the aggressive form is quite prevalent and is indeed aggressive. Second that there are many putative markers, blood borne, which can provide reasonably determinations as to the aggressiveness.

Thus the USPTF recommendations are in our opinion without merit since the deny the severity and prevalence of the aggressive PCa status. The work herein is of significant merit and should be closely followed as one gets a better understanding of this disease.

There are however several issues which need clarification. They are:

1. Pathway Implications: As we have argued extensively before, understanding the pathway interactions is essential. For example, what does the NAALADL2 gene do and how specifically does it do what it does. This would lead us to understand whether this is an issue of that gene itself or of some promoter of that gene, and if so what promoter. The genetic network is essential to be a part of diagnosis, prognosis and therapeutics.

2. Stem Cell Issues: As with so many issues regarding PCa there is always the issue of a stem cell. Is the stem cell the one forcing the overproduction? The questions are quite substantial once we address this area.

3. Localization: Blood borne markers have significance but the question is from where these molecules originate. The concern we have expressed internally is that they may be early mets and not the localized tumor. To some degree that is the advantage of the urine based test, it provides a modicum of localization.

4. Statistical Significance: These tests are on small samples. One needs larger scale trials to determine the proper prognostic result. However with all of the putative markers available one could expect to see this being done in a parallel trial. The reason is because perhaps there are linkages which may come about in such a trial. We believe that single thread trials may fail to bring forth the power of multiple markers.

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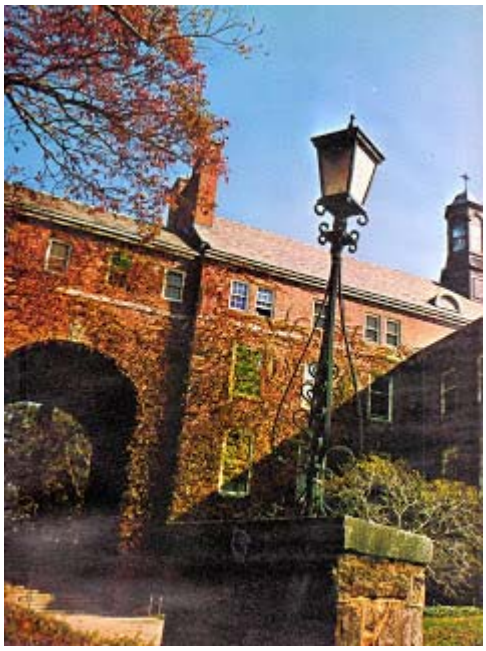
Labels: Cancer

FRIDAY, NOVEMBER 22, 2013

FIFTY YEARS AGO



Fifty years ago, on a wonderful late Fall day, I had just gotten out of my Logic class, it was a good old 14th Century Logic class, and walked across the campus when I was told that the then president was killed. I recall my first remark, " ..., Johnson's President!".

Then, less than a year later, there was the Gulf of Tonkin incident and we were off and running. We had managed through the Cuban missile crisis, I was in New York and that was target number one as we were told. We even had Nike Hercules missiles on Sandy Hook ready with nuclear warheads to blast the Russian out of the sky, yes nuclear warheads ready to explode over my home on State Island, to prevent the larger Russian warheads from exploding over Manhattan. The logic of the times was a bit strained, even for one who was then being trained in

good old Logic.

We had managed the Cuban invasion, threats from the Soviets, strikes, the beginning of the civil rights explosion in the South, and this event was just one amongst many.

The subway going South to home was filled with people reading the various New York newspapers all with massive headlines and pictures. The silence was deafening. It was the first time that I could go from 242nd Street to South Ferry without another passenger talking. Utter and complete silence for the hour trip. Things had changed, at least for a while.
Labels: Commentary

SUNDAY, NOVEMBER 17, 2013

REALISM IN WASHINGTON

I had a friend whose spouse received a very prominent appointment as a sub-Cabinet level position for a prior Administration. Before this person went to DC, the person was a very renowned academic, well known for their capabilities in the specific field; I told them that they should find someone "to watch their back", as the first hire they made. Find a good "back watcher" and then you had a chance to survive. Then I told them that they must abandon all lofty goals and try to survive long enough to allow something good to happen. It may not be what they expected, but to get something done one must survive long enough, but not too long. I finally told them that there are people in Government whose sole job is to "back stab". It is nothing personal, just their job. An appointee must understand that and take appropriate measures, again nothing personal.

Well, as expected, they thought my view of Washington was jaded. Then after a brief while, their career in DC cut short for the predicted reasons, we met and they told me that my advice had been the only true and spot on advice they received. Everyone else said they should "make a difference". Yet how could one do that if they were continually stabbed in the back. And, yes they told me that there was, indeed, a cadre of professional "back stabbers". If only they had listened.

I had seen this in the 70s during my stay in the City of No Good. It has just gotten worse and the one thing our Founders did that was just brilliant was to place the Capitol in a swamp, a metaphor for future generations. They kindly took it from New York, and sat it on the banks of the Potomac, just below the Falls.

Thus when I read the complaints of a recent academic having gone to DC I saw again the same story, and perhaps this individual had no one to tell them what would happen. What would you expect, especially if your goal is to change something that half the country out the gate despises? Just because you think it is good does not mean anything.

As this more recent academic who journey into the belly of the beast states[21[1]]:

[21[1]] http://jama.jamanetwork.com/article.aspx?articleid=1769898

Few lobbyists in Washington are more powerful than organized medicine and organized hospitals. Were they to demand a new health care system, they would prevail. But their agendas, mostly, are not yet about change; they are about surviving the current storm.

Survival is and has always been the mantra of those in DC. So what is the surprise, if one had ever sought advice then this would hardly have had been news.

The author continues:

Local, state, and national governments all affect health care. For instance, the safety net for the poor tends to be based in communities and states, whereas Medicare is, of course, national. Because of this chimeric structure, almost any proposal for federal action as ambitious as the ACA exposes ambivalence about federalism making the politics of reform contentious. For example, there is chaotic variation among states in how Medicaid expansion and exchanges will coordinate enrollment processes under the ACA.

People do not really trust the Federal Government much. Never did and never will. The old adage, "I am from the Federal Government and I am here to help you." has always been a joke. It gets a laugh every time it is told. One must understand that and not have some ambiguity of expectations. The Constitution, the law of the land, is structured to allow blocking on one branch by another. Yes, "elections have consequences", and since we do not yet have a monarchy the House can block the Executive. That is the way it works.

A final comment is made:

The ACA has begun the most significant tectonic shift in the nation's health care since Medicare and Medicaid arrived in 1965. Professionals have an opportunity to guide this country out of the battleground and into the creativity needed. The toxins of politics have only one effective antidote: the memory of the shared purpose of care, which is to heal. The needs of the patient come first. That is the guidepost to success for a nation whose vision is clouded at the moment by the fog of conflict.

The ACA has clearly begun to collapse under its own weight, which frankly is only beginning to be shown. The ACA does everything but put the needs of the patient first. In fact one need just look at the past few weeks. The needs of the patient, as the patient sees them, have been put dead last. The "needs" as the Central Governmental Executive sees them is another thing. Academics are always amazed when they face reality, either in business or Government. Reality is ruthless, and it is often in that ruthless combat that solutions are forged. Good solutions are compromises, bad solutions are mandates.

Another Academic who has managed their way through Washington says we need another goal, another Space Program. He states[22][2]:

[22][2] http://jama.jamanetwork.com/article.aspx?articleid=1769899

The US health care system needs a new BHAG: By 2020, per capita health care costs will increase no more than gross domestic product (GDP) +0%. That is, by the end of the decade, health care costs per person will not grow faster than the economy as a whole.

By BHAG he apparently means "big hairy audacious goal" which must be Academic speak for something just beyond any reasonable goal. He compares this to the Moon Program. In a previous set of pieces I had argued that the Moon Program actually set the US back a decade or two. For as we sent the best engineers into NASA type jobs the Japanese sent their new engineers into building electronics and a better economy so that by the 1980s they were ahead and we were behind. One should be thankful for the financial incompetence in Washington in the 1970s since it forced the creative minds out of Government work and into the commercial sphere. That led to our boom in the 1990s.

The driving of these Government programs will most likely repeat the failures of the 1970 and 1980s, but on a much grander scale. We no longer just worry about Japan, we have China. As we tighten the noose around a tightly controlled Central Government, China is lessening theirs. That is the risk we see in the future, not just the fact that the ACA is a disaster as a web site.

Labels: Government, Health Care, Politics

THURSDAY, NOVEMBER 14, 2013

WHERE IS RUNNYMEDE?

Do we need to find another Runnymede? Does the King have total sway, what can the Barons do?, The Earls? The current disaster on Health Care was discussed here almost five years ago. This issue and hundreds of others yet to come in a Law that was ill conceived, filled with special interest gifts, overwhelmed with Government controls, and burdened with costs for the consumer and the Economy which will drag the country down for decades if not the rest of the Century.

The Constitution gives to Congress the sole right to write and amend the laws of this land. Not to the executive. But in this case it appears as if this is governing by disaster management. There is no surprise here.

Health Care is a critical issue. But so too is its implementation. For such a complex system a step by step approach works. Even more so a State by State approach works. But an instant overhaul by people who have no clue and worse no competence will not.

For example the chief technical person seems to have but an economics degree from Harvard. This may not be the background one needs to manage a massive software development, possibly the largest undertaken by the Government, an entity not known for such complex projects to begin with.

We now have in the span of a month almost a half dozen back steps; web site, individual plans, union plans, small business plans, and corporate plans. Yes we allow 26 year olds to stay with mom and dad. Perhaps we should have lowered the age rather than increasing it and forcing them to find a job! But allowing them to stay was a backdoor way not to burden them so that they would be insured at the new rates no matter what. It would be an added burden on parents.

For those who think this solves the problem, you have just begun the trip down the rabbit hole.
Labels: Health Care, Politics

MONDAY, NOVEMBER 11, 2013

WHEN DID THE MONARCHY BEGIN?

I read a piece today in Science where the photo said:

"(the current president) Wants More Scientists"
"Where are Their Jobs?
Gone With The Sequester"

Now just think a moment about this placard. One which was professionally made, not cheap, and used at some public protest. The "King" does not want people to become scientists. The love of science makes competent people work hard and defer a great deal to achieve that, oftentimes independent or despite the Government. This placard makes a rather troubling statement. It is reflective of what has happened in just the last few years. It is a 10th Century serf like approach. We seek from the King favors, favors that make the King happy. Rather strange.

The article states:

A survey of public and private U.S. research universities released today finds that 70% of the 74 respondents report that sequestration has caused a reduction in federal research grants to their institutions and has slowed campus-based research. The biggest effects are fewer student positions (31%), a reduction in temporary or part-time staff positions (30%), and a decline in postdoctoral fellows (24%). Some 22% of respondents said they also have had to reduce the number of permanent staff members.

Many of these grants had exploded over the past decade. Some are good and some are a rather excessive wast of time and money. And worse some are funding the education of foreign students who upon completion return home, to China, India, and other nations who have become our competitors.

At what point are the researchers thankful for the funding from the taxpayers. Somehow I have seen a great disconnect here. It is even more so with young Gen X types who have the belief that they are owed this!
Labels: Academy, Economy

A HEALTH CARE SUGGESTION

I saw a piece in the NY Times that perhaps the crack software folks in DC might focus on:

Shortly after 9 p.m. here, Alibaba, the largest online retailer in China, said it had reached its target of 30 billion renminbi, or about $5 billion, in sales for the day via its online payment system, Alipay. That is two and a half times the total yielded last year by "Cyber Monday," the biggest e-commerce day of the year in the United States, which comes after the Thanksgiving holiday in late November. Analysts estimate that Alibaba accounts for two-thirds to three-quarters of total online retail sales in China.

If these folks can do this in China in one day perhaps we should just hand the whole ACA Ops over to them? At least as we say in Math it is an existence proof. I would bet that none of them worked at Bain.
Labels: Government, Health Care

CHURCHILL AND LEADERS

The White House has quelled the rumor that the bust of Churchill was sent back[23][1]. It was just moved so that no one could see it. At least that is what they claim.

As the White House states:

The version lent by Prime Minister Blair was displayed by President Bush until the end of his Presidency. On January 20, 2009 -- Inauguration Day -- all of the art lent specifically for President Bush's Oval Office was removed by the curator's office, as is common practice at the end of every presidency. The original Churchill bust remained on display in the residence.

As Palmer stated[24][2]:

Lenin adopted Marx's governing ideas:

1. *that capitalism exploited the workers,*
2. *that it necessarily produced and preceded socialism,*
3. *that history was logically predetermined,*

[23][1] http://www.whitehouse.gov/blog/2012/07/27/fact-check-bust-winston-churchill

[24][2] Palmer, R., A History of the Modern World, Knopf (New York) 3rd Ed 1965. Palmer was at Princeton when he wrote this first in the early 1950s and then in the mid-1960s. It is doubtful that anyone at Princeton would write this today, in fact one could readily assume they would likely agree with Marx!

4. *that class struggle was the law of society,*

5. *that existing forms of religion, government, philosophy, and morals were weapons of the ruling class.*

Marx's theory is the objective truth. Following the path of this theory, we will approach the objective truth more and more closely, while if we follow any other path we cannot arrive a t anything except confusion and falsehood . From the philosophy of Marxism, cast of one piece of steel, it is impossible to expunge a single basic premise, a single essential part, without deviating from objective truth, without falling into the arms of bourgeois-reactionary falsehood.

Lenin was a convert. He discovered Marxism; he did not invent it. He found in it a theory of revolution which he accepted without reservation as scientific, and on which he was more outspokenly dogmatic even than Marx himself. His powers of mind, which were very great, were spent in demonstrating how the unfolding events of the twentieth century confirmed the analysis of the master.

Thus we should consider the comparison of the current president with Churchill along these lines.

Churchill was fundamentally a capitalist; he saw unions and socialism as a true threat to core British values. Churchill became an opponent of socialism; it took away the drive to produce and destroyed the core of British creativity.

Churchill despised Communism. He saw it for what it was and he saw Stalin as abject evil, despite the blinders that FDR had.

Churchill understood History; he was a writer of History, albeit often for his own purposes. History was highly uncertain for Churchill. There were times when he wondered as to the ultimate outcome, from Gallipoli and especially at the beginning of WW II. The current president sees his work as inevitable, the country will ultimately move to his was of seeing it. It is predestined and those who do not see it are obstructionists.

Churchill saw his Party as a vehicle for his ideas, ideas that were often in conflict with his peers. Churchill changed parties to ensure the integrity of his ideas. Churchill did not see the Party as a way to control the people. He saw that the people needed to be convinced through actions as well as words.

Just some thoughts.

Labels: Politics

MONDAY, NOVEMBER 11, 2013

I THOUGHT THEY ATE HORSES

I saw in Le Monde an article where the Government is taxing horse owners in Paris, and I suspect all of France. It could be as high as 20%, whatever that means. After all it is France and they seem to tax everything.

The article states:

Près de 4 000 responsables et usagers des centres équestres d'Ile-de-France, accompagnés de 200 poneys, ont défilé, lundi 11 novembre, pour protester contre la hausse de 7 % à 20 % de la TVA sur leurs activités. 2 000 établissements et 6 000 emplois seraient menacés par cette mesure gouvernementale, estime le président de la Fédération française d'équitation. **...** *Alors que le gouvernement souhaitait jusque-là conserver un taux réduit pour les activités des centres équestres, il semble avoir plié face aux injonction de Bruxelles et décidé de se mettre en conformité avec le système commun de taxe sur la valeur ajoutée.*

Now I thought they ate horses and did not ride them. Just an observation.

Yet I am reminded of my experience of protests in Paris. One night during a Presidential election, I was in a taxi going from my office to dinner with a colleague. Then, from nowhere, hundreds or protesters with signs, shouting, blocking everything. Then a shout, the signs down, cigarettes out all sat on the curb. The Press was not ready with their cameras and one of the Press had not yet arrived. Thus all sides sat and spoke as if it were just a calm Fall afternoon in Paris.

Then the last camera man arrived, and Voila, the protest began again. Shame we have not adopted such a form. Yet they did have the Robespierre crowd as well.

Labels: Politics

PROSTATE CANCER INDOLENCE VS AGGRESSIVENESS

One of the most critical tools for assessing prostate cancer in its earlier stages is the potential for the tumor to be or become an aggressive tumor. Most PCa tumors are indolent, growing at a slow rate and often not being the ultimate cause of death. However there are a few PCa which are quite aggressive going from a low level to death in a short period, just two to four years. Being able to identify these tumors is becoming a significant area of study. Morbidity and costs can be significantly reduced if one can identify what cell hold the potential for such aggressive growth.

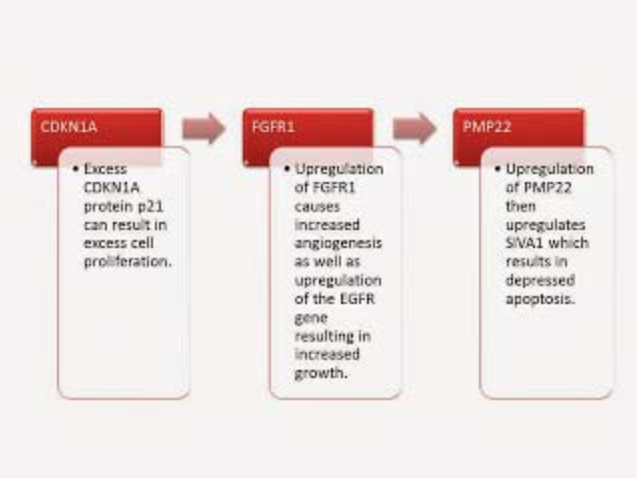
In a recent paper by Irshad et al presents three markers that they contend are significant for ascertaining aggressiveness. The genes and markers are:

1. CDKN1A, a gene which encodes a protein p21. This is a cyclin dependent kinase ("CDK") inhibitor. The CDKs function as cell cycle controls and by inhibiting them the cell cycle, namely proliferation, can be inhibited. p21 expression is controlled by p53 and by the PI3K/AKT pathway which itself is controlled by PTEN. Thus failure of either PTEN or p53 can lead to down regulation of p21 and thus up regulation of cell cycle proliferation. This is a logical gene product to measure.

2. FGFR1: This is a fibroblast growth factor gene. It has a powerful impact on angiogenesis and thus can be a significant factor in the development of blood flow to tumors. Excess expression of the gene may be a significant factor in malignant angiogenesis. It also is a driver for the EGFR gene which in turn is a growth factor modulator as well.

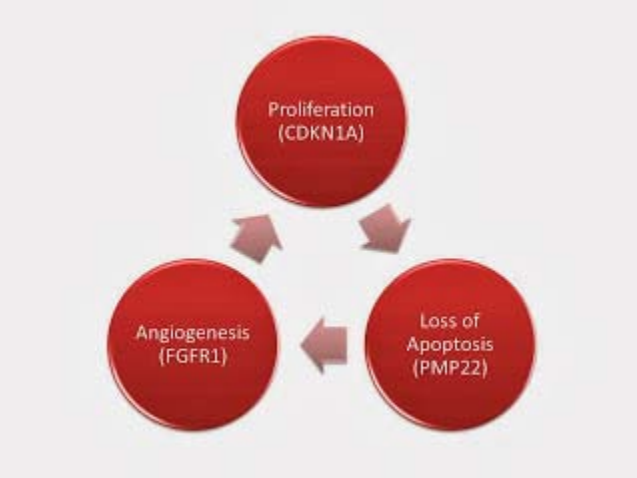
3. PMP22: This gene encodes a protein which relates to peripheral myelin control. Mutations in this gene result in Charcot–Marie–Tooth disease (CMT), a hereditary neuropathy of the distal joints and muscles. However PMP22 controls SIVA1 which is a critical gene controlling apoptosis. Thus any down regulation of this gene would logically down regulate apoptosis and allow the cell to survive. Combined with the CDKN1A dysregulation we then have a potentially lethal spiral.

Thus we have three separate and distinct factors which we summarize below in the graphic.



Thus there may be some significant impact on the aggressiveness of tumors with aberrant expression of these genes.

We therefore have a putatively deadly spiral which results in the aggressive form of PCa as we graphically demonstrate below:



The authors summarize their work as follows:

Many newly diagnosed prostate cancers present as low Gleason score tumors that require no treatment intervention. Distinguishing the many indolent tumors from the minority of lethal ones remains a major clinical challenge. We now show that low Gleason score prostate tumors can be distinguished as indolent and aggressive subgroups on the basis of their expression of genes associated with aging and senescence. Using gene set enrichment analysis; we identified a 19-gene signature enriched in indolent prostate tumors. We then further classified this signature with a decision tree learning model to identify three genes—FGFR1, PMP22, and CDKN1A—that together accurately predicted outcome of low Gleason score tumors. Validation of this three-gene panel on independent cohorts confirmed its independent prognostic value as well as its ability to improve prognosis with currently used clinical nomograms. Furthermore, protein

expression of this three-gene panel in biopsy samples distinguished Gleason 6 patients who failed surveillance over a 10-year period. We propose that this signature may be incorporated into prognostic assays for monitoring patients on active surveillance to facilitate appropriate courses of treatment.

One must ask if these genes are the cause of the effect; if the cause then why and if the effect then what is driving them? We examine some details herein and discuss the results.

Pathways

We briefly examine the three genes and their pathways. These three genes are quite disparate and do not appear to have any common functionality or proximate causality in cell degeneration.

1. PMP22 is a myelin controlling gene which is connected to Charcot Marie Tooth disease a disorder of the distal muscles where in there is a degenerative process resulting in such characteristics as club foot.

2. FGFR is a fibrogen growth receptor which when activated can create fibrogen.

3. CDKN1A is a cyclin kinase and a significant factor in cell cycle activation.

PMP22

Peripheral Myelin Protein 22 (PMP22) is a product of a gene related to myelin production. In addition a disruption in its function is often seen in Charcot Marie Tooth disease, a myelo-disruptive disease of the distal muscles.

As D'Urso et al had stated:

Recent molecular and genetic studies have provided some insights into the structure and function of one of the integral membrane proteins of peripheral myelin, the peripheral myelin protein 22 (PMP22). The pattern of expression of PMP22 is synchronous with myelin formation, and it localizes almost exclusively in the compact sheath

They conclude by stating:

In summary, our data provide the first direct evidence for the formation of P0–PMP22 complexes at the plasma membrane. These protein interactions probably participate in holding adjacent Schwann cell membranes together and in stabilizing myelin compaction. Our results could explain why genetic alterations in one of the two partner molecules lead to very similar disease phenotypes. Normally, a critical number of functional P0 and PMP22 molecules are necessary to maintain membrane adhesion and myelin compaction. Mutations could affect the amount of functional PMP22 or P0 in the myelin membrane through either impaired membrane targeting of the mutated protein or the disability of the altered protein to establish correct interactions with the partner molecule because of changes in their conformation. We believe that

the outcome of the present study provides new insight into the molecular basis of myelin assembly and peripheral dysmyelinating diseases.

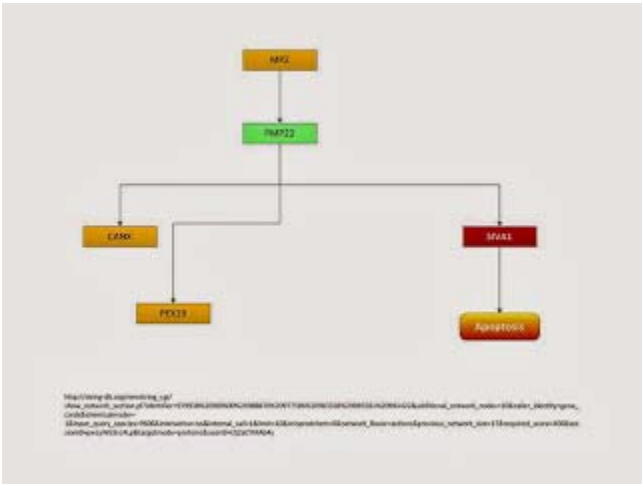
As Sereda and Nave state:

The most frequent genetic subtype of Charcot-Marie-Tooth disease is CMT1A, linked to chromosome 17p11.2. In the majority of cases, CMT1A is a gene dosage disease associated with a 1.5 Mb large genomic duplication. Transgenic models with extra copies of the Pmp22 gene have provided formal proof that overexpression of only this candidate gene is sufficient to cause peripheral demyelination, onion bulb formation, secondary axonal loss, and progressive muscle atrophy, the pathological hallmarks of CMT1A. The transgenic CMT rat with about 1.6-fold PMP22 overexpression exhibits clinical abnormalities, such as reduced nerve conduction velocity and lower grip strength that mimic findings in CMT1A patients

From Bolus we have:

A vast majority (over 70%) of CMT cases are due to a DNA duplication event that consequently leads to abnormal levels of protein synthesis, which disrupts the normal myelin sheath of peripheral nerves. The duplicated section of DNA is approximately 1.5 Mb in length and located on chromosome 17 region p11.2-p12. Within this region is the gene that codes for Peripheral Myelin Protein 22 (PMP22). As the name suggests, this protein plays a significant role in the myelin formation among peripheral nerves. The phenotype of classic CMT is a caused by a "gene dosage effect". A healthy individual will have two normal copies of PMP22, one from the mother and one from the father. Disease is present when this dosage is altered. When there is a single copy of PMP22 (deletion of one copy), a mild phenotype is present; Hereditary Neuropathy with Liability to Pressure Palsies (HNPP). When three copies of PMP22 are present (duplication of one copy), a more severe phenotype is present; recognized as Charcot Marie Tooth Type 1A (CMT1A). Four copies of PMP22 (duplication of both copies), though rare, result in the most severe phenotype Dejerine-Sottas Syndrome (DDS)

The putative simplified pathway elements of PMP22 are shown below:



It demonstrates the effect on SIVA1 gene product and the inhibition of apoptosis. As we have stated from NCBI:

This gene encodes a protein with an important role in the apoptotic (programmed cell death) pathway induced by the CD27 antigen, a member of the tumor necrosis factor receptor (TFNR) superfamily. The CD27 antigen cytoplasmic tail binds to the N-terminus of this protein. Two alternatively spliced transcript variants encoding distinct proteins have been described.

FGFR

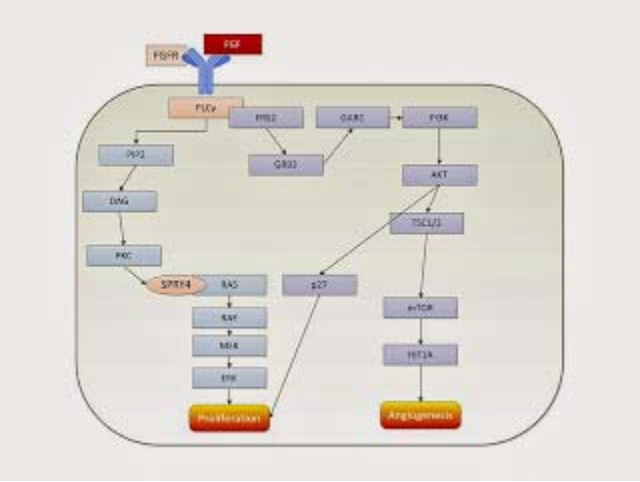
The FGFR appears to have a significant effect on angiogenesis and growth. This is essential for an aggressive tumor.

As Yang et al state regarding the function of FGFR:

The fibroblast growth factor receptor FGFR1 is ectopically expressed in prostate carcinoma cells, but its functional contributions are undefined. … Mice lackingFGFR1 in prostate cells developed smaller tumors that also included distinct cancer foci still expressing fgfr1 indicating focal escape from gene excision. Tumors with confirmed FGFR1 deletion exhibited increased foci of early, well-differentiated cancer and phyllodes-type tumors, and tumors that escaped fgfr1 deletion primarily exhibited a poorly differentiated phenotype. Consistent with these phenotypes, mice carrying the fgfr1 null allele survived significantly longer than those without FGFR1 deletion. Most interestingly, all metastases were primarily negative for the FGFR1 null allele, exhibited high FGFR1 expression and a neuroendocrine phenotype regardless of FGFR1 status in the primary tumors. Together, these results suggest a critical and permissive role of ectopic FGFR1 signaling in prostate tumorigenesis and particularly in mechanisms of metastasis.

Clearly in murine models it is a gene which if uncontrolled has highly aggressive characteristics.

From Acevedo we have the following pathway characterization (as modified and simplified:



Note that it reflects on both angiogenesis and proliferation. The above has been somewhat simplified to highlight the key elements. The FGFR is activated by the FGF, one of many growth factors.

CDKN1A

As Bunz relates there is a direct connection between p53 and the regulation of cell cycle dynamics. CDKN1A is a direct target of p53 transcriptional transactivation. CDKN1A encodes the gene p21 which is a universal CDK, cyclin dependent kinase, which regulates multiple cell cycle transitions. Thus having an activated and over-expressed p21 with excess CDKN1A we have a significant driver to cell cycle activation and resulting cell proliferation.

p53 associates with a binding motif in the CDKN1A promoter and significantly increases CDKN1A transcription. Cancer cells which have impaired p53 also have impaired CDKN1A transcription and thus the cell is restricted in managing cell cycle response to damaged and incompletely chromosomes[25[1]].

As Bau et al state:

The protein p21 (Cdkn1a/Waf1/Cip1), encoded by the CDKN1A locus, is a universal inhibitor of cyclin-dependent kinases (Cdks), which suggests its widespread role in regulating the cell cycle. The human CDKN1A gene consists of three exons of 68, 450 and 1600 bp. In normal cells, p21 exists predominantly in quaternary complexes with cyclins, Cdks, and PCNA to inhibit the activity of Cdks and control the G1- to S-phase transition. The CDKN1A gene has a p53 transcriptional regulatory motif and cells lacking functional p53 tumor suppressor protein express very low levels of p21, suggesting that p53 regulates CDKN1A expression directly. The expression of p21 induces differentiation of normal and transformed cells, and the involvement of p21 in terminal differentiation has been observed in several cell systems. Differential regulation of p21 by p53 and retinoblastoma has been reported in cellular response to oxidative stress. In addition, several recent studies suggest a role for p21 in apoptosis. Quercetin-induced apoptosis in hepatocytes was also associated with the regulation of p21 protein expression in a p53-independent pathway. [CDKN1A] This gene encodes a potent cyclin-dependent kinase inhibitor. The encoded protein binds to and inhibits the activity of cyclin-CDK2 or -CDK4 complexes, and thus functions as a regulator of cell cycle progression at G1. The expression of this gene is tightly controlled by the tumor suppressor protein p53, through which this protein mediates the p53-dependent cell cycle G1 phase arrest in response to a variety of stress stimuli. This protein can interact with proliferating cell nuclear antigen (PCNA), a DNA polymerase accessory factor, and plays a regulatory role in S phase DNA replication and DNA damage repair. This protein was reported to be specifically cleaved by CASP3-like caspases, which thus leads to a dramatic activation of CDK2, and may be instrumental in the execution of apoptosis following caspase activation. Two alternatively spliced variants, which encode an identical

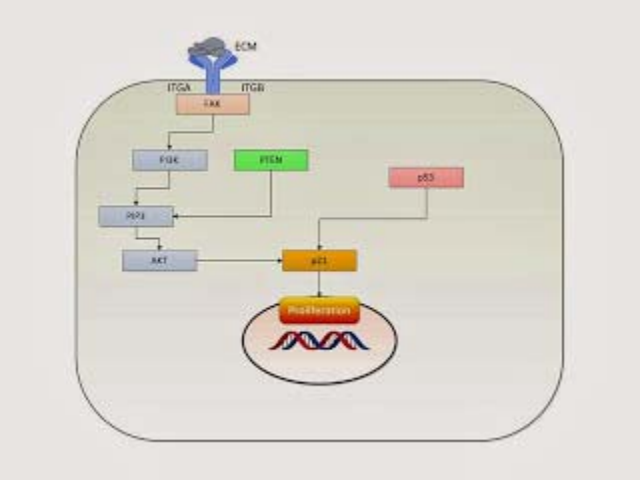
[25[1]] See Bunz, p 222.

[25[2]] http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?db=human&c=Gene&l=CDKN1A

protein, have been reported. Cyclin D is one of the key regulators of the cell cycle. As Bunz states (Bunz, pp 218-221) the cell cycle goes through several well-known phases. There are phase specific kinases which are cyclins which are called that because they were found to increase or decrease in a cyclical manner as the cell cycle phase progressed. [26][2]

From Porath and Weinberg we have:

The molecular circuitry of senescence. p53 and Rb are the main activators of senescence. p53 can activate senescence by activating Rb through p21 and other unknown proteins, and also, in human cells, can activate senescence independently of Rb. Rb activates senescence by shutting down the transcription of E2f target genes. Rb is activated either by p21, or by the p16INK4a product. p53 activation is achieved by phosphorylation, performed by the ATM/ATR and Chk1/Chk2 proteins, and by the p19ARF product of the INK4a locus, which sequesters Mdm2 in the nucleolus. The transcriptional control of the INK4a products is not fully elucidated, indicated are some of these regulators.



In the cycles the cyclin binds with a cyclin-dependent kinas or CDK. The activated cyclin-CDK complex phosphoralates phase specific substrates. Cyclin D along with CDK4 and CDK6 facilitate the transition through G1 to the start of S for example. Cyclin E with CDK2 facilitates the transition from G1 to S. Cyclin A with CDK2 moves through S. Cyclin A/B with CDK1 moves through G2. Thus activation of Cyclin D is a sign that cell replication has commenced.

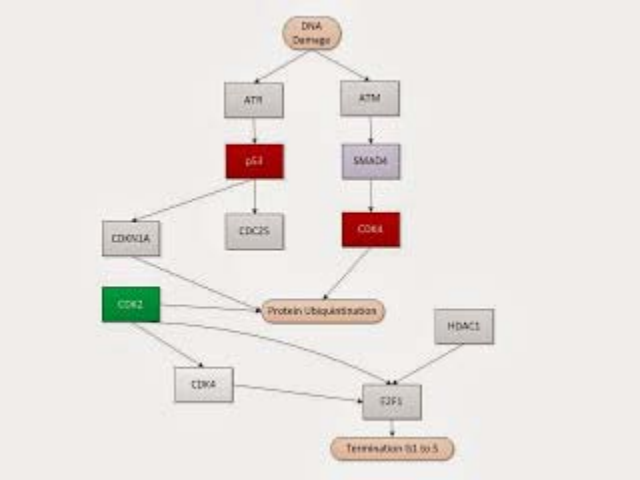
As stated in NCBI[27][3]:

The protein encoded by this gene belongs to the highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance throughout the cell cycle. Cyclins function as regulators of CDK kinases. Different cyclins exhibit distinct expression and degradation patterns which contribute to the temporal coordination of each mitotic event. This cyclin forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose

[26][3] http://www.ncbi.nlm.nih.gov/gene/595

activity is, required for cell cycle G1/S transition. This protein has been shown to interact with tumor suppressor protein Rb and the expression of this gene is regulated positively by Rb. Mutations, amplification and overexpression of this gene, which alters cell cycle progression, is observed frequently in a variety of tumors and may contribute to tumorigenesis

We use the NCI data set for its pathway[28][4]:



Observations

There has been a proliferation of putative gene expression findings related to a multitude of cancers. We have argued that behind any putative marker that there should be some causal model reflective of reality. Our prior focus has been primarily on pathway modifications and specifically the gene which has been changed in terms of expression that is reflected in that pathway change.

Let me provide a few observations:

1. The need to determine markers for assessing aggressive PCa is a critical factor in managing the disease. It is well known that a small fraction is aggressive but the aggressive forms have devastating morbidity and mortality effects. The arguments over PSA testing are oftentimes done by those who have been least affected and even more so least knowledgeable. Having some definitive test is of help.

2. These three genes arguably cover three of the most significant factors in PCa. However one must look at them in the context of the overall networks controlling cells. Namely pathways and causative gene must be studied. What of methylation and PCa? How is that factors assessed?

28[4]

http://pid.nci.nih.gov/search/pathway_landing.shtml?pathway_id=100160&source=BioCarta&genes_a=4089&genes_b=&what=graphic&jpg=on&ppage=1

3. Sampling genes for the protein levels may be much more complex than realized. What cells do we sample? What is a metastatic stem cell has already moved out into distant sites, how is that ascertained? The failure rates of this approach must be seriously studied.

4. This study appears to be better than many others that just do some genome wide study and finding a dozen or so genes with some "correlation". Here we have some genes with putative causative factors for the specific disease characteristics.

5. What of the methylation issue and what of the stem cell issues? How do these fit into this profile?

This work is an excellent step in getting a better hold on PCa. It will be interesting to see how it progresses.

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Labels: Cancer

HAPPY VETERAN'S DAY

From the men on-board the USS Albert W Grant in 1944. Before the fateful day in the Surigao Straits.
Labels: Commentary

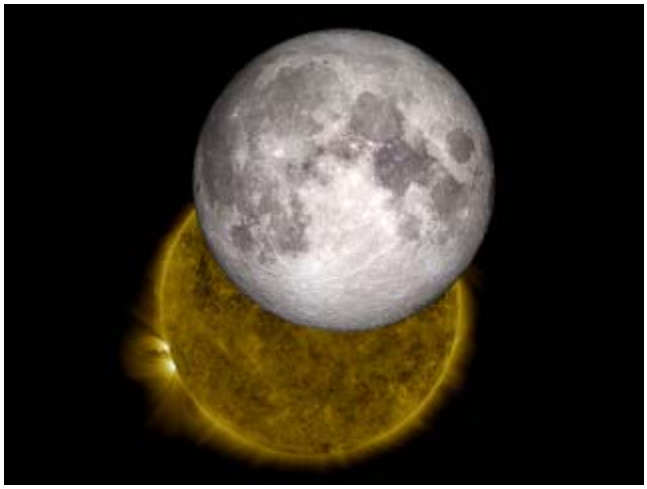
SUNDAY, NOVEMBER 10, 2013

NICE PICS

If anyone is interested NASA has a lot of great images of outer space. Here are a few:

This above is the most recent. Here is another:

and another:



This is rather cool. This just lets us know how far things go. Take a look and enjoy. After all you paid for them!
Labels: Commentary

EXCUSES EXCUSES EXCUSES

A former Administration adviser and one time college president has written in the FT:

Large-scale information technology projects in the private sector are hard enough even without an organised constituency for failure.

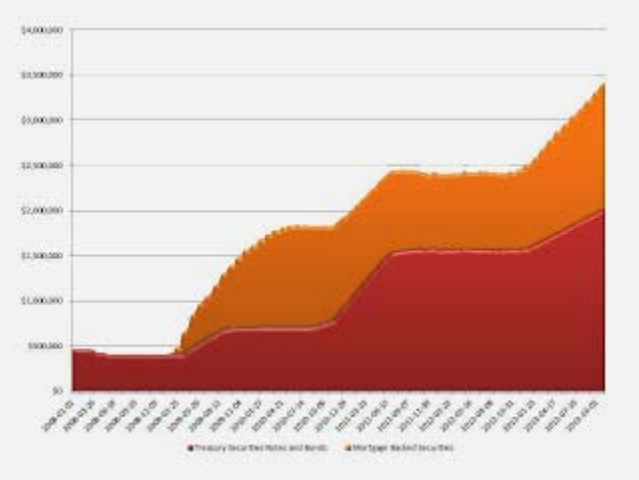
From an economist, well it still makes no sense. I have done a few large scale systems. For example when we delivered roaming in cellular with some 500+ tax jurisdictions and the like it was quite complex. But it cost $24 million, not $700 million. Heads rolled for mistakes. Yes it was hard because it was just a plain stupid design! One should not try and compare this to the real world. Government project never are.

He continues:

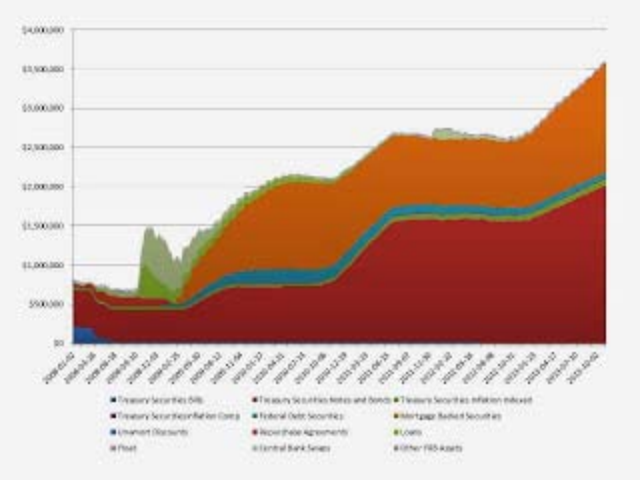
Many people regard it as an obligation when their country is at war – even a war they oppose – to support the troops. In the same way history will not judge kindly those who, having lost a political debate over policy, try to undermine programmes when they are being enacted.
The troops are one thing, the incompetents in Government are another. To paraphrase the current head of the administration; elections have consequences. One party controls two parts but the third part is controlled by another party. That is the consequence of an election. One cannot take credit for one and blame the other. It is illogical. But alas logic never becomes a politician.
Labels: Health Care

SATURDAY, NOVEMBER 9, 2013

FED BALANCE SHEET



Again we look at the FED Balance Sheet and not surprisingly it continues to expand. Above we show the two key elements; Treasuries and MBS. What is surprising is the explosive growth of the MBS. It is as if the FED is just soaking up whatever junk is left after five years. The Treasuries are also expanding but at a slower rate as we had shown regarding the lower deficit.

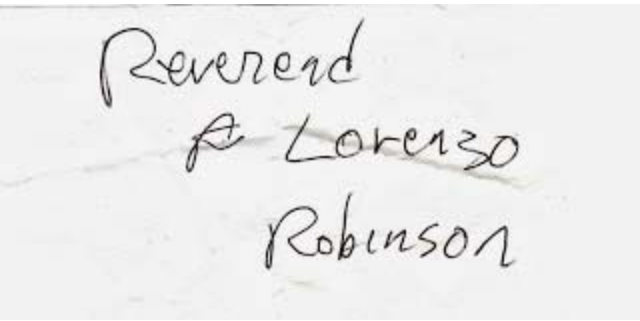


The above shows some more detail. Frankly all other elements are nominal and not significant.

The problem will start with the unloading. The ride down will be worse than the ride up.
Labels: Economy

SATURDAY, NOVEMBER 9, 2013

PASSING OF AN ELEGANT MAN



I have gone to the 21 Club many times over the decades. My great uncle, Bill Dewar, a former Judge in New York, hung out there with a buddy, Henry Miller, his childhood friend from Brooklyn, through the 20s and 30s.

I was last there a year ago last July and I met Lorenzo Robinson again. He passed away recently so I thought I would comment on my experience with him. Lorenzo Robinson was an elegant person[29][1]. He was the men's room attendant at 21, but unlike many other societies we often overlook position and do see the person. It was early, I was there with a longtime friend, my wife and his friend, and my friend had returned to New York to reminisce and we started at the 21.

[29][1] http://www.nytimes.com/2013/11/09/nyregion/an-era-fades-for-help-at-the-washroom-sink.html?hp

I went to the men's room and there was Lorenzo, smile on his face, a warm greeting. It was early so we struck up a conversation. Lorenzo was articulate and we discussed discreetly the humanity he had experienced. I remarked of my history in the 21 Club and he regaled me with his. He was a true gentleman. I often wondered of the many tales hidden in Lorenzo's memory.

You see, there is a class of people, by job not by any human trait, who are often considered by many as invisible, the invisible people. We often do not seem them. They hide in plain sight. They are the men's room attendants, the receptionist, the guard, the secretary, the waiter, the mailman, the UPS guy. We never know their name, we never speak with them.

Yet they may know many secrets in our lives. What conversations happened in front of Lorenzo? What secrets was he privy to? The current discussions on monitoring massive data files is nothing compared to the Lorenzos of the world. They are the smartest and most efficient intelligence gatherers in the universe, yet all too often ignored. Lorenzo know the many strengths and weaknesses of humans. If I were to hire someone I would have used Lorenzo as the final judge, for the true nature of a human is often revealed by how they deal with the invisible people.

It is sad to hear of Lorenzo's passing. He was a wonderful person to listen to and always had a smile. He will be missed. It is also a passing of a generation.

The above note was given to me by Lorenzo a year ago. I found it in a suit pocket just a few weeks ago, about the time of his passing. I had meant to follow up, to bring my grandson in to meet Lorenzo, but alas it is too late. I will have to do just with memories, and this note.

Labels: Commentary

DON'T TOUCH MY DNA!

I read a piece in Healio on what people want regarding their genetic testing. The article states:

Sixty-five percent of respondents indicated that clinicians should be involved in explaining the results of direct-to-consumer genetic testing; 9% desired no clinician involvement and 26% did not offer an opinion.

Fifty-seven percent of respondents believe the federal government should increase funding for genetic research, while 27% said spending should not change and 15% said it should be reduced.

The Genetic Information Nondiscrimination Act of 2008 was deemed "important" by 82% of responders.

Now I suspect that less than 1% of the respondents had any clue about genes and their impact on their health. Furthermore I suspect less than 0.05% had a clue that say methylation played a more

critical role than genes in many cases.

I also suspect, based on my exposure to physicians in daily practice, that very few, less than 10-15% can truly and knowledgeably discuss genetic effects. Take prostate cancer for example, since we really do not know then how do we explain it.

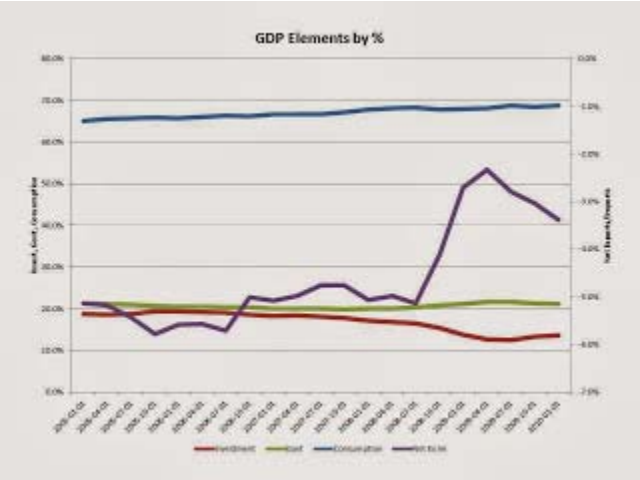
Thus if we increase Federal Funding, then where and why? Now I think NIH and NCI do a super job, but what input can the general public provide.

In general one wonders what data gathering like this is worth.
Labels: Health Care

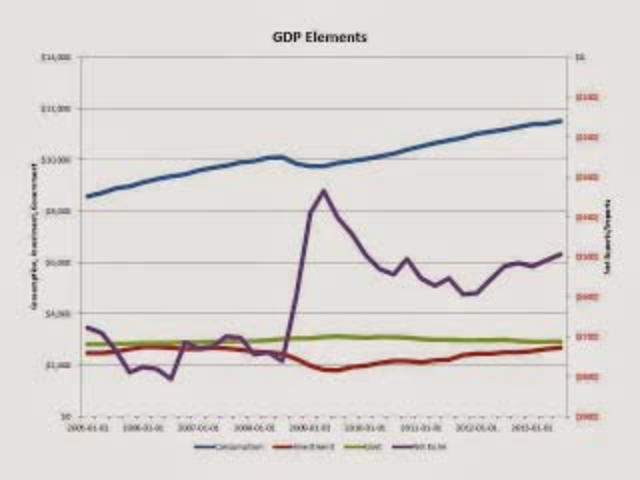
FRIDAY, NOVEMBER 8, 2013

GDP AND EMPLOYMENT

This week we obtained both Q3 GDP data and Employment data. We review them here.



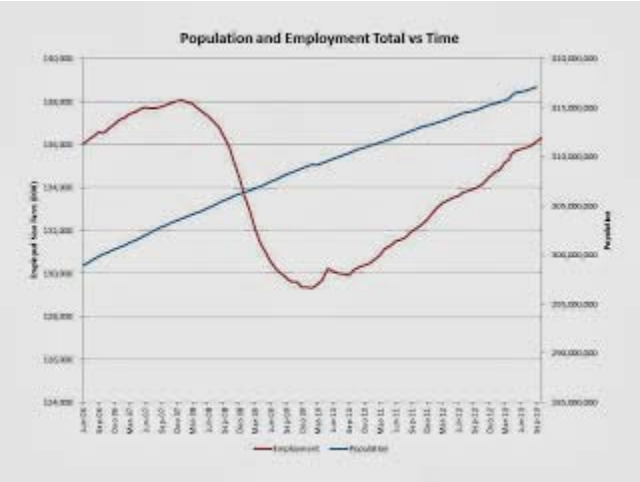
We start with GDP %. Note that consumption is becoming a greater amount as compared to investment. Government spending as a percent seems quite flat.



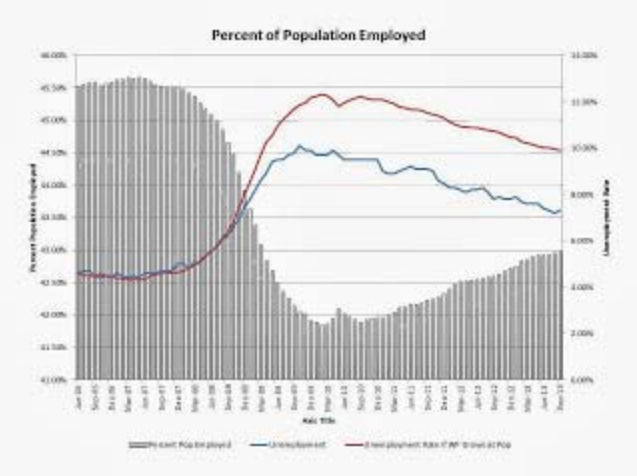
The actual values are above. We can see a rise in consumption which is driving GDP. Government is fixed, with some slow real growth.

Thus there is a strong sense of GDP growth, albeit slow.

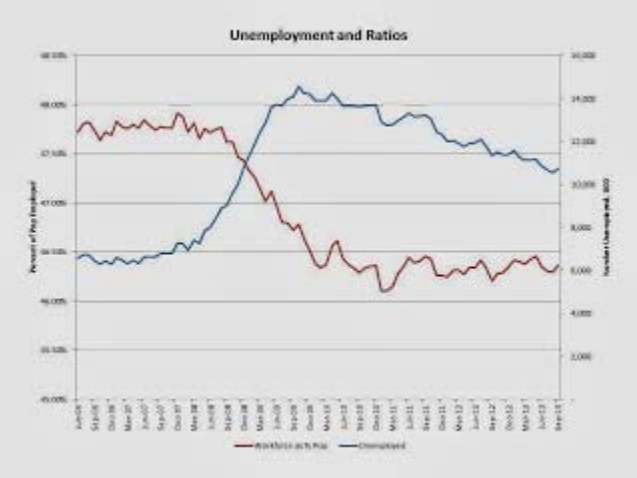
Now for employment. Remember that last month there were no reports.



Above we have employment and population. Frankly it appears that the gap between total employed and the population appears to be closing. Especially when we look back some four years ago.



This also shows the gap improving. But we are still at 43% of the population employed as compared to 45.2% in June 2008. That means that based upon that rate we are still at 10% unemployment not the 7.3% stated by the Government.



The above shows this difference. Employment is not improving as much as it should or could. That is reflected in the GDP changes as well. We do not expect any improvement in the near term until a change in administration.

Labels: Economy

SCIENCE, ACCURACY, HONESTY, AND REPEATABILITY

Science has and most likely be two steps forward and one backward. Purportedly the use of "peer review" was to enable the culling out of wrong results. As I have argued for a while in today's world of open Internet critique, in a non Anonymous manner, allows for improved openness in research publications. Namely publications should be open and subject to criticisms from named people with some form of editing, for keeping things professional and not allowing the Internet type of bantering that is non-productive.

A few recent articles discuss this point. One by Marcus give an reasoned overview of some of the more recent critics. He states:

The half-life of nonsensical findings has decreased enormously, sometimes even to before the paper has officially been published." The wholesale shift in the culture of how scientists think about their craft is at least as significant a meta-story as the replicability crisis itself. But the prophets of doom never let their readers in on this happy secret.

It is absolutely correct for onlookers to call for increased skepticism and clearer thinking in science writing. I've sometimes heard it said, with a certain amount of condescension, that this or that field of science "needs its popularizers." But what science really needs is greater enthusiasm for those people who are willing to invest the time to try to sort the truth from hype and bring that to the public. Academic science does far too little to encourage such voices.

That is there is a tendency by certain "scientists" to seek significant press coverage and all too often it is their desire for such coverage and the weakness of their speculations that give rise to the bad reputations. Replicating results is not what scientists like to do, they like to build on results. It is when they are building on them that at times the foundation may be made of clay or even sand. But it is self correcting. The issue is can we find out about the feet of clay before time is wasted? Good question. But perhaps an open literature would facilitate this.

Horgan makes some remarks on this topic, of which Marcus responded, and he states:

My 1985 investigation of Petrofsky, which I toiled over for months, made my editor so nervous

that he wanted to bury it in the back pages of The Institute; I had to go over his head to persuade the publisher that my article deserved front-page treatment. After the article came out, the IEEE formed a panel to investigate not Petrofsky but me. The panel confirmed the accuracy of my reporting.

Since then, I keep struggling to find the right balance between celebrating and challenging alleged advances in science. After all, I became a science writer because I love science, and so I have tried not to become too cynical and suspicious of researchers. I worry sometimes that I'm becoming a knee-jerk critic. But the lesson I keep learning over and over again is that I am, if anything, not critical enough.

Arguably the biggest meta-story in science over the last few years—and one that caught me by surprise–is that much of the peer-reviewed scientific literature is rotten. A pioneer in exposing this vast problem is the Stanford statistician John Ioannidis, whose blockbuster 2005 paper in PLOS Medicine presented evidence that "most current published research findings are false."

"False" may be a bit too strong and "most" may be a bit exaggerated. Ioannidis states:

Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Ioannidis has an interesting statistical methodology but when facts are taken into account one may still question his results. Thus grabbing headlines is always problematical. Was Watson and Crick wrong? We know that Pauling was just weeks before, his triple helix. Does that make almost everything wrong. It is after open speculation with an expressed thought process and measurements. Yet at time we have true fraud. It seems however to be often caught. The essence of the Ioannidis paper is that upon examining the research results he just claimed them to have less power in their results than claimed or alleged. This does not make it "wrong" as much as a fully disclosed data set which may be stretched a bit too far.

In the Economist recently there was another rant:

The idea that the same experiments always get the same results, no matter who performs them, is one of the cornerstones of science's claim to objective truth. If a systematic campaign of replication does not lead to the same results, then either the original research is flawed (as the replicators claim) or the replications are (as many of the original researchers on priming contend). Either way, something is awry. To err is all too common.

The article continues:

Statisticians have ways to deal with such problems. But most scientists are not statisticians. Victoria Stodden, a statistician at Columbia, speaks for many in her trade when she says that scientists' grasp of statistics has not kept pace with the development of complex mathematical techniques for crunching data. Some scientists use inappropriate techniques because those are the ones they feel comfortable with; others latch on to new ones without understanding their

subtleties. Some just rely on the methods built into their software, even if they don't understand them.

Yes statisticians have evolved their techniques. But beyond that there are even better approaches. I recall in the late 1960s as we developed nonlinear estimation theory that many statisticians had no clue. These same techniques can now be used in genomic networks, will the statisticians reject that also?

The article continues:

The number of retractions has grown tenfold over the past decade. But they still make up no more than 0.2% of the 1.4m papers published annually in scholarly journals. Papers with fundamental flaws often live on. Some may develop a bad reputation among those in the know, who will warn colleagues. But to outsiders they will appear part of the scientific canon. Blame the ref. The idea that there are a lot of uncorrected flaws in published studies may seem hard to square with the fact that almost all of them will have been through peer-review. This sort of scrutiny by disinterested experts—acting out of a sense of professional obligation, rather than for pay—is often said to make the scientific literature particularly reliable. In practice it is poor at detecting many types of error.

Scientific papers are a process. They report results, hopefully correctly and fully. From that statisticians can then complain that not enough data was used. Let that go to the side. When journalists then catch on and push the story even further is where we have the problem. In none of the above papers do we see that problem reflected. Marcus does comment upon his experience but the others defer.

In an Atlantic article the author states:

THOUGH SCIENTISTS AND science journalists are constantly talking up the value of the peer-review process, researchers admit among themselves that biased, erroneous, and even blatantly fraudulent studies easily slip through it. Nature, the grande dame of science journals, stated in a 2006 editorial, "Scientists understand that peer review per se provides only a minimal assurance of quality, and that the public conception of peer review as a stamp of authentication is far from the truth." What's more, the peer-review process often pressures researchers to shy away from striking out in genuinely new directions, and instead to build on the findings of their colleagues (that is, their potential reviewers) in ways that only seem like breakthroughs—as with the exciting-sounding gene linkages (autism genes identified!) and nutritional findings (olive oil lowers blood pressure!) that are really just dubious and conflicting variations on a theme.

Again, the inherent deficiencies of the classic peer review. One should recall that peer review as classically understood is the taking of an article and then sending it to persons who the editor knows and who are assumed to know something. Then the reviewer performs an Anonymous review. It may take months and may even be done by some graduate student as a professional building exercise. Then the author gets a pile of the reviews with comments from unknowns. All too often no one "reviews" the experiment. They just try to see if holds up to what they fell is the way it should be done. If it is something new then most reviewers reject it. Often rejection says it

was done before by someone else but no reference is given. The Editor all too often assumes the reviewer is "without sin". In fact the reviewer may be both clueless and an interested third party. Thus unlike the comment above, peer review may actually be a barrier to entry or a way to justify prior work. This is especially true when they are anonymous.

Thus again, the Internet age allows for expanded review, a continual process, if the formula is correct.

Labels: Academy

HURRICANES, CLIMATE CHANGE AND HISTORY

Let no disaster go to waste has often been the cry of the left. In a recent Science article they state:

Many climate scientists winced earlier this year when a well-meaning nonscientist tried to use extreme weather to argue that global warming is real. "We can choose to believe that Superstorm Sandy, and the most severe drought in decades, and the worst wildfires some states have ever seen were all just a freak coincidence. Or we can choose to believe in the overwhelming judgment of science—and act before it's too late."

That was (the) President ...a in his State of the Union address. The fact is, there is little or no evidence that global warming steered Sandy into New Jersey or made the storm any stronger. And scientists haven't even tried yet to link climate change with particular fires.

Now for those of us who lived through the early 1950s on Staten Island we should well remember the hurricanes which were even worse, twenty feet of water flowing over the shore. Is it s freak coincidence? No it is just a repeat of what happens every fifty years or so. Mother Nature has been doing this again and again. There are even Nor'easters. Storms happen and the causal link with any form of climate change is a true and oftentimes unsubstantiated stretch if not a false fabrication.

The article continues:

In March and September 2012, for example, climate and media researcher ... surveyed more than 1000 Americans. In September, 74% of those polled agreed that "global warming is affecting weather in the United States." That was up by 5% from March, after a summer of record drought, high temperatures, and powerful storms. And substantial majorities said global warming had worsened every one of six recent extreme weather events in the United States—from high temperatures to forest fires to a blustery "derecho."

A survey is NOT the way to do science. One should at least look at the history of the place. They continue:

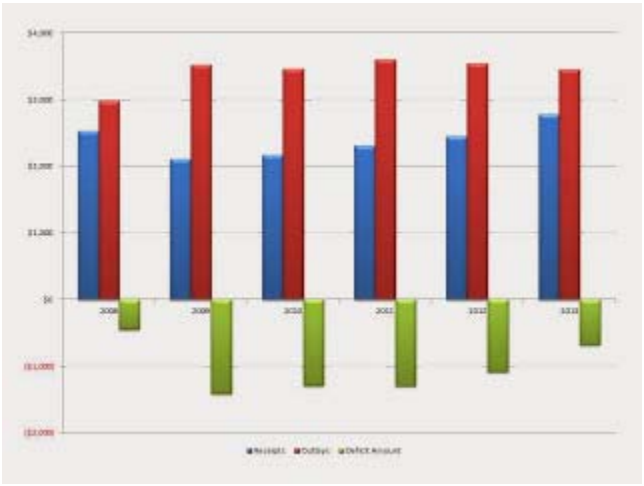
Links between extreme weather and climate change are not only often scientifically suspect, they may also be a risky strategy for persuading the public to take climate change seriously. "What disturbs me is assigning anything that comes along to global warming," says professor emeritus of meteorology John M. Wallace of the University of Washington, Seattle. "That may work in the short run, but I don't think that kind of conversion has staying power." Indeed, surveys coming out on the 1-year anniversary of Hurricane Sandy's landfall (29 October) show the concerns about hurricanes that spiked in the wake of the disaster have nearly faded away.

Fading away is the key problem. On Staten Island they went and totally disregarded history, almost recent history at that. The built a massive Hospital and Mental Health home on the very land that even thirty years ago would be under water in a rainfall. Then they built a road that made the lend a veritable bucket to hold any water flowing in. Namely the water would flow in but since the land was lower than the ocean side street it just stayed there and got higher. Much of the damage on Staten Island was due to building where one should not have done so and the very construction done by the City to expand roads. Global warming was not the problem, it was humans disregarding nature.
Labels: Climate Issues

THURSDAY, NOVEMBER 7, 2013

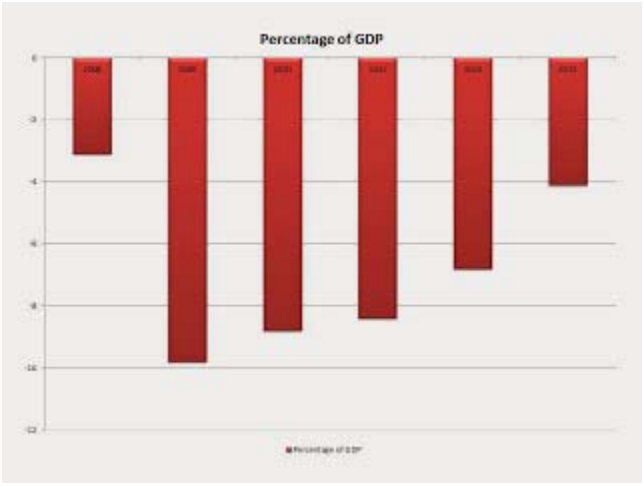
DEFICITS: NOW AND THEN, AND LATER?

The CBO issued a report on the Deficit for Fiscal 2013. We show it below:



We see the reduction and it is still well above 2008 despite the limitations placed upon the Administration.

The percentages are shown below:



These depict the reduction. The problem will be that with the ACA we expect an added $300B of unfunded Health Care expenditures driven by the Medicaid expansion of the ACA. Simply at the added 30 million people at $11,000 per person per year we have the $330 B added costs not covered. One would also expect added costs to those receiving benefits despite the increase in fees. Thus we anticipate an added $450 B in costs due to the ACA as currently structured.
Labels: Economy

THURSDAY, NOVEMBER 7, 2013

QUALITY: ILLUSIONS IN HEALTH CARE

Quality was a key element in the ACA and when it was being bantered about I expressed significant concern. Mainly because it is illusive. No one can define or measure quality. I wrote extensively about it in mid 2009 as the ACA was raising its evil head. I then detailed it in my Health Care book in 2010. Thus when I see articles now regarding the ACA I am not surprised about anything.

One paper in NEJM states[30][1]:

... the Affordable Care Act (ACA) created the "value-based payment modifier," or "value modifier," a pay-for-performance approach for physicians who actively participate in Medicare. By 2017, physicians will be rewarded or penalized on the basis of the relative calculated value of the care they provide to Medicare beneficiaries….

The value modifier is meant to provide differential payment to a physician or physician group under the Medicare Physician Fee Schedule on the basis of the quality of care furnished as compared with the cost; it will result in a reward or penalty amounting to 1 to 2% of payments for groups of 100 physicians or more in 2015 and for all physicians by January 1, 2017. CMS anticipates increasing the percentage of payments at risk as positive experience accrues. To reduce the burden on physicians, CMS has based the value modifier on the Physician Quality Reporting System (PQRS).

As usual the problem is the term quality, or worse the value of care. Quality is the term which drove the main character in Zen and the Art of Motorcycle Maintenance stark raving mad. Value on the other hand should have a quantitative measure, but in the context of the CMS one will wonder. But here we have a confluence of Quality and Value, as in the last sentence, thus the creation of a true schizophrenia.

The author then states:

The challenge of accurately assigning costs to an individual physician is similarly daunting. Current methods for case-mix adjustment do not adequately capture variations in patients' illness severity, complicating coexisting conditions, or relevant socioeconomic differences — differences beyond the physician's control that affect the cost of care. And we currently don't know how to attribute to an individual physician the costs that Medicare beneficiaries generate across the health care system.

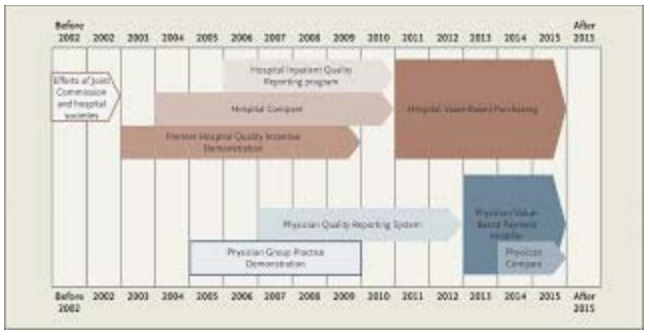
The observation is spot on. As the authors state in their opening:

[30][1] http://www.nejm.org/doi/full/10.1056/NEJMp1312287?query=featured_home

the practical reality is that the Centers for Medicare and Medicaid Services (CMS), despite heroic efforts, cannot accurately measure any physician's overall value, now or in the foreseeable future. Instead of helping to establish a central role for performance measurement in holding providers more accountable for the care they provide and in informing quality- and safety-improvement projects, this policy overreach could undermine the quest for higher-value health care. Yet the medical profession has been remarkably quiet as this flawed approach proceeds.

That is absolutely correct. Not only cannot they measure an individual physician's value they cannot do so with quality, and even more so.

In contrast there was a second NEJM article praising this program[31][2]. They praise the ACA and CMS and its efforts as demonstrated by the chart below from the article.



(Note: The above is from this article and demonstrates *"Medicare's Quality-Incentive Programs Leading up to Hospital Value-Based Purchasing, as Compared with Those before the Launch of the Physician Value-Based Payment Modifier."*)

They state:

The PVBM reward formula is a simple, relative system in which performance is assessed in two dimensions (quality and cost), with payments accruing to physicians who have above-average performance along both dimensions. Physicians who perform worse than average or choose not to be involved will be paid less; physicians with average performance will experience no change. The maximum bonus is about 2% of Medicare fees, and the maximum penalty is approximately 1%. For CMS, scoring physicians relative to one another achieves budget neutrality. For physicians, it eliminates the effects of common shocks to performance, such as an influenza epidemic or vaccine shortage. The key disadvantage of this incentive structure is the inherent uncertainty for physicians about the amount of improvement that will be necessary to receive a bonus or avoid a penalty.

How does one make such a comparison? For example, an Internist and an upscale area versus a poor community GP, what is there to compare.

[31][2] http://www.nejm.org/doi/full/10.1056/NEJMp1311957?query=featured_home

They continue:

The lack of experience with physician-level measurement and reporting has important implications for the PVBM. First, far greater numbers of physicians will need to become engaged in reporting of quality and cost performance. This challenge should not be underestimated: there are nearly 150 times as many physicians who bill Medicare as there are hospitals, the physician population includes physicians of all types (primary medical, surgical, and subspecialists), and many of these physicians work in a wide array of smaller practices that are still acquiring the basic infrastructure (e.g., health information technology) or organizational affiliations (e.g., independent practice associations) needed to measure and improve the quality and cost of care.

We have asked physicians to expand record keeping, billing, Electronic Health Care Records, and no we demand they measure quality. Re-read Zen and the Art of Motorcycle Maintenance, quality measurement and definition will drive one insane! What will happen are more costs related to gaming the system.

One area that could improve health care would be balancing patient expectations with outcomes. All too often the patient's dissatisfaction is based upon an outcome that they were not expecting because they were not informed. Questionnaires which measure patient psychographics as well as other factors and them assist them in matching treatments, holistically, may help. But that is delimited by not including family expectations. For example for a man with prostate cancer there may be several options. How would we best treat that patient? It would be critical to understand his psychographic profile. That all too often is not done. Then on a post basis we verify that the proper choice is made and we can create a good Bayesian methodology to maximize patient satisfaction, namely they had no surprises.

Thus quality and value are just more terms that confuse rather than enlighten. To paraphrase Osler, "If all else fails listen to the patient."

Labels: Health Care

THOU DOTH PROTEST TOO MUCH

Whenever one sees a person protesting a bit too much one should become suspect. Take the recent protestations of a Noble winner in Economics, that field of philosophy which deals with the rather obtuse interconnections of data from the economies of various countries.

His protestations state:

Critics of "economic sciences" sometimes refer to the development of a "pseudoscience" of economics, arguing that it uses the trappings of science, like dense mathematics, but only for show. For example, in his 2004 book Fooled by Randomness, Nassim Nicholas Taleb said of economic sciences: "You can disguise charlatanism under the weight of equations, and nobody can catch you since there is no such thing as a controlled experiment."

Economics as we currently see it is half political philosophy, there really is no political science unless one tries to include the polling of putative voters, and half data gathering. The philosophy and data gathering are all too often layered upon by pseud mathematical justifications. This does not make it a science.

He then states:

But physics is not without such critics, too. In his 2004 book The Trouble with Physics: The Rise of String Theory, The Fall of a Science, and What Comes Next, Lee Smolin reproached the physics profession for being seduced by beautiful and elegant theories (notably string theory) rather than those that can be tested by experimentation. Similarly, in his 2007 book Not Even Wrong: The Failure of String Theory and the Search for Unity in Physical Law, Peter Woit accused physicists of much the same sin as mathematical economists are said to commit.

But this is theoretical physics. After all when Einstein proposed his theory of relativity it took more than a decade to demonstrate it. It was theoretical but it could be proven and was. One could do an experiment and the experiment could be repeated and the results were the same. Try that one in economics.

He continues:

But all the mathematics in economics is not, as Taleb suggests, charlatanism. Economics has an important quantitative side, which cannot be escaped. The challenge has been to combine its mathematical insights with the kinds of adjustments that are needed to make its models fit the economy's irreducibly human element.

Mathematics in science is done to do predictive tasks. Like how heavy will a tower of water be and how strong must the beams be to support it. Economics cannot do anything of that simple tasks with any of its mathematics.

Thus the attempt to call is science fails on the most critical point, ability to predict. It is not a science but a philosophy, like political philosophy. Let's stop trying to put lipstick on the pig!
Labels: Economics

MONDAY, NOVEMBER 4, 2013

THE ACA: MANAGEMENT AND IMPLEMENTATION

I started the Blog some five years ago initially to examine the collapse of any pretense that economics has a scientific basis and then moved to Health Care as the current Administration started up the ACA project. I was one of the few who read every word of every bill and commented on the disaster that would result. Some even noted the comments. Let my words stand for what is to come next.

The ACA has several major flaws:

1. The implementation of the sign on was developed by incompetent individuals. No incompetent in all, best as I know, they are after Harvard educated, but incompetent in ever having managed and delivered a project such as this.

The Cutler letter to Summers published by the Washington Post shows this was known even in the inner circles. As stated in the letter:

A good deal of reform implementation needs to occur at the Centers for Medicare and Medicaid Services (CMS). You were dealt a bad hand here. The agency is demoralized, the best people have left, IT services are antiquated, and there are fewer employees than in 1981, despite a much larger burden. Nevertheless, you have not improved the situation. The nominee to head that agency, Don Berwick has never run a provider organization or insurance company, or dealt with Medicare or Medicaid reimbursement. On basic issues such as the transition from fee-for-service payment to value-based payment, Don knows relatively little.

Little is an understatement. He is a pediatrician but even more so an academic. Remember he also pushed the EHR which is now bumbling around failing to achieve anything. Also look at my writings here as well.

The letter continues:

Above the operational level, the process is also broken. The overall head of implementation inside HHS, Jeanne Lambrew, is known for her knowledge of Congress, her commitment to the poor, and her mistrust of insurance companies. She is not known for operational ability, knowledge of delivery systems, or facilitating widespread change. Thus, it is not surprising that delivery system reform, provider outreach, and exchange administration are receiving little attention. Further, the fact that Jeanne and people like her cannot get along with other people in the Administration means that the opportunities for collaborative engagement are limited, areas of great importance are not addressed, and valuable problem solving time is wasted on internal fights.

She is a Harvard educated attorney with a history degree and never managed a single thing! No wonder we have a disaster. Also note she got promoted.

The Cutler memo is most telling on the fact that it was known internally that a disaster was coming.

2. Panels are planned to control almost everything focusing on what they consider to the evidence based research. The problem here is that those judging the evidence are all too often just political appointees as the above with little understanding of the specifics of the problem at hand. I would not want a dermatologist to deliver a baby. They may have done so in Med School a few times to get their card punched but other than in a real emergency would I seek their assistance. Likewise the many other panels will be disasters in the waiting.

3. Payments will be the next shoe to drop. The only way to keep "costs" down is to reduce payments. That will drive out competent folks and drive in marginal at best. This will result in a lowering the standards and the mass admittance of third world trained physicians.

The list of problems goes on.
Labels: Health Care

SATURDAY, NOVEMBER 2, 2013

MAE EUROPE AND THE CHANGE IN THE INTERNET

In 2001 I visited several PTTs in Central and Eastern Europe and proposed what I termed MAE Europe. At that time all Internet traffic peered back in the US at MAE East and West and we all knew who was looking at all that traffic. By that time we also knew that it was necessary to have alternative peering just for traffic load balancing. I suggested in the paper:

This paper presents a review of the alternatives for Internet access in Central Europe and the evolution of the market, the regulation, and the technology. The change in peering, the reduction in transport costs, the reduction in transit costs have dramatically changed the overall supply side of the market for Internet services in Central Europe. This paper assess the current market and how these regulat ory and technological changes are accelerating the demand side as well and how such alternative paradigms for interconnection may impact other regional markets.

I held talks with Telcom Austria, Czech Telecom, France Telecom and TPSA, the Polish PTT. No one really understood the total implications. They all trusted the US to do the right thing.

Shortly thereafter I wrote a paper regarding Privacy and the Internet. Therein I stated:

Privacy is a complex issue and the Internet takes this issue and compounds it in many ways. In this paper we take the issue of privacy, examine it in terms of current laws, US and European, and then examine the impact of the Internet on the broadly defined issue of privacy. This paper evaluates the various definitions of privacy and at the same time examines how the Internet presents both a threat to these "rights" and an opportunity to expand these rights and to sustain them in a global economy and environment of living.

In a recent Guardian piece they state:

The vast scale of online surveillance revealed by ..... is leading to the breakup of the internet as countries scramble to protect private or commercially sensitive emails and phone records from UK and US security services, according to experts and academics. They say moves by countries, such as Brazil and Germany, to encourage regional online traffic to be routed locally rather than through the US are likely to be the first steps in a fundamental shift in the way the internet works. The change could potentially hinder economic growth. "States may have few other options than to follow in Brazil's path," said Ian Brown, from the Oxford Internet Institute. "This would be expensive, and likely to reduce the rapid rate of innovation that has driven the development of the internet to date ... But if states cannot trust that their citizens' personal data – as well as sensitive commercial and government information – will not otherwise be swept up in giant surveillance operations, this may be a price they are willing to pay."

It need not break up. The suggestion of more than a decade still stands as does the privacy stand. It is a shame that it has taken an even like this to bring these issues to the fore. Alternatives exist. Openness is key and movement from a US based system is essential.

Ironically it was at the same time I was Vice Chair of the Internet 2 Presidential Commission and our report, despite my efforts, did not deal with any of these issues. Ironically the Chair is currently the Chair at Google. Trying to get issues like this through early on were fruitless. Now there seems to be an audience for them, hopefully.
Labels: Internet, Politics, Privacy

GETTING A JOB

The NY Times had a piece on the unemployment amongst PhDs. Frankly if one gets a PhD in Celtic languages one should assume that it would be difficult to support oneself with such a degree. In fact even English would be tough. A PhD in EE, Computer Sci, Chem E, Civil Engineering should be no problem. Some one wants those talents. Early Medieval History is not a the top of the current job lists.

The questions posed are threefold:

1. Who should take these degrees?

2. What is the duty of the Academy?

3. What is the responsibility of the student?

Frankly one should start with the first. Rather than asking a teenager what he wants to do when he/she grows up the proper question is what are you going to do to support yourself! That seems to be a missing question. If the student provides an answer of Celtic languages, then wish them well and send them packing. That is not a sane employment choice.

The Times states:

According to a 2011 National Science Foundation survey, 35 percent of doctorate recipients — and 43 percent of those in the humanities — had no commitment for employment at the time of completion. Fewer than half of Ph.D.'s are expected to land tenure-track jobs. And many voluntarily choose another path because they want higher pay or more direct engagement with the world than monographs and tenure committees seem to allow. Though graduates have faced similar conditions for decades, the past few years have seen a surge in efforts to connect Ph.D.'s with gratifying employment outside academia and even to rethink the purpose of doctoral education.

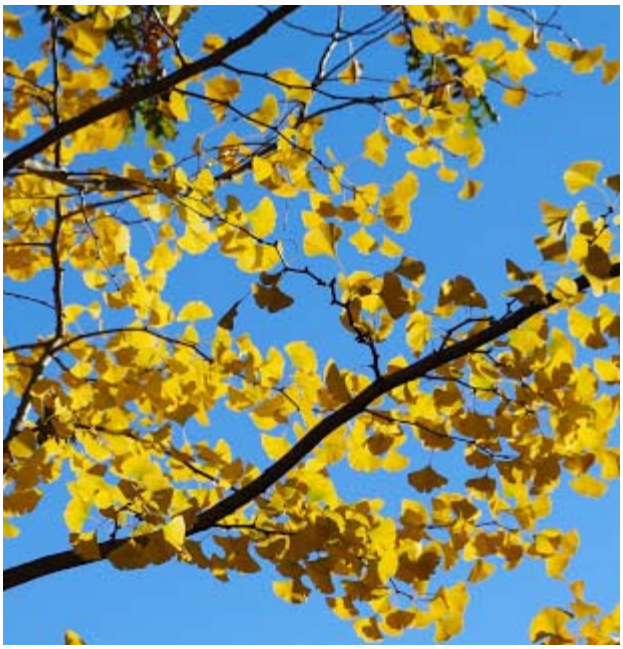
One should be surprised that employment is even that high. Now to the other two questions.

Who should take such degrees? Well if you are independently wealth and have no idea what to do with the money then go do whatever you want. But if the student is from middle class or lower class America then they have a responsibility to get a job, not be educated. Get a job, make money, and then get educated. That works. But adding tons of student debt does not.

As for the last question, the duty of the Academy, well they have left that behind ages ago. After all the Government provides the money so why do they care.

Thus a PhD is a step worth the effort, assuming one is even qualified, if and only if it leads to employment. No job, why waste the time.
Labels: Academy, Economy

THE WONDERFUL GINKGO



The recent book, Ginkgo, by Peter Crane is an exceptionally well written tale about a tree. Not just any tree, but one of the longest surviving species around. This tale covers the history of its discovery, the people involved, the biology of the tree, and it discusses the trees interaction with man from both the Eastern and Western perspective.

If you have never met a ginkgo, then you are in for a surprise. Just walk down any street in Manhattan and I would bet there are a half a dozen or more around. They are indestructible and live upon the urban exhaust from cars and trucks. They can survive quite well in most temperate environments, just add CO2, water and sunlight. Not too cold and not too hot and they take off.

I have been growing ginkgoes from seed for a couple of decades. Each tree is different and one grows three feet a year. After twenty years it is over sixty feet tall. It gets abundant water sitting

on the edge of a daylily garden. Others are slow growers, just a few inches. Yet they all have the distinctive leaf, and in the fall the distinctive golden yellow leaf, and then they all drop on the same day. It is a wonderful orchestrated act of nature.

Crane goes through this tree and uses it to tell many tales. Tales of paleobotany and the paleobotanists. People who look for plants in the rocks from millions of years ago. Then he explores the biology of the ginkgo. It is a plant which has male and female versions, and both are often necessary for reproduction. The seed is coveted as an edible treat whereas the seed covering is quite distasteful.

Also Crane discusses the evolutionary placement amongst on the one hand ferns and on the other hand conifers. Ginkgoes are gymnosperms, naked seeds, unlike what we have in flowering plants. Yet in many ways Crane argues they have a linkage to ferns as well.

Crane takes the reader on a journey from discovery, through understanding and ultimately to uses. Ginkgo is used for decorative purposes, it is used as a medication, and its wood has value in such areas as fine wood art.

Crane leaves the reader off with a broad discussion of the survival of species. Ginkgo is an example of a species which had dwindled down but as a result of man's attraction to the plant has thrived. They have gone everywhere. A sort of Intelligent Survival to play on words. Crane speaks of the good and the less good in the area of survival, with his discussion of treaties which meaning well have deteriorated to protection of national interests that often do not benefit the species.

The book is exceptionally well written and is accessible to the general reader. For those who may know a bit more this is not a significant step forward. It is obviously a book for the general public and as such serves that purpose masterfully. Having a bit more knowledge I kept asking for more, but alas that was not the purpose of the work.

For example, color photographs would have been helpful, albeit costly. Also a better discussion of the reproductive cycle of the ginkgo would be helpful with some useful graphics. It is so unique that it is truly worth the effort. Yet the uniqueness presupposes that the reader understand basic embryology, alas not met by many a reader. Finally the genetic analysis would have been enlightening. The placement of the Ginkgo is some form of evolutionary tree based upon DNA analysis would have been exceptionally well received. That I believe is not asking too much since most High School students have some knowledge there.

Overall I strongly recommend this book to anyone interested in plants, their evolution, association with mankind and their preservation. Ginkgoes may very well help mankind through dramatic climate changes since they managed many over their 200 million year lifetime.
Labels: Books

MONDAY, OCTOBER 28, 2013

SINGLE PAYER: REALISTIC OR JUST POLITICS?

There has been a growing push from the left wing to do a single payer system because of the complexity of implementing the ACA. There are obvious reasons why any Government attempt will be flawed, especially if the Government tries to do anything leading edge. Just look at DoD, it takes dozens of tries before anything gets done. In addition in DoD, just take a destroyer or a Littoral craft, they thrown everything including the kitchen sink into the design. In WW II we could build a destroyer in months, now it takes a decade. Why? Because everyone gets a chance to add and change. The cost is irrelevant.

Now the Princeton Professor has a piece arguing that as a result of the fiasco we should really do a single payer. He states:

Imagine, now, a much simpler system in which the government just pays your major medical expenses. In this hypothetical system you wouldn't have to shop for insurance, nor would you have to provide lots of personal details. The government would be your insurer, and you'd be covered automatically by virtue of being an American.

Now is this the easiest and best way? Well it depends. A little more than four years ago I wrote a piece on how Health Care could be delivered to all using subsidies but via a private mechanism. Just like home, car, life insurance. It works, and often times better than any Government plan. Just look at Flood Insurance, the Government stalls and stalls just due to Government's inherent incompetence.

Now what are the benefits of Private insurance? Simple:

1. It already exists.

2. It is competitive and can be made more so.

3. It allows choice.

4. It is the negotiator for the buyer.

Now when I proposed such a plan I did so making a few changes:

1. The individual was responsible for their own insurance. No company or union paid plans. Also I would not allow a tax deduction. By the way, that is how Medicare works. It is the individual's plan, it is after tax dollars and you still pay even after you retire, often a high amount depending on your income.

2. The plan should really be for catastrophic coverage, not for oil changes. If some one wants a "oil change" plan so be it but they pay. It is not required. The biggest problem with the ACA is its demands for so extensive a coverage plan. For example, take a PSA test, one should not have to have that included but if you want one then you may pay out of pocket. Birth control, and

many other life style choices should remain that way, individual choice and payment.

3. Penalties for life style based disease should be present and allowed. Thus for smokers, obese individuals, drug users, etc the prices should reflect the risks they have assumed. The same is true for life and auto insurance. If one has dozens of speeding tickets then the premium should and frankly must reflect the higher personal risk.

I then worked through the financial details. It worked! The Gnome from the South does not present any such plan or details. He suggest we just put it all on the Government tab.

Individual choice and responsibility is a core to our society. If we agglomerate everything to the Government we create a Collapse of the Commons syndrome, no personal choice or responsibility and abuse of the system. Frankly the explosive expansion of Food Stamps is a clear example. Childhood obesity is much more of a problem than starvation. I would argue that the obesity problem is a Collapse of the Commons.

As the Professor concludes:

In saying this I don't mean to excuse the officials and contractors who made such a mess of health reform's first month. Nor, on the other side, am I suggesting that health reform should have waited until the political system was ready for single-payer. For now, the priority is to get this kludge working, and once that's done, America will become a better place.

In the longer run, however, we have to tackle that ideology. A society committed to the notion that government is always bad will have bad government. And it doesn't have to be that way.

There is no proof that America will be a better place. There is no evidence that a single payer is the better system. One can envision many deleterious "unintended consequences" from a single payer. It is a monopsony, with the Government as the single buyer, and the single arbiter, a rather off-putting thought.

Finally one should remember the two prime elements of Marxist dogma; centralized control and planning, and Government (in Lenin's view the Party) control over all. Namely for any good Marxist there is a belief in the ultimate a predictable movement of society and the beneficial and necessary need for central planning by the select few. Sound familiar? One should read Asimov, Foundation Trilogy, the Gnome's idol.
Labels: Health Care

SUNDAY, OCTOBER 27, 2013

ECONOMICS AGAIN

The Noble Prize in Economics, it is not really a real Noble Prize but let's not split hairs, went to two opposing schools of thought. One of those schools went about telling everyone they could why they were right and the other fellow was wrong. Today's NY Times presents one of the arguments.

The author, one of the "Winners" states:

Actually, I do not completely oppose the efficient-markets theory. I have been calling it a half-truth. If the theory said nothing more than that it is unlikely that the average amateur investor can get rich quickly by trading in the markets based on publicly available information, the theory would be spot on. I personally believe this, and in my own investing I have avoided trading too much, and have a high level of skepticism about investing tips.

But the theory is commonly thought, at least by enthusiasts, to imply much more. Notably, it has been argued that regular movements in the markets reflect a wisdom that transcends the best understanding of even the top professionals, and that it is hopeless for an ordinary mortal, even with a lifetime of work and preparation, to question pricing. Market prices are esteemed as if they were oracles.

This view grew to dominate much professional thinking in economics, and its implications are dangerous. It is a substantial reason for the economic crisis we have been stuck in for the past five years, for it led authorities in the United States and elsewhere to be complacent about asset mispricing, about growing leverage in financial markets and about the instability of the global system. In fact, markets are not perfect, and really need regulation, much more than Professor Fama's theories would allow.

Point well taken, indeed there is all too often insider information, timing variances and technological leverage, and finally cost leverage. High speed trading is a way to beat the market, a way that actually drives values of equities, not just responds to them. The price may reflect many things, the last trade, the latest financial release, the health of the president. It may reflect the past, present and future. Furthermore it may reflect guesses and hopes.

I wrote a piece on the Rowe Conjecture a few years ago. This was a conjecture by Nick Rowe where he speculated the idea that perhaps the real world oscillates between reality and assumption. Rowe is one of the more realistic of economists, often rationally questioning assumptions and not just pontificating on high. Rowe often brings a sense of the common to economics.

Now to refresh on the Rowe Conjecture. We can assume that the EFH, efficient market hypothesis, actually is in play or not, and likewise we can oscillate between what people think, that it works or not. The result as I demonstrated using a simple analysis is an oscillating market of highs and lows all do to what people think and what reality is doing. This is kind of balancing the views of the two contestants in the economics war of words, which seems to be just one sided now.

But last week the Times had a piece by some Harvard economist alleging that fundamentally Economics was a science. The author states:

It is true that the answers to many "big picture" macroeconomic questions — like the causes of recessions or the determinants of growth — remain elusive. But in this respect, the challenges faced by economists are no different from those encountered in medicine and public health.

Health researchers have worked for more than a century to understand the "big picture" questions of how diet and lifestyle affect health and aging, yet they still do not have a full scientific understanding of these connections. Some studies tell us to consume more coffee, wine and chocolate; others recommend the opposite. But few people would argue that medicine should not be approached as a science or that doctors should not make decisions based on the best available evidence.

As is the case with epidemiologists, the fundamental challenge faced by economists — and a root cause of many disagreements in the field — is our limited ability to run experiments. If we could randomize policy decisions and then observe what happens to the economy and people's lives, we would be able to get a precise understanding of how the economy works and how to improve policy. But the practical and ethical costs of such experiments preclude this sort of approach. (Surely we don't want to create more financial crises just to understand how they work.)

Yes, go pick on medicine. They are just a bunch of "witch doctors". Or as the author appears to argue they are just like economics. Not really.

Consider Biology; in the first half of the 20th century it was slowly moving from a study of classifying "stuff". After all Jim Watson was originally an ornithologist, a studier of birds. But in the early 1950s Biology went from something akin to economics, a collector of data, and a proposer of relationships, to a real science. DNA made that possible. Now regarding science we have the ability to predict and then test our predictions. We now know that BRAF V600 is a gene which enables melanoma to aggressively metastasize. We know where it is in the internal pathway of the cell and we can, understanding the structure of the gene, deliver a therapeutic to block it and stop the growth. We also know that MEK can then become aberrant and we have a way to block it. We have a road map, we can make predictions, we can design a therapeutic, and it works, every time. Can any economist say that? No way. So the author of the above piece, Harvard not withstanding, has somehow missed what has happened to medicine. It is now truly a science.

Economics is where plant classification was in the 19th century, at best. One collects data, looks at relationships, and perhaps fins a new species. One cannot not predict what will happen. Medicine can, everything that is a science can. The introduction of imatinib for CML, a kinase inhibitor, was the first break out point for medicine in such a new world. There is no such example for macroeconomists.

Consider one of the final statements:

Using a data set with anonymous records on 2.5 million students, we found that high-quality teachers significantly improved their students' performance on standardized tests and, more important, increased their earnings and college attendance rates, and reduced their risk of teenage pregnancy. These findings — which have since been replicated in other school districts — provide policy makers with guidance on how to measure and improve teacher quality.

In my opinion this is an ad hoc propiter hoc argument. Bad teachers are just that, bad. I had a few, so what does one do, find a way to work around them. No, not every student can do that, but it does challenge the good students to actually get better.

Overall, economics is at best two things; (i) the collection of data and its analysis, and, (ii) the proposal of political views oftentimes using ersatz mathematics. Mathematics for building a bridge is good mathematics. Mathematics for proposing a social policy is "shingling the roof in the fog".
Labels: Economics

TUESDAY, OCTOBER 22, 2013

WOULD YOU BUY A CAR FROM THESE PEOPLE?

Now I do not think a great deal about economists and their "science". But the CEA, the Administrations economic mouthpiece, remember Romer and her "scientific" predictions, have now analyzed the closing of the Government.

They state:

A number of private sector analyses have estimated that the shutdown reduced the annualized growth rate of GDP in the fourth quarter by anywhere from 0.2 percentage point (as estimated by JP Morgan) to 0.6 percentage point (as estimated by Standard and Poor's), with intermediate estimates of 0.2 percentage point and 0.5 percentage point from Macroeconomic Advisers and Goldman Sachs respectively. Most of the private sector analyses are based on models that predict the impact of the shutdown based on the reduction in government services over that period. Very few of them are based on an actual analysis of economic performance during the period of the shutdown and very few take into account the secondary effects on the private sector of the cessation of government services or the effects on confidence and uncertainty associated with both the shutdown and the debt limit brinksmanship. But we know that these effects can be large; for example, the debt limit brinksmanship in the summer of 2011 had an adverse economic impact even though it was not accompanied by a shutdown nor did it lead to an actual default on U.S. government obligations. While useful in understanding the costs of the shutdown and brinksmanship, the available private-sector analyses present only part of the picture.

This report attempts to estimate the actual impact of the shutdown and default brinksmanship on economic activity as measured by eight different daily or weekly economic indicators. Overall it finds that a range of eight economic indicators combined in what this report calls a "Weekly Economic Index" are consistent with a 0.25 percentage point reduction in the annualized GDP growth rate in the fourth quarter and a reduction of about 120,000 private-sector jobs in the first two weeks of October (estimates use indicators available through October 12th.)

Assuming anything in the above is even close to true, remember we have one of those rating agencies who got us in this mess it is alleged, and an bank receiving near free money from the FED, one could ask as Congress pays for non working hours will that pop up the numbers again?

Also are we just measuring noise at this level of granularity?

Labels: Government

SOFTWARE: MAKING IT WORK

First, there is a law of Nature that is immutable: Government never makes any software work the first time, or the second, or the third. The Corollary is that any Government software projects take five time longer and costs ten times as much as any commercial project.

Thus the obvious collapse of the ACA sites is hardly unexpected. Add to that a Canadian company with I gather a less than exemplary record and what would one expect. Now I started programming in 1962, a while ago, and worked on a few projects over the years. They all had their problems. But they all went through independent validation and verification, IVV. That way we knew if they dd what we expected them to before they were released. Also they were incremental.

Thus when I see people who apparently have had no experience opining on the topic I just am not surprised that they do so, after all they apparently have been doing it all their lives. Now an example is in the Times today:

What went wrong? My diagnosis is that there were three big mistakes.First, the ... administration acted too slowly. It waited too long to release specific regulations and guidance on how the exchange would work. It also waited too long to begin building the physical Web site. These delays were largely because the administration wanted to avoid election-year controversy.

Yes, but. Was there an architecture, architect. Did they get the best people or was it purely a political mess. I suspect the latter. So what have we changed to eliminate this factor? Nothing. Just a new political player.

Second, the ostensible quarterback of the federal health care exchanges, with responsibility for integrating all the various components, is the Centers for Medicare and Medicaid Services. While the agency has expertise in issuing reimbursement rules and overseeing large-scale claims-processing operations, it has little expertise in creating a complex e-commerce Web site.

First this is not a Web Site. This is a transaction processing system interconnected to other existing systems with a front end web page which is tertiary at best. Also good web design means simple not one filled with useless pictures. Look at Google. Simple. Form follow function and having smiling people does not reflect function, especially if it does not work.

Finally, this was not the first health insurance exchange ever created. Massachusetts has had years of experience with its exchange, and there are private exchanges, like eHealth, where individuals can shop for insurance. In addition, many states, like California, Connecticut and Kentucky, had already spent around two years building their exchanges, gaining experience and proving it was possible to create a good customer shopping experience. It does not appear that the Centers for Medicare and Medicaid Services or its contractors spent much time reviewing these models and adopting best practices.

And by the way CMS will be the same set of humanitarians controlling people's lives. Yes there

are many functioning sites, even the Government has its own for employee registration every year. Why not just expand that? Because they wanted total control to reflect their own agenda.

So what would one do in the commercial world? Fire the management, get people who can do the job, and reward success and punish failure. And get the Government out of the way. But alas it will go in the other direction.

So despite what the author of the above suggests it will not happen.
Labels: Government

MONDAY, OCTOBER 14, 2013

THE FRENCH MIND, THE FRENCH SOUL

The book by Carroll, Brave Genius, is a wonderfully and lucidly crafted exposition of two major French figures at mid twentieth century; Camus and Monod. In CP Snow's book, The Two Cultures, written about the same time of these events of the book which bemoans the gap between the cultural intellectual and the scientist. This book clearly belies that tale.

This is a tale of two men, from and in different walks of life in their day "jobs" and yet drawn to a common theme by the invasion and capture of France in the early 1940s (1940-1944). It tells the tale of each of them, their divergent lives and the convergence of common interests. It is, in many ways, a uniquely French tale of intellect, action, culture and friendships.

Monod is the biologist, seen first as a student seeking, albeit slowly, what to focus on. Monod clearly has little personal angst due to his coming from a solid middle class family, his mother even being American. He is a multi-talented young man, married to a Jewish woman. Camus on the other hand is from Algeria, from near poverty, but educated and with the intents of being a writer. His early work is marginally accepted yet he continues to extol the ideas of what was to become broadly speaking, the Existential School.

Camus is well known for his works such as The Plague and the Myth of Sisyphus; Monod, for explaining the details of DNA to protein synthesis. Monod complemented the work of Watson

and Crick, it let those of us in the late 50s and early 60s to say; oh, that is how it works. Camus also framed the challenge of life for many in the same period, as a clear voice for those seeking the meaning of existence, and also as a strong counter voice to Sartre.

This book throws these two together, not in an artificial way, but as a telling of the factual interaction of what would become two Nobel Prize winners; Camus for Literature and Monod for Medicine and Physiology.

The book starts before the War and its main discussion is during the War itself and the actions of Camus on the underground paper Combat and Monod as a significant participant in the underground. The book details their exploits, of frustrating the Germans and of their cat and mouse games of avoiding being identified or capture. Monod is a most interesting character since at one time he is trying to pursue his research career while at the same time he is rapidly moving up in the Resistance hierarchy. Camus, still hindered by his Tuberculosis, manages to continually get his underground newspaper out which is an ongoing assault to the Germans. Both Monod and Camus have by this time interacted but their lives are each dominated by their goal to defeat the Germans by deed or word.

The book does discuss the significant ambivalence of many of the French during the occupation. Many just wanted to allow the Germans to occupy them and not make things worse. In effect whether in Occupied France or in Vichy the attitude was that they would like to have things as "normal" as possible. In contrast it was truly a small band of quite brave resistors like Camus and Monod who took a stand which not only placed them at odds with the German occupiers but also with many of their French compatriots. The book does tell the tale of the German opposition side but could have somewhat better explored the dissonance in the French people at large. For it was the latter that often created the greatest risks?

The last part of the book concerns the two of them and the post War life and politics in France. French intellectuals of many types were often Socialists and Communists. That included Camus and Monod. But the challenge came when the Stalin and his extreme treatment of the people and truth became common knowledge. For Monod it was Lysenko and the Stalinist theory of genetics.

For Monod this was a breaking point and he took a public stand and denounced Lysenko and by default Russian Communism. For that he received the reprobation of the French Communists. For example on p. 279 the author states: "…The fundamental flaw in Mendel's … and other Western scientists' theories…was this insistence that inheritance was independent of the conditions experienced by animals and plants, such that no characteristics acquired during their lives were passed on to the next generation…the Lenin Academy objected to the idea that the hereditary substance of animals and plants was not influenced by the conditions experienced by the organism and that it acted alone in determining inheritance…"

To this Monod took a strong negative position. Ironically it would take another fifty plus years to somewhat alter the facts. Although the gene was the controlling factor, and genes were passed on in a manner according to Mendel, the impact of conditions of the parents, not just their genes, could give rise to hypermethylation, which could them be imprinted and in effect be passed

down. The irony was that this was being demonstrated as a result of the German starvation of the Dutch people (Dutch Famine 1944-1945).

Probably the most moving part of the book is the letter Monod wrote to the US Counsel Office after his visa to the US was rejected because of Communist affiliation. This letter on 305-306 is worth reading several times, and it was subsequently published in Science.

For Camus it was the denouncing of Stalinist tactic of suppression of Russians and their imprisonment. This was exemplified by the classic battle in the press between him and Sartre. Sartre remained a devout Communist and Camus moved into what at best could be termed the French anti-Communist camp.

By the mid-50s Camus had begun to be well recognized for his writings and in 1957 he is awarded the Nobel Prize for Literature. To some this was a surprise but to others who had seen his reputation and literary influence spread it was anticipated.

The book is exceptionally well written and smoothly interlaces the stories of each man. Overall it does a superb task of blending together two lives, arts and science, into a coherent tale which is truly French; Camus and the absurd and Monod and the control of cellular metabolism at the genetic level. It would have been an improvement if the author, a skilled research in the field, took the reader a bit more thoroughly along the details of Monod's work and the problems he was addressing. Understanding the work of Watson and Crick, and then taking it to another level, via brilliant experimental technique, would have truly brought this work to the fore. The Watson book, The Double Helix, reads like a detective novel, and one can feel the excitement as they progress to the discovery of the DNA structure and function. This book takes you down the path with Monod but somehow it lacks the intensity.

Secondly the Camus tale could also have discussed his world view a bit more, by using context, and it would have been interesting to see his works in contrast to say Sartre, who became an antagonist in later parts of his life. There are discussion regarding this but they assume a somewhat well-read reader.

Overall, the book is a wonderful addition to the literature on Camus and adds to an understanding of Monod, a man of dimension and character.
Labels: Books, Commentary

SUNDAY, OCTOBER 13, 2013

COLLEGE AND BENEFITS

The Becker-Posner posts speak of the benefits of college albeit the rising costs. They state:

As Posner discusses, tuition and other college costs have risen greatly during the past 30 years. So too have the many benefits from college, including the greater earnings, health, and even marriage rates of college graduates compared to high school graduates. Moreover, the return on a college education has also increased, as measured by the higher benefits of college net of the increase in college costs. As a result, college is even a better deal than it was 30 years ago for

most of the students who can afford the higher tuition.

This I find impossible to believe. Take 1963, fifty years ago. Two numbers. The cost per year at MIT was about $1,250 Tuition. Back in those days tuition equaled room and board. Today room and board is a fifth of tuition. Now look at starting salaries. Then it was $9,600 per year. That is 8 times annual tuition. Now the tuition is approaching $60,000 and to my knowledge we are not seeing students getting starting salaries of $480,000. Just a reality check for the Profs.

So why does someone go to college. If you are not a Trust Fund Kid, TFK, you go to get a job. Yes, that is right a job. You do not go to learn English, Fine Arts, or even History. You learn Chinese to be a translator, Accounting, Engineering, Biology, or possibly Chemistry. Fine Arts majors will have a tough job, unless they are just gritty and connected.

Now what type of job do you get educated for? Simple. One that earns money, for a while. For how log, well just look at the last few decades, Chemists have seen mass reduction in demand, why?, because their job has been automated. Chemical Engineers however have remained steady. Civil Engineers are also in demand, not great, but there is a demand to build things. Electrical Engineers and Computer Engineers still have a future, unless Chine gets all the jobs. Biotech is a hot area but more than half the new papers are from China also. So will those jobs remain here?

Thus if one looks at the risk factors and one does a discounted cash flow, even with a zero risk for cost of money the added risk due to the market will discount the future earnings dramatically. That means the "value". net present value if one desires, of a college education is highly problematic.

If one were an economist, or teaching at a business school, or say a legal scholar in the economics area, one would have used a DCF approach. In this case the DCF would have a risk discount factor in double digits, percent wise.

Thus, despite the dramatic reduction in initial salary from fifty years ago, and despite the dramatic discount factor, we see these folks saying the sky is not falling, even as chunks of it are hitting our heads!

Then the author states:

Increased competition for better students has gone hand in hand with greater competition for better faculty. Just as returns to college have increased more for better students, it is likely (there is little quantitative evidence on this) that returns from college have also grown more from an education with better faculty and a more effective education program. In any case, the stronger competition for college faculty has been one important source of the growth in college costs since faculty is by far the dominant cost of a college education.

Back fifty years ago the better students were very hard working street kids who were the top 5-10% of the US graduating High School classes, remember not all went to college. But the instructors were also pretty good, just look at the literature. Yet they were not paid as highly and

the schools did not have monuments they had to feed and Administrative overhead that provided just added loads and no benefits.

Reality seems to contradict the Professor in this case, and a reality that I suspect he should have considered. Perhaps being an electrician would be better. I can always go back and renew my license, PhD not withstanding.

In the corresponding Posner post he discusses costs and then MOOCs. He states:

I see hope, however, in the MOOCs—massive open online courses, which offer enormous potential cost savings and quality improvements for colleges. They can eliminate most of the living expenses associated with college (students can live at home, presumably cheaply) while enabling a reduction in faculty size (because there is no limit to the number of students in an online course) coupled with an increase in average faculty quality, since there is no limit on the number of students that a superb teacher can teach online. The MOOCs are not a panacea, but they are the most promising response to the problem of the high costs of a college education in America.

I am still not convinced with MOOCs. They lack the student inter-communications, and often are dominate by anonymous blather. Also the problem I have is that the software is still a bit messy. When they first came out it was a disaster. Now, say with MIT's 7.00x, it almost is there but it still has some problems. Perhaps the kids brought up with the approach will do better, I still like paper to scribble on and the hand, eye, keyboard screen efforts still face a challenge.

As to costs, Posner states:

The causes are various. They include the enormous—I am tempted to say the stifling—increase in legal and other regulation of colleges (and universities, but for simplicity I'll use "college" to denote all higher education), the decline in financial subsidies to state colleges, the increased cost of scientific equipment, and the expense of computerization and other electronics. But another important cause,paradoxically, is the increased cost of college education, which tilts the student body toward richer kids—and rich kids and their parents expect superior amenities in the way of housing, food, athletic facilities, and police protection. Such students expected to be treated as consumers, rather than as kids with no rights or representation (the situation of students at Yale in the 1950s; there was no student government, and no appeal from expulsion).

Again I disagree, looking at the MIT and Harvard costs, especially MITs, I see the explosive burden of overhead on massive construction. The maintenance costs are excessive. The second is the Administrative burden, we now have Deans for everything. Frankly all we need is a Dean of Science, Engineering, and well Business, kind of. So what are the other Deans for, overhead!
Labels: Academy

SUNDAY, OCTOBER 13, 2013

WILSON: AN EXAMPLE OF A PROFESSOR IN THE PRESIDENCY

The book by Knock, To End All Wars, is a superbly written analysis of Wilson, WW I and his attempts to use it as a vehicle for his world view. This is not a biography of Wilson nor is it an analysis of the Treaty that ended WW I. It is as the author states an interweaving of Wilson, the man and the President, into, through and after the War. Wilson was a complex person, at times very idealistic, and at others quite pragmatic. However as the author demonstrates the more idealistic Wilson prevailed through his attempts to reach agreements at the end of the War which he felt promoted World peace.

The author commences with an excellent discussion of Wilson and some elements of the Socialist movement. On the one hand he saw them as fellow progressives and on the other hand, as the case with Debs and my grandmother (she was one of the heads of the Socialist Party in NY and I recall many of the details of Wilson and he somewhat heavy handed way of dealing with differing views; she is third from the right above just before Wilson ordered the imprisonment of all of the women above in Lorton), he saw them as threats to his unlimited power. Thus there was a love and hate relationship. The author focuses on the productive parts of the relationship in the early years when their interests coincided. Yet the Socialists were not just one group, there were many flavors of Socialism and this, in itself, made it difficult to understand. Wilson as the author indicates tries to benefit from their support.

Then the author discusses the internationalism of Wilson. His interactions with Croly of the New Republic and also with Lippmann, were positive initially and they were supporters. But those relationships were to falter as Wilson exercised his approach to Presidential power.

Wilson seemed to deal with international relations in the almost academic framework that he did with most everything else. For example and as discussed the Mexican War was an out and out fiasco. The US Army wandered around Mexico without maps searching for Villa as an attempt to solidify American interests. It accomplished nothing other than demonstrating that Pershing and his forces were totally unprepared to even capture one wandering band of “outlaws”. Regrettably the same leadership sent the Army to France, often coatless and untrained and ill equipped.

The author spends a considerable amount of time discussing the negotiations and Wilsons almost arrogant teacher like approach dealing with very sophisticated politicians in France and the UK.

On p 210 ius the most telling of all descriptions: “Everything reminded me of a faculty committee meeting, rather than a gathering of statesmen.” is the quote from one observer. On p 204 the author effectively tells why: “Wilson wrote two constitutions for the League of Nations…”

Namely Wilson had the continuing desire to do the work himself and then try to cajole the others into his way of thinking. These observations are just a few of the battery of focused observations made by the author that demonstrate better than almost all other writers on Wilson his true weakness. Namely he believed he could lead all the others by the power of his intellect and delivering in words fait accompli. But to the old European players at the table the work was often done in classic Byzantine manner, no pun intended.

There are several points which the author has noted adequately covered which I believe are germane to this topic. Specifically:

1. Wilson’s Health: Wilson had significant cardiovascular problems, most likely suffering from mild strokes on prior occasions and ultimately, while pushing the League, suffered a massive stroke. His health was always an issue, delimiting the time he spent on ever more complex issues. It would have been fruitful to have melded the health issues into the timing of many of the decisions.

2. Wilson’s Second Wife: The death of his first wife and the near instant remarrying to a strong and controlling second wife was undoubtedly a significant factor in his thinking. Yet understanding that has always been a complex task and the author sidesteps this issue. The author treats Wilson as the President and does not reflect on this type of influence. How important this was can be debated but her influence cannot.

3. Wilson and House: House, the self-appointed Colonel, had attached himself to Wilson and for years was apparently the driving force for many of Wilson’s efforts, especially towards the end of the War where House actually represented the US with foreign entities, albeit having no real recognized official position. Then almost suddenly at the end of the negotiations there is a break with House, Wilson just seizes the moment and send him off. One can look at the positive and negative side of the Wilson-House relationship but it was clear that House was a significant factor. The author correctly acknowledges House’s presence but his influence should have been more extensively explored.

4. Wilson’s Limited International Exposure: American Presidents all too often have delimited international experience. Teddy Roosevelt just seemed to bluster his way about and was in effect the first internationally influencing president. But TR’s impact was limited. On the other hand Wilson was the first President to fully step upon the world stage. Unlike FDR who had multiple internal advisers as well as building his relationships with Churchill and Stalin, Wilson had not real exposure to the field of international diplomacy. In fact when he completed his PhD at

Hopkins he barely got passed his German requirement, and some say barely is being generous. Thus having no alliances, having no experience, and having no understanding of the depth of historical precedents, he walked into the middle of negotiations assuming them to be created of whole cloth. He soon found to the contrary. This would have been of interest to have been developed a bit more.

Notwithstanding the above fine points, personal in nature, this is one of the best works on Wilson available. It manages to tie together all of the key facts and allows the reader to have a better understanding of the man and his abilities and lack thereof. I would strongly recommend this to anyone trying to understand Wilson and more importantly anyone trying to understand the Presidency and the issues that can arise from a poorly prepared person who attains that position. In this case the past is always prologue to the future.
Labels: Books, Government

FRIDAY, OCTOBER 11, 2013

REAL PEER REVIEW

Over the past fifty years or so I have become less and less enamored with peer review. The problem? First is the anonymity. Who is this person? Why do they think they know the issue better? They may, but then I would like to know. Better yet are reviews that flatly state that all of this has been done before. Oh, but where? They never say. What of peer review of peer review. And the list goes on.

In a recent set of articles in Science this is all discussed in light of Open Access publishing. They state:

"Peer review is sick and collapsing under its own weight," he contends. The biggest problem, he says, is the anonymity granted to reviewers, who are often competing fiercely for priority with authors they are reviewing. "What would be their reason to do it quickly?" Tracz asks. "Why would they not steal" ideas or data?

Anonymous review, Tracz notes, is the primary reason why months pass between submission and publication of findings. "Delayed publishing is criminal; it's nonsensical," he says. "It's an artifact from an irrational, almost religious belief" in the peer-review system.

As an antidote, the heretic in January launched a new venture that has dispensed altogether with anonymous peer review: F1000Research, an online outlet for immediate scholarly publishing. "As soon as we receive a paper, we publish it," after a cursory quality check. Peer review happens after publication, and in the light of day. F1000Research selects referees, who post their names and affiliations alongside their critiques. Papers become like wikis, with reviewers and authors posting comments and revisions as the need arises.

I have advocated this before. Peer review is a non-anonymous process post public release. What does this accomplish? The following:

1. You get to judge the author and the reviewer side by side.

2. Reviewers with an axe to grind are exposed.

3. Anyone can review the piece subject to certain rules. Anonymity is prohibited. You must list your name and contact information. Your review must contain details and data and backup.

4. The Editor still plays a role but a role of orchestrating the reviews. Some reviews will be just junk, as usual there are always people with "stuff" to say. Let then say it elsewhere.

5. Self policing is essential. The readers should police the comments so as to drive out the bad ones, again policing must never by anonymous. If you decide to vote out a comment then you do so in the light of day. There has been the argument that Grad students could never put out bad comments on say a Department Head. But others could and should. Perhaps the truth will out.

6. It then begs the question of; what is the paper? Is it the original posting or the amalgamation of it and all the comments? If so then who is the author? This is a challenge, yet one we face all the time.

The article concludes:

Tracz acknowledges that in reshaping peer review, he's taking on a sacred cow. "There will be some growing pains," he says. But his maverick ideas tend to become mainstream over time. "At the beginning of open access," one colleague says, Tracz "was ridiculed by other [publishers]." No one ridicules open access now.

"He's not radical," Eisen insists, "just sensible. Sensible doesn't [usually] happen in scientific publishing." The coming years will see whether open peer review is sensible—or too radical for most researchers to stomach.

The comments above are suggestions based on thinking about this for a while. The driver is the change in the distribution channel for scientific data. Namely the Internet changes everything. One can put things out there and see what happens. I have placed Drafts on line and have seen tens of thousands of downloads on several ones. Who, why, what did they think of it? That process is not working yet as one would like but the spread of the information does work.

A change in peer review is essential. Today it protects the interests of a few. It should be useful by expanding the interests of the many.
Labels: Academy

THURSDAY, OCTOBER 10, 2013

PSA IS STILL A BATTLE GROUND

In the European Cancer Congress of 2013 one of the authors states in the Abstract the following:

We estimated the number of individuals needed to harm associated with PSA testing by applying different side effect estimates to a virtual population of 1,000 men aged 55–69 exposed to PSA

testing and another 1,000 not exposed to PSA testing.

Following a systematic literature review, we extracted results of PSA testing, biopsy rates and impact on prostate specific mortality from the European Randomized Study on Screening for Prostate Cancer (ERSPC) which is the study with the most favourable outcome to PSA screening.

We also extracted, from reports with such information, data on mortality following prostatic biopsy, on mortality associated with radical prostatectomy as well as side effects of radical prostatectomy and hospitalisation rates following prostatic biopsy....

Overall, under the best scenario of screening efficiency, the prevention of 1 death from prostate cancer is associated with a significant additional adverse-effect burden from the biopsy and from the treatment of the additional prostate cancer diagnosed.

These will severely impact the quality of life of patients and argues against using PSA testing for mass screening of prostate cancer.

Note the phrasing, "number of individuals needed to harm.." , as a phrasing that any biopsy harms the patient. The problem often is that the biopsy may have been done poorly thus subjecting the patient to infection. That is a problem with practice and not procedure. Also note the phrase "severely impact the quality of life". What does that mean. If you have a biopsy and no PCa then you may have a small chance of an infection. If you have prepped properly and the Urologist is skilled and you take care afterwards, it is fairly probable that there is no problem.

On the other hand if you have PCa, then the issue is what to do. Is is indolent or aggressive? Most likely you cannot readily tell. So then what? Here is where the real issue is. Some men will look at family history to help. If your father died 20 months after diagnosis you may want to hedge your bets and be aggressive in treatment. But if dad and Uncle Joe died with it and it never did much to them, perhaps a different story. Thus, it all depends. No good answer!

As is stated in Healio:

"When discussing the use of the PSA test with patients, physicians should make them aware of the limitations of the test and the likelihood of it causing harm," Boniol said. "We hope that our research findings will help clinicians to make decisions as to when to propose a PSA test, and to help the patient to decide whether or not to accept this recommendation."

Now the problem with PCa in the first place is that like many cancers it does not behave the same in all people. Some few are very aggressive. Many are indolent. But to know which are which is still a work in progress.

In my Draft volume on Prostate Cancer I have tried to examine this as best as possible. However even there we have missed may subtle but now potentially powerful forces in the epigenetic areas. Methylation may be playing a significant part as are miRNAs and lncRNAs. Thus, although we understand many pathways and translocations that may cause an aggressive PCa we

do not fully understand the epigenetic forces.

Thus a blanket denial of use of PSA is a "head in the sand" strategy that will harm more than help, at least in my opinion. As for the above mentioned European Study, I have discussed its fatal flaws in my opinion and thus have no basis for its reliance.
Labels: Cancer

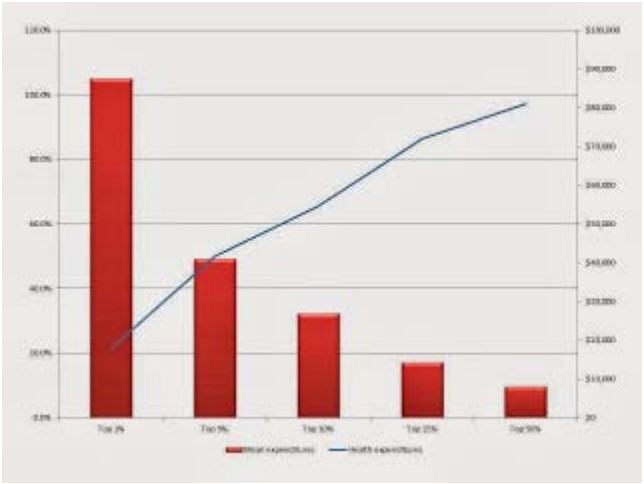
HEALTH CARE COST ALLOCATION

In a recent AHRQ study there is an analysis of the distribution of health care costs. It is instructive. Two major conclusions are of merit:

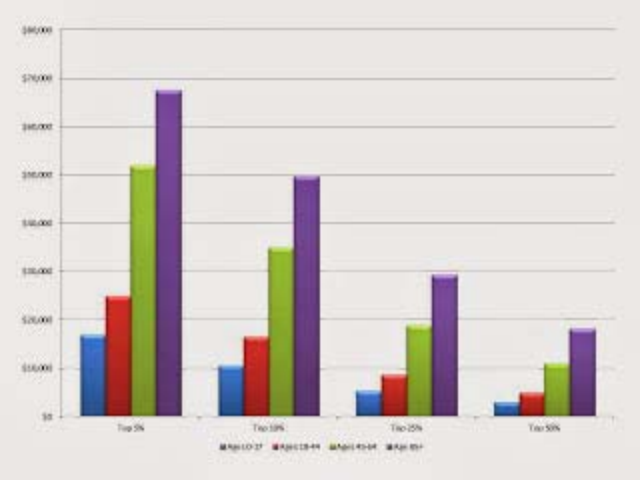
In 2010, the top 1 percent ranked by their health care expenses accounted for 21.4 percent of total health care expenditures with an annual mean expenditure of $87,570. Overall, the top 50 percent of the population ranked by their expenditures accounted for 97.2 percent of overall health care expenditures while the lower 50 percent accounted for only 2.8 percent of the total.

The top 5 percent of individuals with four or more chronic conditions accounted for 29.7 percent of health care expenditures for this subpopulation with an annual mean of $81,790. Based on chronic condition status, persons with four or more chronic conditions had the lowest concentrated levels of health care expenditures and the highest annual mean expenses at the top quantiles of the expenditure distribution.

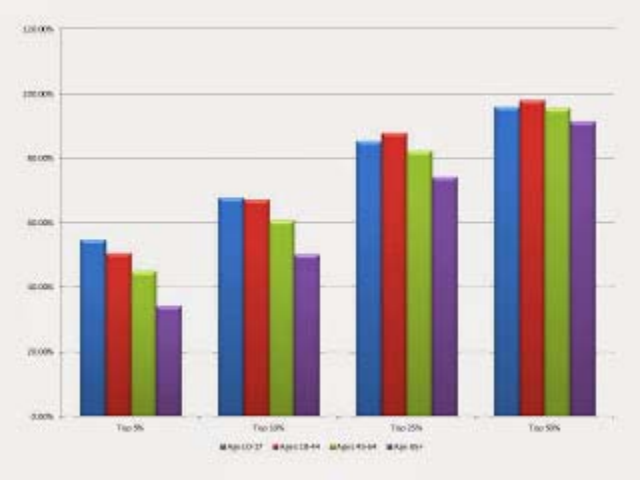
Let us consider the total costs as shown below:



Note the high level of the highest users, over $80,000 per year. The average is well below a tenth of that number.



Then by age we have the above expenditures. As would be expected the oldest dominate the amount in the top 5% level. The younger are less than a fourth of the older. This ratio holds throughout.



Finally we have the percentages above.

The conclusion is simply that a small percentage are the dominant users. Similar results are the same in many insurance claims. The question is; can we find ways to reduce the costs of this higher group or is this the nature of the problem?
Labels: Health Care

WEDNESDAY, OCTOBER 9, 2013

A SECURE INTERNET?

Back in 2001 I was the Vice Chairman of the Presidential Commission on the Internet and we published a report entitled The Internet's Coming of Age. Today there is an article in the NY Times bemoaning the lack of security in the Internet.

Having been involved in what the Internet was from 1972 onwards I can say at least until the present that the intent was to have an open network with all of then intelligence on the periphery. This would be totally unlike the old telephone networks with dumb devices on the end and complexity in the middle.

Inherent in this hourglass principle was that the Internet would be simple and the burden would be on the end users to seek whatever services they sought.

The article states:

But while such vulnerabilities are worrisome, equally important — and because of their technical nature, far less widely understood — are the weaknesses that the N.S.A. seems to have built into the very infrastructure of the Internet. The agency's "upstream collection" capabilities, programs with names like Fairview and Blarney, monitor Internet traffic as it passes through the guts of the system: the cables and routers and switches.

The concern is that even if consumer software companies like Microsoft and telecommunications companies like AT&T and Verizon stop cooperating with the N.S.A., your online security will remain compromised as long as the agency can still take advantage of weaknesses in the Internet itself. Fortunately, there is something we can do: encourage the development of an "open hardware" movement — an extension of the open-source movement that has led to software products like the Mozilla browser and the Linux operating system.

Just what this means is confusing. The Internet is open, by definition, design and deployment. The problem is that the service providers are in collusion with others often to use that openness to third party advantages.

The IETF had established various open support options to allow enhancements at the edge. These RFC, Requests for Comments, were the ultimate in open source. There is very little proprietary "stuff" unless one adds it deliberately in a proprietary network.

Frankly the piece in the Times makes no sense. The threats to privacy can be controlled by end to end secure encryption and authentication. They can be made, or at least for a short while. Using a Government approved encryption is an oxymoron, it is not secure, at least not between the sender and the Government. But anyone who knows anything knows that.

One suspects that anyone desiring to be secure may seek secure ways to be secure! They still exist but get more complex in today's world. But creating open source stuff just does not make any sense.
Labels: Internet

ARE THERE ANY TEACHERS LEFT?

There is an article in the NY Times speaking of a proposed and at times implemented technique of having students watch video lectures and then spend class time doing homework. They state:

one where students watch teachers' lectures at home and do what we'd otherwise call "homework" in class. Teachers record video lessons, which students watch on their smartphones, home computers or at lunch in the school's tech lab. In class, they do projects, exercises or lab experiments in small groups while the teacher circulates.

Frankly one then wonders what the teacher is doing? I have seen this in certain environments. It is a MOOC at Grade School. It is a cop-out for teachers to just wander and leave the burden on the student.

The problem with US education is the continual introduction of new techniques while having all too often poor teachers. Or worse, having good teachers made poor by technique.
Labels: Education

WEDNESDAY, OCTOBER 9, 2013

THE BRITISH CONSTITUTION

The book by Loughlin, entitled The British Constitution, begs the question of what is a constitution. This is a timely and challenging book. The author does a splendid job of addressing the somewhat amorphous idea of a British Constitution within the execution of its long held principles in its Government actions. This book is both and excellent introduction to the British Constitution, as idea and action, as well as a superb discussion of the challenges that are presented when a country accepts this "cultural" form of governing.

As Americans we understand the US Constitution as a single document and an amalgam of how the Government works and what they can do and the rights that we as citizens have in such an environment. In a sense the US Constitution, especially the Bill of Rights, was and is a clear written statement of how far the Government can go, and no farther. The problem, of course, is that it is often open to interpretation. In contrast the British Constitution is much more of an amalgam of written as well as unstated rights and responsibilities going back to the Magna Carta of 1215. It is built upon the tri-partite English relationships amongst the Crown, the Aristocracy, and the commoners. Each of these players has a role in this British Constitution. This is in stark contrast to the US Constitution wherein there is no room for any differences amongst the citizenry, the "three-fifths" rule notwithstanding. To understand the British Constitution one must understand and accept the class structure of the English society. To understand the American culture one must also accept the alleged classless structure.

Loughlin's book is a small but significant contribution to this area of legal thought. It is especially important now because Britain is going through massive changes with the devolution or separation of its parts; Scotland, Wales and Northern Ireland. Scotland may very well find itself a separate country and if so one wonders what part of this Constitution it takes.

Loughlin presents the British Constitution through several Chapters. The overall challenge is that there is no document that one can point to as such a Constitution. Thus he takes this challenge and tries to make the best of it.

In Chapter 1 he spends time discussion what a Constitution is. In my view the best remark is that by Paine, which clearly defines a constitution as a written document containing principles. Paine was a contretemps to Burke, and Paine knew all too well what went into the American Constitution and also the coming chaos of the French process, post the Revolution. Burke was a traditionalist, one who could say, "...we all know what we mean by …" whereas Paine wanted clarity of definition.

In Chapter 2 he discusses writing a Constitution. As with the previous Chapter there is a substantial challenge, and he meets that in the very first part of the Chapter. Namely he states (p 23):

"…the British have always been reluctant to commits its basic rules to writing … the types of knowledge it embodies cannot easily be expressed in books or conveyed through formal instruction…"

Then he states that it is conducted via rules of procedure rather than principle. That is the challenge of such an idea. On the other hand one may argue that the US Constitution is also at the other extreme. For example the right to bear arms means what in a 21st century, the same as it did in the eighteenth. Also the US has no express right of privacy and yet it was evoked solely for the "right" to have an abortion. One may have a delimited right of privacy but when it comes to Government monitoring and intrusion of electronic media the right somehow disappears. Thus even in an environment where principle is in writing the interpretation often taking precedence.

The key elements of the British Constitution as Loughlin states (p 26-27) are based upon the Magna Carta, The Petition of Right (1628) and the Bill of Rights (1689). The commentaries of Blackstone, Dicey and Bagehot establish a written fabric for better understanding what the Constitution may be as a result of these rights. The principle of the Crown in Parliament is one of the major corner stones that is essential to the British but would be incomprehensible to Americans. How much the Constitution has "evolved" is also discussed.

Chapter 3 discusses Parliamentary Government. It is dramatically different that the US system. It in many ways combined legislative, executive and even judicial powers in this strange concoction. The Crown has a role, but clearly a slowly disappearing one. The Crown may call for a new election but that is now a formality. But the British Parliament is an evolving entity as well.

Chapter 4 speaks somewhat of the expansion of the state and of particular current interest is the devolution of the entities such as Scotland. This is covered quite well in the book (see pp 80-83). In contrast to the South or Confederacy leaving the Union the separation of Scotland, namely devolution, can be seen as within the confines of the Constitution.

Chapter 5 discusses the issues of civil liberties. Here one must wonder how well this Constitution has worked. The author does speak of the Irish atrocities and deprivation of any civil liberties on pp 92-93. This in a sense is a clear example of where the "tradition" of an unwritten Constitution is defective as compared to a written form where all have equal rights.

Loughlin ends with some interesting thoughts on where the British Constitution may go to. For him it is the process and not any specific set of words. For Loughlin there are continual concerns that its evolution may have some substantial concerns.

This book is best read along with two others; Wilson's Congressional Government and Bagehot's The English Constitution. Wilson reveals in his book his great distaste of the US Constitution which was comprised of a balance of powers amongst the branches and he lays

forth well before he ascended to the Presidency his desire for a position which combined the powers of the Crown with those of the Prime Minister. In contrast Bagehot provides an interesting and timely, 1867, understanding of the English Government and its roles while using the US in post-Civil War times as less than a sterling example of another Constitution.

Overall this is a very worthwhile read especially for Americans. It is a contre temps to our own Constitutional battles as well as the expanding power of the Executive.

There is an excellent review in the LRB by Sedley. As Sedley states:

Although it took a while to settle in (monarchs continued purporting to suspend legislation into the early 18th century), the essential purpose and effect of the Bill of Rights were to make the crown, which had long since been forced – in principle at least – to delegate its judicial authority to the judges and was shortly to begin devolving its administrative authority to parliamentary ministers, subordinate to Parliament. In return, the state undertook to conduct all three core functions in the monarch's name.

Thus far we have the structure, but very little of the content, of the British constitution. Blackstone, in the late 18th century, took its content to be assured by three institutions: Parliament for the redress of grievances, jury trial for the protection of the innocent and habeas corpus for the restriction of state power, the latter two springing from article 39 of Magna Carta and assured by a judiciary whose independence had been guaranteed by the 1701 Act of Settlement. It was Dicey, a century after Blackstone, who sought to encapsulate the content of the constitution in what he called the rule of law: the idea that because the constitution itself derived from the rights of individuals, its fixed purpose was to guarantee those rights by the equal application of the same law to everyone from the prime minister to the postman.

Namely there was a great deal of effort in evolving this erstwhile Constitution. In the final paragraph by Sedley appears a somewhat dire warning:

We are approaching a point, in other words, where departmental housekeeping is being used not to rebalance but to unbalance a central element of the constitution. Thanks to the ill-considered merger of the two functions, a secretary of state for justice is now able to use his departmental powers to occlude his own constitutional role as Lord Chancellor.

Namely the executive appears to be consolidating power to an absolute. This struggle appears to be the same in the US as well. One can argue that here it started with Wilson, but Teddy Roosevelt was in a great sense the true usurper of the power of the executive totally unto himself. It was Wilson who refined it to where it is going now. This direction of flow of power should always be countered by the opposing branches, That simply is what we see in Congress today, the natural wisdom of the Founders, not just obstruction of the will of the executive.
Labels: Books, Government

TUESDAY, OCTOBER 8, 2013

THE THIRD AMENDMENT

The Third Amendment states:

No Soldier shall, in time of peace be quartered in any house, without the consent of the Owner, nor in time of war, but in a manner to be prescribed by law.

Now I suspect that no one ever really uses this, namely it would just be assumed that the Military would never even assume to take refuge in an individual's home.

But then I read the EFF note regarding the NSA. First, the NSA is part of DoD, thus the military. Second, their intrusion mechanisms places electronic soldiers in citizen's homes, namely their computers. Think of them as a small room in our homes.

As the article states:

In order to accomplish the first step of getting a user to visit a site under your control, an attacker might email the victim text that contains a link to the website in question, in a so-called phishing attack. The NSA reportedly uses phishing attacks sometimes, but we've learned that this step usually proceeds via a so-called "man-in-the-middle" attack.

The NSA controls a set of servers codenamed "Quantum" that sit on the Internet backbone, and these servers are used to redirect targets away from their intended destinations to still other NSA-controlled servers that are responsible for the injection of malware.

So, for example, if a targeted user visits "yahoo.com", the target's browser will display the ordinary Yahoo! landing page but will actually be communicating with a server controlled by the NSA. This malicious version of Yahoo!'s website will tell the victim's browser to make a request in a background to another server controlled by the NSA which is used to deploy malware.

Once a victim visits a malicious website, how does the attacker actually infect the computer? Perhaps the most straightforward method is to trick the user into downloading and running software. A cleverly designed pop-up advertisement may convince a user to download and install the attacker's malware, for example.

This could be considered a quartering of "soldiers" in a house. Namely they send their ***SoldierBOTs*** down to our homes and they then take up residence whereby we feed and clothe them, metaphorically, and thereby we have been breached in our Third Amendment rights. Namely we have these small electronic military forces entering our homes without our permission and being fed, that is they get our paid for electricity, and thus we are housing and feeding them. Kinda like quartering them, ya think?

Just a thought!
Labels: Commentary, Government

THURSDAY, OCTOBER 3, 2013

DESIGNER CHILDREN

Apparently the PTO has considered issuing a Patent to a US company for the ability to select male and female gametes to "design" a child with certain features. From a Nature Genetics in Medicine article the authors state:

...the US Patent and Trademark Office in June 2013, and it will issue as US Patent No. 8543339 on
24 September 2013. It contains claims to a computer system and to a computer program, but our focus here is on the patent's claims to a method for gamete donor selection:

"A method for gamete donor selection,1 comprising (i) receiving a specification including a phenotype of interest that can b be present in a hypothetical offspring; (ii) receiving a genotype of a recipient and a plurality of genotypes of a respective plurality of donors; (iii) using one or more computer processors coupled to one or more memories configured to provide one or more computer processors with instructions to determine statistical information including probabilities of observing the phenotype of interest resulting from different combinations of the genotype of the recipient and genotypes of the plurality of donors; and (iv) identifying a preferred donor among the plurality of donors, based at least in part on the statistical information determined, including comparing the probabilities of observing the phenotype of interest resulting from different combinations of the genotype of the recipient and the genotypes of the plurality of donors to identify the preferred donor."

It appears as if the company believes that by selecting male and female gametes based upon a full genetic determination of the parentage that one can determine the characteristics of the offspring. Surprise. Welcome to epigenetics. Things do not always work out that way.

Now perhaps the authors of the piece doth protest a bit too much. In fact one of them apparently got into a comment fight on a PLOS Blog of a highly respected Genetics Blogger. Thus this topic seems to have raised the ire of many folks.

The problem is that the epigenetic elements associated with combining male and female gametes is quite complex. Thus just choosing them assuming the genes are fine is at best an interesting first start but no guarantee.

This will be an interesting battle to watch.
Labels: Genetics

NEVER FORGIVE, NEVER FORGET

Well, I thought I would tread lightly on this one. So Scotland wants to become its own country. So says the NY Times. If they do does that mean that the Irish can send the Scots back from Northern Ireland and take that back as well? What of Wales? Not really that much there but what the heck. Then think of what that does to the English flag, just Saint George, the dragon guy.

As the Times states:

The Scottish first minister, Alex Salmond — head of the Scottish National Party, whose raison d'être centers on independence — has been cozying up to Rupert Murdoch and Donald J. Trump. There's been much talk of an Ireland-style business-friendly environment. Before that Mr. Salmond's model was Iceland. Imagine all the small nations of the world saying a collective prayer that Alex Salmond doesn't mention them in a speech and jinx their economy.

Just think of how this concept could spread. Quebec could again get back in the play. Tax havens could become the wave of the future, creating a new nationalism. You do not really need Armies and the like, just a secure broadband connection with great encryption and lots of PO Boxes.

This could start a whole new blast of economic growth. They could sell citizenships, sell residences, namely your PO Box, and then have a great business. Then when the taxes in New York City explode in the next few years all those rich folks could move to say Aberdeen, or perhaps a better and nicer environment, especially if Spain fragments as well. I wonder what the tax rate is in the Vatican State? Could I get a PO Box in the Vatican's Post Office?
Labels: Commentary

NUCLEAR WEAPONS: THEN AND NOW

The recent book, Command and Control, addresses an interesting and still vitally important topic. Namely, it examines nuclear weapons control and safety. We all too often fail to remember that the prime job of the Secretary of Energy is no electric cars but management and oversight of the nuclear weapons development and distribution. This book presents a diorama of many of the events surrounding the deployment and control of such weapons.

However, as many other reviewers had noted, the style of the book can be very frustrating at times. The author uses the Damascus incident as an ongoing connector to other historical tale recounting the development of nuclear weapons control and the mistakes that have occurred over the decades. After a while this approach becomes not only distracting but an annoyance. For example the author will take the Damascus Incident, an incident when the maintenance of a liquid fuel Titan II was damaged by a Tech apparently not following protocol, and then ultimately exploding, as a metaphor for each of the Chapters which are interspersed. Thus one is supposed to be drawn to see mistakes in the small and mistakes in the large. Nice idea but it just does not seem to work.

Now, I will discuss the text in toto. If one can work around the style, the book tells a compelling tale. It begins at the beginning, Los Alamos, and then proceeds to detail the many developments in the evolution of nuclear weapons. There are excellent discussions of the political in-fighting and the pros and cons of military control over the weapons. LeMay plays a key role during this early period as well he should. LeMay was a pivotal player whose world view of war was massive total destruction. LeMay viewed war as a total destruction of the enemy, as he had done in Europe and in the Pacific. Lemay in a sense was the driving force for military use and deployment.

The author does an excellent job in developing the issue of who control nuclear weapons, by going over the various ways in which the weapons flowed into military hands. The design and building of the weapons was done under AEC and then DoE aegis with the support of such places as Sandia Labs in Albuquerque. Sandia was managed by AT&T under a Government contract and was a massive facility adjacent to Kirkland AFB which itself was adjacent to the airport at Albuquerque. Sandia developed various weapons and weapon security systems. Tests of the weapons were often done by DoE or its predecessor the AEC. The author integrates these efforts into the text. It would have been interesting to have developed the significant interplay between DoE and DOD as weapons systems evolved.

The author interweaves many other near miss events into the text in a chronological basis between the evolving tale of the Damascus event. Such near misses as the explosion of a B-52 over North Carolina and the loss of 2 H bombs over Span and but a few.

The author does a reasonable job in describing the safety procedures employed but it would possibly have been more enlightening to have some first-hand descriptions. Many “fail-safe” procedures had been developed but as the author states each time an improvement to a fail-safe was done it potentially impeded the effectiveness of the weapon.

There are several areas, in my opinion, which the author has missed or touched lightly upon and should have been included or expanded upon:

1. Soviet Nuclear Weapons: On almost a one to one basis the Soviets matched the US for weapons of vast killing power. The Soviets often played games of chicken with US SAC forces and this would frequently be at the risk of deployment of weapons, especially tactical weapons. In addition the use of the nuclear submarine fleet and the games played there also presented dramatic threats. It would have been useful to have had this interplay discussed somewhat. The classic Triad of aircraft, submarines and missiles would also have been useful to draw together. Understanding Soviet capability and control would have made an excellent counterpoint.

2. Tactical Weapons and Special Weapons Depots: Tactical weapons were always considered just a step above a large non-nuclear weapon, and early on not w real nuclear weapon. The author does discuss the Davy Crockett weapons but in reality there were hundreds of Special Weapons Depots, SWD, across the globe which contained these types of weapons. The SWDs were reasonably well guarded but their very number often gave one concern not just because of what they contained but often because one could not reasonably expect to get the best personnel at this many locations. They also were DOD controlled and thus were subject to the change of staff which raised the risk of failure to follow protocols. Thus the proliferation of Tactical weapons, 1KT ranges, were in reality a serious byproduct of the enthusiasm early on for nuclear solutions.

3. Other National Weapons Controls: The British, French, Chinese, Israelis, Pakistanis, Indians, and South Africans as well as North Korea and Iran all have dabbled in nuclear weapons and many have collections in their arsenals.

4. Nuclear Weapons Treaties: There were many discussions between the US, UK and Soviets from time to time. They typically dealt with testing and proliferation. I spent the latest 70s as an advisor to ACDA and the CTBT during the Carter Administration and dealt with the Soviets firsthand. Neither side trusted the other, yet side conversations between the parties were about children and grandchildren. Thus, although both sides were prepared for ultimate destruction, both sides also had a view of the humanity of the others. The author discusses Professor Pipe’s works at that time, and I knew Pipes well, and as a refugee from Poland Pipes knew firsthand the Soviets. Thus somehow there had to be a convergence of interests. MAD and Reagan’s efforts, in my opinion, on pushing what “could happen” did eventually get the sides to stand down, somewhat. The author discusses this issue but it could have been more fully developed.

5. Strategists: The influence of Herman Kahn and thinks like him also has an overpowering role to play. Kahn is recognized as the promoter of the MAD or Mutually Assured Destruction strategy. Namely if both sides are rational and both sides have so much excess nuclear capabilities then no side would rationally start a first strike. Kahn started out at Rand and ended at the Manhattan Institute but it would have been useful to integrate these efforts a bit more including the many such efforts at Rand.

6. Technological Elements: The WWMCCS discussion was lightly approached and in a sense it could have been a section unto itself. The whole concept of command, control, communications and intelligence came out in this period. However these were massively complex systems with detailed methods and procedures and whose very structure could very well have overburdened any rational response capability. The author's example of the Burroughs computers is but one simple example of grand technological ideas and ideals supported by antiquated technical implementations.

Overall the book contains some relevant materials that explain a world in the past. The current environment, however, with proliferation of such weapons, dramatically changes the landscape. For example, would the US try a MAD strategy on a rouge state nuclear capable nation the effect may be de minimis. Thus how would one address such factors? Here the past may only be partly prologue to the future. Thus the book is well worth the read even if at times it can be a bit off-putting in style.
Labels: Books, Nuclear Weapons

WEDNESDAY, OCTOBER 2, 2013

NON SEQUITUR

A non sequitur simply is that one thing does not follow from another. So why am I not amazed that the left and erstwhile economists seem to fall into the trap.

Take the Washington Post:

The top story all day was that Republicans had shut down the federal government because President Obama wouldn't defund or delay the Affordable Care Act. The other major story was that the government's servers were crashing because so many people were trying to see if they could get insurance through Obamacare.

So on the one hand, Washington was shut down because Republicans don't want Obamacare. On the other hand, Obamacare was nearly shut down because so many Americans wanted Obamacare.

The first tale about the Republicans is somewhat factual, after all that is what they are saying. The second is a non sequitur. The collapse of the servers is most likely the direct result of a poor system or technical design. After all it was the Government who did it and we all know deductively that they never get anything right. There is no evidence that it was the demand. The system should have been designed for a peak load, and the designers knew that. So the first

logical conclusion is a faulty design, way ahead of unexpected demand. The second logical conclusion, given the shutting off of the Panda etc is Government interference, namely deliberate shutting down.

Thus the answer is hardly what the left wants, it may, and most likely be, due to the Government itself! It does help to know something about computers and networks. But alas these folks are all too often clueless!

Now consider the logic:

1. Observed fact: The Government designed, controlled and operated web site malfunctioned on its first day.

2. Reasonable Assumption 1: Since this was a new thing of sorts one would expect a high level of curiosity at the beginning and thus the initial load would be exceedingly high. Thus the system should be designed to deal with that.

3. Reasonable Assumption 2: There has been thousands of Internet services that have been designed and operated which have had to deal with high arrival rates. Thus the problem, its solution and the allied technology is well at hand and should have been included in the design.

4. Possible Causes: There are many possible causes of the Observed Fact. The excess demand combined with proper design is not the most obvious. In an Ockham like manner one will proffer the simplest. Namely the design failed. But perhaps that is NOT the most obvious since such systems had been designed before as we have noted and thus one could reasonably assume that such was taken into account. Then this leaves a simple logical cause as direct adverse Government interference. Why would this be a most likely Ockham like solution? Because it reflects the Administrations general actions elsewhere, the Panda again being an example, and the result creates a beneficial issue of over demand.

Thus using simple logical deduction one can ascertain that the most likely cause was the Government itself. Pity.

But the key fact to take away from this posting is as follows. If the cause was a poor design, then think of how the ACA is being implemented in toto. If on the other hand the fault was deliberate, then one should be quite fearful of a Government which would commit such an act.
Labels: Economics, Government, Health Care

TUESDAY, OCTOBER 1, 2013

PERHAPS CLOSURE IS NOT REALLY THAT BAD

Back in the Cold War days there was a joke about: "How do you defeat the Americans", "Stall a Ford Pinto on each exit of the Beltway.".

I guess it was a timely humor but the point was to bring the Government to a halt. Now for

anyone who has walked the Halls of Agriculture, for example, one sees thousands of drones working away on something; corn, wheat, food stamps, lunch.

But the latest casualty was a Panda as per the NY Times. They state:

One casualty of the impasse in Washington is the public's look at the newborn panda at the Smithsonian National Zoo on the "Giant Panda Cam."

The popular live video stream was turned off Tuesday as part of the federal shutdown. Visitors to the Web site were greeted by a black screen carrying the message, "Error loading stream."

"The cams require federal resources, primarily staff, to run and broadcast, and they were deemed not essential in the case of a shutdown," zoo officials said in a statement, adding that the animals would still be fed and cared for.

How dumb do they take us for. There are now expenditures required? It is a simple Internet camera! They already have the camera and the network runs no matter what. This is a classic example of how the Government is a truly selfish and manipulative body. Are they starving the Panda, have the set him free to fend for himself? Has he been put up for Panda adoption, sent back to the Chinese Embassy? Does the Government official who wrote this get paid to do so, are they essential?

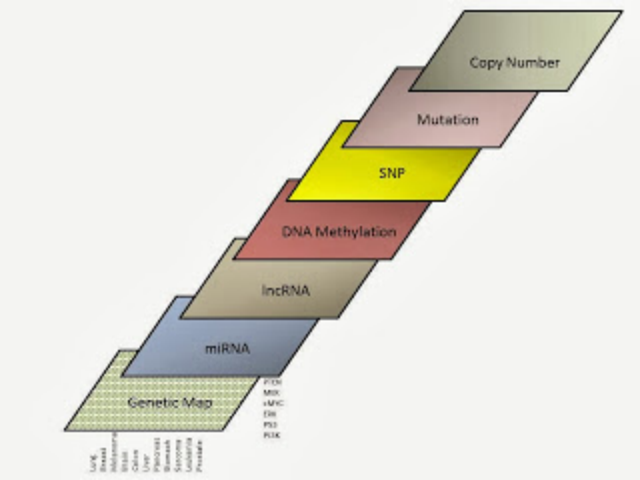
This is like a divorce proceedings. Without a Judge to arbitrate. Poor Panda, hope the Chinese recover it from Administration abuse. This is Panda abuse! We need a "Save the Panda" protest. A new a powerful movement, sent forth by all those opposed to this foul treatment. Perhaps a new Tennis Court Oath!
Labels: Government

MONDAY, SEPTEMBER 30, 2013

THE COMPLEXITIES OF CANCER

There are a collection of papers in Nature Genetics discussing the data collection efforts around various cancers. In summary it states:

The Cancer Genome Atlas (TCGA) Research Network has profiled and analyzed large numbers of human tumors to discover molecular aberrations at the DNA, RNA, protein and epigenetic levels. The resulting rich data provide a major opportunity to develop an integrated picture of commonalities, differences and emergent themes across tumor lineages. The Pan-Cancer initiative compares the first 12 tumor types profiled by TCGA. Analysis of the molecular aberrations and their functional roles across tumor types will teach us how to extend therapies effective in one cancer type to others with a similar genomic profile.



Simply viewed we have many layers of data for a variety of cancers. We have pathways that are disturbed, we have BRAF or BRCA changes, we have miRNA interference, we have lncRNA or methylation changes, as well as translocations, SNPs and the like. How do we record all of this and how do we relate this to management of cancers?

There are many paths connecting the various layers. The following are some of the questions they pose:

- *What is the spectrum of nucleotide- and dinucleotide-level changes associated with different carcinogenic etiologies (for example, tobacco, pathogens or inflammation) operating in different parts of the body?*
- *Will integration of additional data sources, including additional tumor types from TCGA and other projects, increase the power of analysis in useful ways?*
- *How can characterization based on molecular changes complement pathological analysis for classification of cancers into tumor lineages with potentially different clinical management?*
- *Can molecular profiles effectively categorize cancers for therapeutic decision-making?*
- *Are there predictive expression-based signatures for genomic events that transcend tissues, reflecting pathways disrupted by the alterations?*

The collection of papers is interesting. However it does point to the ever growing complexity of the cancers we study. What appeared as just a process understanding paths is but one of many layers of complexity.
Labels: Cancer

HEALTH CARE AND SOB STORIES

In a recent piece in The New Yorker a physician who also is a writer bemoans the fact that anyone is opposed to the ACA[32][1]. He starts off with the obligatory sob story of some poor unemployed person who no longer has insurance and gets ill, at lease this person appears to have a biopsy on some "pre-malignant" disorder. Then the poor guy gets the bills. Surprise.

He then states concerning the roll-out of the ACA:

How this will unfold, though, depends on where you live. Governors and legislatures in about half the states—from California to New York, Minnesota to Maryland—are working faithfully to implement the law with as few glitches as possible. In the other half—Indiana to Texas, Utah to South Carolina—they are working equally faithfully to obstruct its implementation. Still fundamentally in dispute is whether we as a society have a duty to protect people like Paul Sullivan. Not only do conservatives not think so; they seem to see providing that protection as a threat to America itself.

That is the way the law was written by the Democrats. One should not blame those who did not even vote for the law. Secondly, and this is the first sob story part of his piece, if someone loses their job, they still have home and auto insurance. No auto insurance no car registration, no driving. No home insurance and some may default on their mortgage and get the home repossessed. So why let health insurance lapse. Because people assume they will be taken care of on someone else's dime. It does not always work that way. So find a job, any job, and get two or three to survive. Some of us have been there.

Then he bemoans:

Obstructionism has taken three forms. The first is a refusal by some states to accept federal funds to expand their Medicaid programs. Under the law, the funds cover a hundred per cent of state costs for three years and no less than ninety per cent thereafter. Every calculation shows substantial savings for state budgets and millions more people covered. Nonetheless, twenty-five states are turning down the assistance. The second is a refusal to operate a state health exchange that would provide individuals with insurance options. In effect, conservatives are choosing to make Washington set up the insurance market, and then complaining about a government takeover. The third form of obstructionism is outright sabotage. Conservative groups are campaigning to persuade young people, in particular, that going without insurance is

[32][1] http://www.newyorker.com/talk/comment/2013/10/07/131007taco_talk_gawande

"better for you"—advice that no responsible parent would ever give to a child. Congress has also tied up funding for the Web site, making delays and snags that much more inevitable.

The state exchanges will also entail Medicaid expansion. Why? After all the Feds are paying. Well first where do the Feds get the money, simply from us. Second, and this is critical, the Fed support is but for a short while. Then the States must pay. That is excessive. Especially since in some states they are doubling or tripling the Medicaid roles. Take New Jersey, there will almost be a tripling of the roles. Now it is not as if they are not getting care, just go to any ER. But now it gets loaded onto private insurance fees. Taken out of corporate and individual coffers. But when the size triples, it will be all out of the remaining taxpayers pockets, along with the sizeable subsidies. Imaging getting a subsidy even if your income is just shy of $100,000!

And he continues:

Some states are going further, passing measures to make it difficult for people to enroll. The health-care-reform act enables local health centers and other organizations to provide "navigators" to help those who have difficulties enrolling, because they are ill, or disabled, or simply overwhelmed by the choices. Medicare has a virtually identical program to help senior citizens sort through their coverage options. No one has had a problem with Medicare navigators. But more than a dozen states have passed measures subjecting health-exchange navigators to strict requirements: licensing exams, heavy licensing fees, insurance bonds.

Is there any concern in the above statement? Should states just allow anyone to "assist" people in selecting how to spend money on 18% of the economy? The navigator program is open to massive fraud and corruption. The navigators need de minimus training and can put themselves forth as experts and who knows what they will do. We regulate attorneys and accountants and even hair dressers. People will be making tremendous personal and financial decisions on getting insurance. We regulate those who purvey home and auto and life insurance. But this writer seems to consider it some evil to regulate the purveyors under the ACA. Why? Do we trust Government agents any more than others? Just look at the IRS. Argument ended. As for the Medicare program, first we paid for it, second we keep paying for it, third, there is no navigator, there is one program, and fourth it delimits my choice of physicians.

So what is wrong with the ACA? I started this blog in late 2008 recognizing two things. First that the economy was in a mess and not a single academic economist had a clue. A few admitted it but most such as the gnome from the South kept mouthing off as to what should be done. The classic case is the Romer curve, predictions that were not even close, even now! And that person is still teaching on the state dole. Second, was the issue of Health Care? I complained about Hillary Care in the early 90s and when I saw train wreck number two approaching I again was concerned.

In my opinion Health Care should be as follows:

1. Universal coverage. Everyone needs to have it.

2. Commercially available. Insurance entities should market it nationally.

3. Provide catastrophic coverage only by mandate. You get terminal cancer, a stroke, massive MI, you are covered. You have a cold, it is your dime. You can always buy more insurance, but the law must not mandate some full package. That includes birth control.

4. Individual purchases and after tax dollars. That is correct, just like your home and auto insurance.

5. Government subsidies for the lower incomes. That means poor folks. Poor because they cannot find a job. Not poor because they just like hanging out at mom's through their 20s and 30s.

6. Penalties for lifestyle risks. Smoke and you [pay more, Obese and you pay more. Drugs and you pay more.

7. No Government control. The Government can require it, as a tax if you will, but they get no information, provide no regulations, and demand no specific performance.

Simple. As we have shown this can be done today with a lower expenditure than we have now for everyone.

The author ends with:

This kind of obstructionism has been seen before. After the Supreme Court's ruling in Brown v. Board of Education, in 1954, Virginia shut down schools in Charlottesville, Norfolk, and Warren County rather than accept black children in white schools. When the courts forced the schools to open, the governor followed a number of other Southern states in instituting hurdles such as "pupil placement" reviews, "freedom of choice" plans that provided nothing of the sort, and incessant legal delays. While in some states meaningful progress occurred rapidly, in others it took many years. We face a similar situation with health-care reform.

I guess every Democrat needs to bring in racism, it seems to be part of the Party rant. No one's rights are in dispute here. All have a right to buy health care. No one is denied health care because of sex, race, and religion. No group is being barred from hospitals. This in my opinion is just a classic cheap shot. Making this the same as racism is akin to calling a person a Nazi. It is both out of place and destroys the logic of the argument, if ever there was any. It now seems almost obligatory to rant in this manner. Frankly it dilutes whatever argument one may have.

The problem is that we need health care reform, we need universal health care but the Government as controller is the worst of a bad set of options. The regulations resulting from the Law are minion. They are confusing, some contradictory, and a great financial and unnecessary burden. Is this segregation? Hardly. It is the people speaking out against something jammed down their throats.

It would be nice if some of these academics and physicians had a modicum of financial acumen. Just a little bit.

Labels: Health Care

WHAT DO YOU MEAN BY BLUE?

I have from time to time had to deal with the epistemological issue of; what do you mean by blue? It seems that in the small but combative world of daylily fans there is the debate as to whether or not one can grow a blue daylily.

Now it eventually begs the question of: what do you mean by blue? I have written on this issue but alas the doubters remain. I have just read a brilliant paper on the Costa Rican river called the Sky Blue River, and it is a brilliant paper. It seems that there are two rivers in the country that when they meet the pH changes just enough and the molecular content of each river changes by the same so that the result is a brilliant blue river.

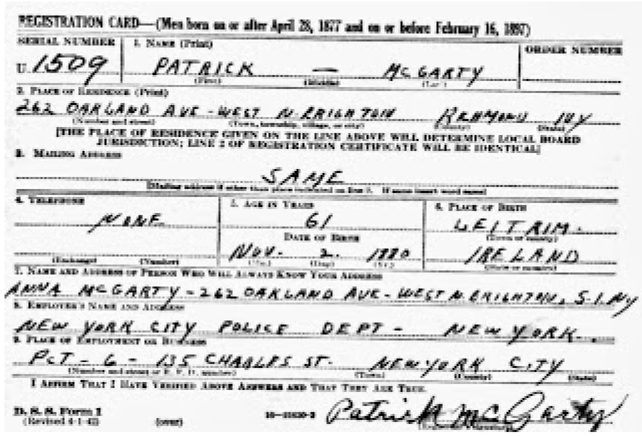
The paper by Castellon et al is superbly well done and complete. Simply the molecules from one river combine with those of a second and form an almost uniform molecular size molecule at about 566 nm and thus reflect the light back at a very narrow wavelength, the brilliant blue color.

For any of you who are interested in a wonderful explanation of a natural phenomenon this paper should become a classic!

Castellon, E., et al, Scattering of Light by Colloidal Aluminosilicate Particles Produces the Unusual Sky Blue Color of Rio Celeste, PLOS, September 2013, V 8, N 9.
Labels: Commentary

SUNDAY, SEPTEMBER 29, 2013

THE DRAFT AND THE GENERALS


REGISTRATION CARD—(Men born on or after April 28, 1877 and on or before February 16, 1897)

SERIAL NUMBER U. 1509 | 1. NAME (Print) PATRICK — McGARTY | ORDER NUMBER

2. PLACE OF RESIDENCE (Print)
262 OAKLAND AVE - WEST N. BRIGHTON ... N.Y.
[THE PLACE OF RESIDENCE GIVEN ON THE LINE ABOVE WILL DETERMINE LOCAL BOARD JURISDICTION; LINE 2 OF REGISTRATION CERTIFICATE WILL BE IDENTICAL]

3. MAILING ADDRESS
SAME

4. TELEPHONE NONE | 5. AGE IN YEARS 61 | DATE OF BIRTH NOV. 2. 1880 | 6. PLACE OF BIRTH LEITRIM. IRELAND

7. NAME AND ADDRESS OF PERSON WHO WILL ALWAYS KNOW YOUR ADDRESS
ANNA McGARTY - 262 OAKLAND AVE - WEST N. BRIGHTON, S.I. NY

8. EMPLOYER'S NAME AND ADDRESS
NEW YORK CITY POLICE DEPT - NEW YORK

9. PLACE OF EMPLOYMENT OR BUSINESS
PCT - 6 - 135 CHARLES ST. NEW YORK CITY

I AFFIRM THAT I HAVE VERIFIED ABOVE ANSWERS AND THAT THEY ARE TRUE.

D. S. S. Form 1 (Revised 4-1-42) (over)
Patrick McGarty

The Draft has been around for a while, on again and off again. Recently Generals who have "retired" from various branches of the Military, the Army especially, has been out and about advocating the Universal Draft.

Let us deal with a few facts.

Costs:

One of the Generals, one who seems to have let his own people run amok, says we should draft everyone, for two to three years of Universal Service. Let's take a look at the costs. Now the Census shows the following age groups[33][1]:

Age	Number	Percent Total Population
15 to 19 years	22,040,343	7.1
20 to 24 years	21,585,999	7.0
25 to 29 years	21,101,849	6.8
30 to 34 years	19,962,099	6.5
Total	84,690,290	27.4

So let us begin. Do we draft a group? Say we draft anyone 20 to 24 years of age for three years. That is 7% of the population and some 22 million people. That is a rather big Army but let us assume our Generals have thought through this process, after all they are the one running our Wars and also the NSA. They are real smart, are they not?

So we have 22 million taken from colleges, jobs, startup companies, Medical School and the like, we take them for three years, and we send them to where? Well, most would never make the Marines, they have standards, the Navy has just about 300 ships, and at most a third are active at a time, so the Navy really does not need them, the Air Force is using drones, so well that does not require much, the Coast Guard is not in DoD so we eliminate the, thus they all must go into

[33][1] http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_10_SF2_SF2DP1&prodType=table

the Army. To manage them we need thousands of more Generals, and thus West Point is happy. But let us look at the costs. A prisoner costs $100K to $150K per year to maintain.

Let is assume we treat the Army grunts the same, say $100K per year in food, uniforms, housing, health care, benefits etc. Thus we must spend $2.2 Trillion annually for the crowd. Yes, bottom line, with no other stuff, not even bullets, it adds $2.2 Trillion. Perhaps these Generals did not learn math at West Point. As we know, no good Army General would be unable to find tanks, mortars and the like to train these folks on, thus easily doubling the amount! Make it a round added $5 Trillion!

Loss of Opportunity

Thus we take the best and brightest out of their education process and have them do what? Send them to what war? Peel potatoes. The Army, when loaded with people, spends a great deal of time peeling potatoes and sweeping parade grounds, it is “hurry up and wait”. But what of the people? We take them from colleges, graduate schools, Medical Schools, and send them where? To the Army? Why? Because some General believes we should have everyone “serve”. What does he think the entrepreneur is doing? He or she is creating new businesses, new technologies, and new opportunities, often despite our Government. Serving is an interesting idea but it appears that these generals just want more bodies to push around. Think of all the start-up companies that will never happen and the loss of any chance to a China or other aggressive country.

Fighting Enemies has changed

Fighting our enemies, yes we have enemies, have changed or should be changing. We have few enemies who are “countries”. Not that it could not change, but at the present time we most likely will not go to war with China or Russia, frankly it would be devastating and there is little cause. Secondly or enemies are groups with belief systems alien to ours. They are not amassed in large armies that blend with the populace and to fight them we need alternative means which are pari passu with theirs. Namely we need intelligence networks and covert operations. We need the folks at the bar in Istanbul or at the market in Islamabad. We have to have flows of information from the mechanic in Bangkok or the baker in Mumbai. Then to join the enemy we need covert forces who do not announce themselves and a Government who takes no “credit” for the neutralization of the problems. The tanks and Carriers have at best a tertiary role. Thus it begs the question of what the good Generals want to do with all these people.

Thus when one listens to these Generals we need only ask; how much does it costs, what do we risk as a loss, and how are we dealing with our real enemies? The simple answer is that in no case do we need to draft 22 million people. Thus to paraphrase McArthur, “Generals should just fade away” and “keep quiet”.

Labels: Commentary, Military

MONDAY, SEPTEMBER 23, 2013

ACADEMICS AND CLEAN OFFICES

Frances Woolley again raises a compelling academic issue, clean offices. As she opens her post with the morally provoking dictum:

It happens at universities across the country. Professors do it. Administrative staff do it. Some sneak onto campus on evenings or weekends, and quietly do it when no one is around. Others are bold enough to do it during regular office hours. I'm talking about cleaning.
Dusting. Vacuuming. Sweeping. And, for the truly bold: Painting. Unblocking drains. Retrieving and repairing discarded furniture.

Now the above little guy was as close to a cleaner of my office at MIT that I could remember. Got him a beaker, do not worry, I released him in the park down the street. But back in the 60s at MIT my office was in Building 20, the old Radiation Lab buildings from WW II. Wooden, loaded with asbestos, riddled with mice, and I do not think anyone cleaned anything anytime. My desk and chairs were left over from WW II as well, undoubtedly having some historic value. The green leather cover with grey handles and legs and a grey linoleum top metal desk, and if one placed their lunch in the drawers the fellow above or his relatives would find it before lunch and take their share.

The walls were unpainted since 1944 and the windows in Winter were as windy as the Grand Canyon in January. Snow would blow in and accumulate on the ledges and the pigeons would on a sunny day sit there and make a racket when one was trying to assist some student.

But the building had character, or at least that is what we told ourselves, how lucky and honored we were to have been housed in such an historic site. I only later found it to be in error, there just was no room in the building with the AC in the summer time.

So as usual with Frances, you are not alone in having the burden of self reliance, but perhaps you have not yet had the opportunity to meet my many friends shown above. Remember, things can only get worse!
Labels: Academy

SUNDAY, SEPTEMBER 22, 2013

EAT YOUR BROCCOLI!

In a recent paper by Traka et al the authors state:

These findings suggest that consuming broccoli interacts with GSTM1 genotype to result in complex changes to signalling pathways associated with inflammation and carcinogenesis in the prostate. We propose that these changes may be mediated through the chemical interaction of isothiocyanates with signalling peptides in the plasma. This study provides, for the first time, experimental evidence obtained in humans to support observational studies that diets rich in cruciferous vegetables may reduce the risk of prostate cancer and other chronic disease.

As NCBI states:

Cytosolic and membrane-bound forms of glutathione S-transferase are encoded by two distinct supergene families. At present, eight distinct classes of the soluble cytoplasmic mammalian glutathione S-transferases have been identified: alpha, kappa, mu, omega, pi, sigma, theta and zeta. This gene encodes a glutathione S-transferase that belongs to the mu class. The mu class of enzymes functions in the detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins and products of oxidative stress, by conjugation with glutathione. The genes encoding the mu class of enzymes are organized in a gene cluster on chromosome 1p13.3 and are known to be highly polymorphic. These genetic variations can change an individual's susceptibility to carcinogens and toxins as well as affect the toxicity and efficacy of certain drugs. Null mutations of this class mu gene have been linked with an increase in a number of cancers, likely due to an increased susceptibility to environmental toxins and carcinogens.

GSTM1 is a significant factor in many cancers, especially melanoma. They conclude:

First, we demonstrate that routine prostate needle biopsies can be used for global gene expression analyses in addition to histological assessment, and that it is possible to monitor changes in expression with time. It is notable that men within both dietary arms of the study had significant changes in the androgen receptor pathway.

It is possible that these changes in androgen signalling are associated with aging and independent of diets, or they may have been induced by a common component of both the broccoli-rich and pea-rich diet.

To our knowledge there is no data on the rate of change on androgen signalling in men of this age with HGPIN. This observation suggests further study is warranted. Analysis of the rate of change of gene expression of men diagnosed with either HGPIN or localized prostate cancer through sequential biopsies may provide reliable biomarkers to measure the likelihood of both carcinogenesis and progression to aggressive cancer, and complement histological examination of needle biopsies and measurement of plasma PSA levels.

Secondly, stratification of global gene expression profiles by genotype has been informative, and

this approach could be extended to other genes to dissect patterns of gene expression in prostate or other tissues.

Lastly, it is conceivable that other dietary phytochemicals, such as polyphenolic derivatives, could also chemically interact with signalling peptides in the plasma, in a similar manner to the suggested mechanism of action of isothiocyanates.

This is an interesting study especially from the perspective of following the gene trail as well as understanding the detailed chemistry related to its control. We have examined HGPIN in some detail and it has been argued elsewhere that it is a necessary precursor of PCa. However we have also noted that in certain men with HGPIN, after an high density number of cores in a prostate biopsy, 24 or more, that the HGPIN regresses to the point that none can be observed on subsequent exams.

This paper may be of use not only in understanding the nature of phytogenic control but also for remission.

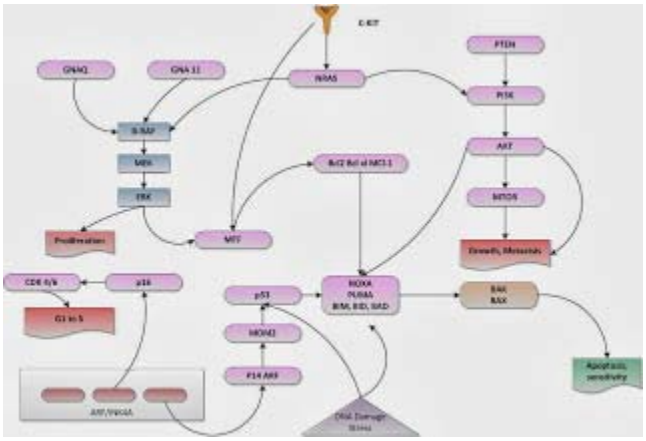
Reference

Traka, M., et al, Broccoli Consumption Interacts with GSTM1 to Perturb Oncogenic Signalling Pathways in the Prostate, PLOS, July 2008, Volume 3, Issue 7

NCBI, http://www.ncbi.nlm.nih.gov/gene/2944
Labels: Cancer

BRAF, MEK, PI3K AND MELANOMA

Pathway analysis has become a significant element in developing therapeutics for various cancers. Melanoma was first attacked using the BRAF V600 mutation as a target and then the MEK change was added. However as is seen in many cancers other mutations then occur making the initial therapeutic no longer functional. The pathways for melanoma are shown below.



In a recent paper by Villanueva et al the authors have demonstrated that a tri-partite treatment has efficacy in melanoma.
They state:

Although BRAF and MEK inhibitors have proven clinical benefits in melanoma, most patients develop resistance. We report a de novo MEK2- Q60P mutation and BRAF gain in a melanoma from a patient who progressed on the MEK inhibitor trametinib and did not respond to the BRAF inhibitor dabrafenib.

We also identified the same MEK2-Q60P mutation along with BRAF amplification in a xenograft tumor derived from a second melanoma patient resistant to the combination of dabrafenib and trametinib. Melanoma cells chronically exposed to trametinib acquired concurrent MEK2-Q60P mutation and BRAF-V600E amplification, which conferred resistance to MEK and BRAF inhibitors. The resistant cells had sustained MAPK activation and persistent phosphorylation of S6K.

A triple combination of dabrafenib, trametinib, and the PI3K/mTOR inhibitor GSK2126458 led to sustained tumor growth inhibition. Hence, concurrent genetic events that sustain MAPK signaling can underlie resistance to both BRAF and MEK inhibitors, requiring novel therapeutic strategies to overcome it.

This is an excellent example of a triple therapeutic attack on a cancer. The problem is that the malignant cells seem always to change again so in effect one must continually measure the cell and add a new element to the treatment. It would be useful if one better understood the natural evolution, if such an assumption is viable.

The authors conclude:

Combination therapy with BRAF and MEK inhibitors appears to be more effective than single-agent approaches; however, this combination could have limited activity in resistant tumors, particularly in the context of concurrent resistance mechanisms that hyperactivate the MAPK pathway. Our studies suggest that this combination is likely to be more effective if used as first-line therapy before resistance emerges. Moreover, effective therapies are sorely needed for patients who progress on BRAF/MEK inhibitors.

Targeting the MAPK pathway downstream of MEK at the level of ERK, S6K, or RSK is a potential approach to overcome resistance. We have demonstrated that a triple combination strategy using BRAF, MEK, and PI3K/mTOR inhibitors led to sustained tumor growth control, with no overt signs of toxicity. This type of strategy will need to be further refined and evaluated. Various issues that could be explored include alternative dose scheduling, drug sequencing, drug combinations comprising specific inhibitors of downstream targets, and efficacy in tumors bearing other mechanisms of BRAF- and/or MEK-inhibitor resistance or other tumor types.

Alternative combination strategies, such as the one we tested, warrant preclinical and clinical investigation as potential approaches to treat patients refractory to BRAF and MEK inhibitors.

The opportunity exhibited by this approach is significant. However it raises several questions.

1. Is there a "natural" and predictable progression of melanoma mutations which can then be therapeutically addressed? Namely, can one anticipate future changes and perhaps deal with them early?

2. How does one know what the full complements of changes are in a single patient? We can extract part of a localized tumor and from that sample and determine but what of the cells that lodged in the brain for example. We know that cells which cross the blood brain barrier exhibit differing surface markers and these may very well be reflective of further mutations. One may then seek to target these as well, which is a significant challenge.

3. Back to the old stem cell problem, namely if there are stem cells in melanoma then do we target them and if so how do we identify them? Are the cells we target merely subservient to the stem cell which avoids being targeted?

4. Does this approach mandate a therapeutic strategy which is truly patient specific? Namely do we now genetically deal with each patient separately or are their reasonably large classes?

There are substantial issues but the results in this paper a quite significant and promising.

References

Villaneuva, J., et al, Concurrent MEK2 Mutation and BRAF Amplification Confer Resistance to BRAF and MEK Inhibitors in Melanoma, Cell Reports 4, 1–10, September 26, 2013.
Labels: Cancer

FRIDAY, SEPTEMBER 20, 2013

CANCER CELL MOVEMENT THROUGH THE BLOOD

The movement of cancer cells from the initial site of development and to distant sites is a complex problem. We have previously provided a high level model for this process but it makes significant assumptions of the movement parameters which may not necessarily be reflective of the prime biochemical processes actually involved[34][1]. In a recent paper by Chen et al the authors have modeled the movement from the blood stream into distant organs.

The metastatic process is a complex concatenation of loss of cell localization and cell survival and proliferation in new environments. Generally as cells mature into specific cell types they become localized to their environment, such as in melanocytes and the E cadherin binding[35][2].

[34][1] http://www.telmarc.com/Documents/White%20Papers/93%20Cancer%20Cellular%20Dynamics.pdf

[35][2] http://www.telmarc.com/Documents/Books/Melanoma%20Genomics%2007.pdf

Cells also work within their own environment via communications with the extra cellular matrices[36][3].

The authors state:

We demonstrate tight endothelial cell–cell junctions, basement membrane deposition and physiological values of vessel permeability. Employing our assay, we demonstrate impaired endothelial barrier function and increased extravasation efficiency with inflammatory cytokine stimulation, as well as positive correlations between the metastatic potentials of MDA-MB-231, HT-1080, MCF-10A and their extravasation capabilities. High resolution time-lapse microscopy reveals the highly dynamic nature of extravasation events, beginning with thin tumor cell protrusions across the endothelium followed by extrusion of the remainder of the cell body through the formation of small (1 mm) openings in the endothelial barrier which grows in size (8 mm) to allow for nuclear transmigration. No disruption to endothelial cell–cell junctions is discernible at 60 X, or by changes in local barrier function after completion of transmigration. Tumor transendothelial migration efficiency is significantly higher in trapped cells compared to non-trapped adhered cells, and in cell clusters versus single tumor cells.

Specifically the investigators have developed a mechanical model of the vasculature, one they can manipulate for analytical purposes, and then they demonstrate the movement of the malignant cells across the interface into a quasi-cellular environment.

As Chu states:

Now researchers at MIT have developed a microfluidic device that mimics the flow of cancer cells through a system of blood vessels. Using high-resolution time-lapse imaging, the researchers captured the moments as a cancer cell squeezes its way through a blood vessel wall into the surrounding extracellular matrix.

She continues:

As tumor cells make their way through the circulatory system, some "arrest," or pause at a particular location, adhering to a blood vessel's wall — the first stage of extravasation. Scientists have thought that this cell arrest occurs in one of two ways: A cell may send out sticky projections that grab onto the vessel lining, or it may be too big to pass through, literally becoming trapped within the vessel. To investigate which possibility is more likely, the researchers grew a network of tiny blood vessels from a solution of human umbilical-cord endothelial cells. They injected a solution containing vascular cells into a small microfluidic device containing a reservoir of hydrogel, along with growth factors normally present in the developing circulatory system. Within days, an intricate system of microvessels took shape, with

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36[3]

http://www.telmarc.com/Documents/White%20Papers/88%20Extracellular%20Matrix%2002.pdf

each about one millimeter long and 10 to 100 microns in diameter — dimensions similar to the body's small capillaries. The group then pumped tumor cells through the vascular network, using a line of breast cancer cells known to be particularly invasive. Using high-resolution confocal microscopy, the team watched as tumor cells flowed through the miniature circulatory system. They observed that the majority of cells that arrested along a vessel did so due to entrapment — that is, they simply became stuck.

The observations are unfortunately in vitro and in a constructed environment and lack much of the biochemical elements that often make up for the transport. Although this is interesting in principle it fails to substantiate all of the elements which make up an in vivo process.

Then she concludes:

In addition to observing the extravasation of single tumor cells, the group also looked at the behavior of cell clusters — two or more cancer cells that accumulate in a blood vessel. From their observations, the researchers found that almost 70 percent of cell clusters broke through a blood barrier, compared with less than 10 percent of single cells. But some cells that make it out of the circulatory system may still fail to metastasize. To see whether a cell's ability to extravasate correlates with its metastatic potential, the group compared the efficiency of extravasation of different cancer cell lines. The lines included breast cancer cells, cells from fibrosarcoma (a cancer of the connective tissue), and a line of nonmetastatic cancer cells. Sure enough, the team observed that the most metastatic cells (fibrosarcoma cells) were also the most likely to extravasate, compared with breast cancer and nonmetastatic cells — a finding suggesting that targeting drugs to prevent extravasation may slow cancer metastasis.

The problem is that the cancer cells move in and out. There is a continual flow and at the same time they have the problem of mutating as well.

Observations

This is an interesting and strongly visual result. However, there are several observations:

Mutations: Cancer cells are continually mutating. Mutations results oftentimes in new surface receptors due to the changes in the internal proteins. The cell surface receptors may respond differently to the passage through such a cellular membrane. Thus this model may be reflective of itself but not of reality.

Localization: One of the most intriguing things about cancers is the localization of the metastases. Why, for example, do we so often see prostate cancer go to the bone, melanoma to the brain, across the blood brain barrier, and the same with so many other cancers. There is a predisposition to transfer at specific sites. How does this approach deal with such localization effects?

Stem Cells: Stem cells are a potential significant factor in understanding metastasis. One question is; do stem cells move as easily as others or more so? Or, are stem cells just active wherever they are and their products are carried through the blood stream to sites where they can continue cellular proliferation, and possibly induce a new set of stem cells there?

In and Out Flows: One of the questions one must ask when looking at cancer cells in the blood, as has been done recently, is if the cell is coming or going? Namely is the cell going from a source site, a primary, to a remote or metastatic site, or from an already metastatic site to another new one? The tagging of such cells would be important. The understanding of the genetic changes would also be of critical importance.

Biochemical Drivers: The nature of cell surface markers, receptors and the like, often dominate how the cells behaves, interacts with the ECM, and can move to the blood system and exit from it as well. We have argued that the cancer cell just flows and diffuses in the blood system and that there is no growth. That is just gross speculation but it is open to debate. Moreover the interaction of the cell with the cell way, and the localization effects of the cell way by organ specificity may be an attractive basis for organ specific metastasis. Or possibly not. But, having all these elements at play in vivo is better than in vitro.

Immune System: Then also is the impact of the immune system as the cells flow through the vessels. The cells are in a massive amount of immune system interactions, and how does this impact the cells?

These are but a few of the unanswered questions elicited by this paper. The simulation is well worth looking at the paper, but taking its results as fact is stretching it a bit too far.

References

Chen, M., et al, Mechanisms of tumor cell extravasation in an in vitro microvascular network platform, Integ Bio, 2013, http://pubs.rsc.org/en/content/pdf/article/2013/ib/c3ib40149a

Chu, J., Watching tumors burst through a blood vessel, MIT News, http://web.mit.edu/newsoffice/2013/watching-tumors-burst-through-a-blood-vessel-0920.html

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Labels: Cancer

DOING YOUR OWN DENTAL WORK

Now I like some Dentists, they generally have a sense of humor, especially for a group of professionals who generally strike more fear in people than the IRS. I like what they can do, fix teeth, an organ of the human body which seems to have been the most poorly designed one. They decay, break, are misaligned, fall out, and all sorts of other such things. But despite that I would never want to do my own dentistry. Nor would I want to learn how to do my own colonoscopy.

Now what made this most obvious was a piece I read in the MIT Tech. I guess students on the newspaper must write about something. Or perhaps the author really believes what they have said.

Programming lies at the heart of a modern education. Whether it relates to engineering, finance, or even the arts and humanities, computation is used across all fields to achieve what was once unimaginable. Yet, despite its ever-increasing prominence in industry and research, MIT has not instituted introductory computer science as a General Institute Requirement (GIR).

Now typing is also at the heart of modern education but I never took a course in that as well. Yes, I know it shows at times, many times. But programming you just pick up as you may need it. I suspect that MIT Sloan does not "teach" Excel. You better have absorbed it somewhere. And they have.

The author continues:

I find it surprising that a good number of students graduate from MIT without any kind of programming experience. I have found that those not familiar with coding often feel strongly about keeping it that way. "Why would you burden me, a student in English literature, by wasting my time to learn programming?" I am often asked with passionate defiance.
Here is why. A few nights ago, a friend of mine spent hours manually filtering and copying data from an enormous, disorganized online database into an excel sheet to perform calculations. After watching his frustration grow exponentially with the number of rows in the sheet, I offered a slight intrusion: a 20-line VBA script that automated this exhaustive task. Upon seeing this in action, his eyes light lit up with fascination and intrigue. "Teach me!" he exclaimed.

Now I watch my plumber install my water softener. It would have taken me twice as long if not longer. Comparative advantage at play, I can do something he cannot do. Same with that root canal. I did not shout when he turned the water back on, "teach me", I said "How much". The moral is that some things we have other people do, we cannot master everything.

The second element is learn to program "what" in "what". In 1962 I learned Fortran Assembly language. Moving registers back and forth on an IBM 704. Then Fortran, Cobol, Snobol, C, LISP, C, Pascal, and the list goes on. Do I program now, no, no need to, we outsource that. Are the principles important, perhaps, but even in 1962 I just picked up the first language. There were no classes, I ended up teaching the first class to lab students. So why force this on everyone since there is o one language, no one approach.

Most 8 year olds have picked up the facility to manipulate their iPad better than most adults. Perhaps it is better to let sleeping dog lie.
Labels: Education

THE FCC AND REALITY

The FCC is typically a mass of attorneys. There are a few economists and a technical type or two. I have been in and out of the place for four decades or more. Their rulings are all too often highly political and their understanding of technology often a decade behind. They are often a

deer in the headlights when it comes to leading edge technology until it runs over them.

But the following from The Hill is truly amazing:

Radio communications has been a persistent problem for public safety officials, hampering the responses to the 9/11 terrorist attacks as well as Hurricane Katrina.

Emergency responders lobbied Congress successfully to authorize a $7 billion nationwide wireless network — which is not yet in operation— that could help improve radio communications during disasters.

"The FCC will continue to monitor, evaluate and respond as needed to help ensure our nation's communications infrastructure works when people need it most. These are the times when Americans must be able to communicate with family, friends and emergency personnel," said acting Federal Communications Commission Chairwoman .... Tuesday.

Of course we spent $7 billion on a wireless network, which is not finished and does not work. But the FCC has no control over any implementation other than slowing them down. Yes people need to communicate and there are many ways to do it. The DC problem was that they went into a secure building, often protected against RF intrusion, so would one not expect that a radio would not work. Try using a cell phone in Langley, unless you are thew Director and DDO.

The FCC does not design radios, it does not develop system designs, it does not attest to specific use, it does not manufacture. It regulates, and in so doing delimits often at the behest of third party interests. One need look no further than frequency re-allocations.

One wonders why politicians make statements that just do not make any sense if one had understood the facts which in effect the person in that position should have. Welcome to Washington!
Labels: FCC

SUNDAY, SEPTEMBER 15, 2013

THIS IS WHY THE UNIVERSITIES ARE SO COSTLY

The NY Times has the ability to have no insight into the obvious. Consider the piece on getting a philosophy degree and then trying to get a job.They state:

Rock music played as the students entered the school's chapel, and then Andy Chan, vice president in charge of the Office of Personal and Career Development — the O.P.C.D., it is called — introduced his team with a video spoof of the television show "The Office." The students played a game in which they could guess, by text, which majors had been chosen by various gainfully employed alumni of the school. (Human-capital analyst at Deloitte? And the answer is . . . German!) And a panel of students shared their own glamorous work experiences: a fellowship in Paris, an internship at a start-up....

Chan, who can earn up to $350,000 a year, raised more than $10 million, mostly from parents,

for a sunny, glass career center with video displays and healthful snacks for students ("It looks like Google," Chan told me). He likes to say he has "supersized" the career-services office, creating an elaborate Web site and hiring enough staff members — close to 30 — to offer conciergelike services to students.

The above is one of the reasons why the costs of college is exploding; more and more VPs and salaries that exceed most college presidents.

Students should decide what to major in based upon where they can get employed, and if that is as a plumber then stay away from paying exorbitant salaries to college overhead folks.

Philosophy is wonderful, I even minored in it, it was great at mixers and telling co-eds about Sartre, well back in the 50s at least. But as a EE major it was based upon what jobs were available. Then you looked in the NY Times on Sunday, counted the number of jobs, and then chose your major. There were no jobs for philosophers. Sorry. Still there are none.

Thus this article promotes the nonsense we see ion many students; Fine Art, Philosophy, History, Classic Languages. If you come from money and are assured to be supported through your life then go do whatever. If however you have hard working parents helping out you owe it to them and yourself to find a job. That is what college is about. Getting a job, pure and simple.

Your parents should not even be there when you arrive at college. They have other things to do, like make a living. If you are 18 then you are on your own. Figuring out what to do is part of life and it may begin with getting to college on your own. Today parents treat their college age children like kindergarten kids decades ago. There is a cost to that, the cost being the salaries of "feel good" hanger on people as described above. If I arrived and saw this I would drag the young one away, sue the school for fraud, and send junior to a good community college. I would also question junior's judgement in selecting such a place to begin with!
Labels: Education

THURSDAY, SEPTEMBER 12, 2013

FAREWELL TO THE HORSES

I loved the carousel at Seaside. It had the old wooden horses and the pipe music from some fake organ and it was a ride fit for a low risk person like me. Today it burned to the ground. It will truly be missed and the best wishes for all those left with the pile of ashes. It was not one of the seven wonders of the world but for every young child to see it for the first time and watch their eyes sparkle, it will be missed. Farewell good friend.
Labels: Commentary

ANOTHER LOOK AT MOOCS

I am trying the MIT 7.00X Biology course taught by Lander. It is amazing. It is a real MIT type course.

First, Lander's lectures in the MIT style. Get three to five key principles across with collateral details so that the ideas are focused. You learn the way they think. This is unlike the Electronics course which was more IIT than MIT. Lander gets you to "feel" the ideas, to be able to intuit what to expect.

Second, the problem sets are also MIT styles. There are a few chick the box types but then the stretch the envelope ones are there as well. The software is explained by videos, the young lady doing it is speaking a bit too fast if one does not know it already, and the TA providing the added backup is great, and reminds me of many of the TAs I had decades ago. Great job!

Third, the pace is just right. The video presentation and board use is exceedingly better than the Coursera Melbourne class. Lander knows his subject, he knows what is essential to grasp the key ideas so you can add to your own wealth of understanding whereas the Aussie is too young and inexperienced and relies on powerpoint slides, the bane of any good educator.

Fourth, I have yet to see the nonsense in the Discussion groups. Perhaps it is filtered.

Bottom line, whether they have improved or that Landers is just great, which he is, this is a five star experience. Look forward to seeing it progress.
Labels: Education

WEDNESDAY, SEPTEMBER 11, 2013

REMEMBERING SEPTEMBER 11TH

After twelve years there is now a set of new buildings and a park. There also is a massive police and National Guard presence. Thus change has occurred.

The New York skyline is ever changing.
Labels: Commentary

MONDAY, SEPTEMBER 9, 2013

SYRIA AND COSTS

The CBO issued a less than compelling report stating:

S. J. Res. 21 would authorise the President to use military force against the government of Syria, for up to 90 days, in response to its use of chemical weapons. Prior to the use of force, the President would be required to provide a determination to the Congress addressing several criteria to show that such action is necessary and in the national interest. In addition, it would require the President to submit to the Congress a strategy for negotiating a political settlement to the Syrian conflict, a comprehensive review of U.S. policy towards Syria, and periodic reports on the progress of military operations. The Administration has not detailed how it would use the

authority that would be provided by this resolution; thus, CBO has no basis for estimating the costs of implementing S. J. Res. 21.

Just a thought.

Labels: Middle East

SUNDAY, SEPTEMBER 8, 2013

SOME THOUGHTS ON SYRIA

I sent the following to my Senator and Congressman. Some thoughts:

Dear Congressman/Senator,

I am writing to indicate my disapproval of any and all U.S. military actions in or around Syria by the United States at the current time. I strongly hope that you can concur in this opinion. My reasons are as follows:

American Interests: One can understand generally an American interest of peace in the region. However this has always seemed to be thwarted by the very nature of the peoples, tribal in construction, and conflict has been a way to negotiate and achieve their tribal goals. Thus an American interest should and must be more than just the reduction of internal conflict, which frankly may be an impossibility. As for establishing democracy this too is at best wishful thinking. Democracy may very well work at this time in civilization only those regions which are capable of working within its confines. Finally there is an argued putative threat to the United States and its people. Frankly the threat is real but not confided to Syria, it is a pandemic Islamic threat to our very existence and to date the current regime in Syria has been the least of the purports of such a threat whereas many of those opposing the regime are at the heart of those making and carrying out the threat. Threats always exist but in this case the threat level post regime overthrow may be higher as we have clearly seen in Egypt. Humanitarian interests are always of concern, but that we can handle by supporting the millions of refugees.

Unintended Consequences: The list of possible unintended consequences is minion. First there are the almost predictable and then there are the deadly unpredictable. One merely understand WW I to see how Governments can incrementally proceed to global war. On the almost

predictable side are; explosion of Islamic terrorist activity, Iranian intervention, Israel attacks, Russian intervention, and the list goes on.

End Game: The current Administration appears to be clueless as how best to execute what they want to do and also have failed to express any end game. As we have clearly seen in so many prior conflicts the articulation of what constitutes success and what constitutes failure are never a priori stated and adhered to. Thus we seem to just plod along in a senseless manner justifying incremental changes. One needs look no further than Iraq or Afghanistan. In Afghanistan we clearly should have had a single goal; exterminate with extreme prejudice any and all perpetrators of the attacks on the U.S. We should not have sought to democratize the country, one which is at best a warring tribal culture and at worst a petri dish for future attacks. One should just have destroyed the attackers and their allies and moved on.

Acting Alone: Acting alone is foolhardy. If this is so critical it is demanded that world support should be involved. It is not. Russia does not want an enemy it does not know. It had several 911 events from Pushkin Square to the ever deadly Islamic Fundamentalist attacks throughout Russia. We seem to have neglected that. Thus for Putin, a man I know, he wants the devil he knows to those he does not. China also sees this globally as an economic drag that it cannot afford, nor should we. The Brits clearly said no. We also should do so.

Expenditure or Resources: Our military is not equipped after more than a decade of war to enter into a massive engagement with disparate players in undefined territory. This would make Vietnam look like child's play. In addition the costs would explode exponentially. There is the classic step to one more try and then another. It would costs hundreds of billions we do not want to take from an already weak economy.

Very truly yours,

As the witch from the East states:

the smooth consensus builder and community organizer, the former constitutional professor and the drive-by senator who must stand by the argument he made when he ran for president excoriating W.'s and Dick Cheney's highhandedness: checks and balances must be observed. As he told Charlie Savage, then reporting for The Boston Globe, in 2007, "The president does not have power under the Constitution to unilaterally authorize a military attack in a situation that does not involve stopping an actual or imminent threat to the nation."

Now first, the current President was not a Professor, he was a Lecturer, one of those fill-in individuals to teach a class that no one on the faculty can do at the time. He was not Professor Tribe at Harvard. Second, words mean something, even if you were the one to utter them. This would be a reckless action with unlimited unintended consequences. Now that we approach the 100th anniversary of WW-I we should remember that some tens of millions of dead resulting from one small misstep after another. So do not take the first one.
Labels: Middle East

TUESDAY, SEPTEMBER 3, 2013

TEEN UNEMPLOYMENT

BILL MOHAN, FRANCIS ESPIPIO, TERRY McGARTY
Life Guards Work to Save Girl After S. I. Rescue

In the late 1950s one looked for summer employment for several reasons. First and most importantly, it was a means to fund college. Yes in those days with tuition some $750-$1,200 a year, and room and board as low as you could make it off campus, you found the best possible job for the most money. Thus as a lifeguard in NYC you got $60 a week, and this for 12 weeks you got $720.00. Almost there on tuition. If you lived in an apartment you could get 4 guys for $120 per month so it cost you $30 per month and food was rutabagas! You survived.

Yet to get the job as lifeguard you had to do one thing. Be one of the top 400 swimmers in NYC. You competed for the 400 slots by swimming 440 yards and you had to rank 1-400 to become employed. Having no access to a pool one ran and exercised and then eventually jumped into the 54th Street pool and swam like hell. It was not a job but your life that was driving you through the water, lungs burning and muscles being used in a way you had not trained for. But year after year one did this.

Thus when is read the articles about the Jobless Generation I also wonder why the Ecuadorans are doing the lawns, the gardens, the painting work, while the college students are "unemployed". The authors state:

The summer work situation for teens is even worse. Sum and his Northeastern colleagues figure that in 1999, 52.6 percent of American teens between age sixteen and nineteen had summer work. Today, only 32.3 percent do. And these numbers are worse for young blacks and Latinos. In 1999, about 33 percent of black teens had summer jobs; now 19 percent do—a reduction by almost half. But the decline is true for all groups: 39 percent of white teens worked this summer—a sharp decrease from the 1999 figure of 63.3 percent.

Somehow the lawns are being done, the houses painted, the windows washed, and yet not a single college kid, not a single teenager. Why. I am certain that if they offered and delivered at competitive prices there would be massive amounts of work. It is less an issue of lack of work than it is an issue of lack of motivation. At 5 AM the Ecuadorans line up to begin their day. I see them as I go off to an early meeting, me and the Ecuadorans. Then in the day time when I am out in the 100F temps dressed to protect my Northern European skin from the sun as I labor on the plants, they say hello and shake their heads to see the old man in hat, long sleeves, long pants and gloves. To them I am the oddity because they do not seen any American youth doing such things, just me the crazy old many, working in the heat of the day, along with the Ecuadorans.

Thus when I read of the lack of jobs, I see that is a whine of the kids who cannot and will not create their own future. The Ecuadorans have taken the future in their hands, the sweaty hot and difficult future and it may very well become theirs. Not the college kid bemoaning the fate of not having a job!
Labels: Economics, Economy

MONDAY, SEPTEMBER 2, 2013

THE CHANGES IN THE WORLD: WHERE IS VALUE CREATED?

Another economist opined on how the world will change. Again the opinions given are in my opinion clearly baseless and fail to understand what moves things forward. Value creation is a fundamental principle. Do something that someone else values well above your cost to do it and you can be successful. However the return you may attain is often more dependent upon society's perception of that value.

Consider the following examples:

1. Banking: People who control money control all. In the old days, some fifty or so years ago, bankers were poorly paid with the exception of those who were the heads of the firms. Today any smart MBA can work themselves into some hedge fund and manage to get 9 figures in short order. It is not that you come from wealth, to the contrary one just needs the technical and personal skills to be positioned properly. Now finance really is a value transfer business. It doe not create value, it allows fore those who have created it to expand it and they get a bit off the top. No banker have ever created true value.

2. Biotech: The next few decades will see explosive growth in biotech. Pathway focused therapeutics, epigenetic controls, and the like are changing both the way we understand disease and how we treat it. However the equivalent people in that profession are often underpaid and over worked. Yet they are the true value creators. They will be the change agents in the next century. As computer types reached a pinnacle in the past decade, these folks will have a chance in the next decades. Unlike banking these folks must really know something and then once attained they must fight daily to keep at the leading edge as new insights flow almost hourly.

3. Education: This professor is another one of the apparently poorly educated regarding the online course area. Getting an A in say Genetics does not mean that you either understand it

properly or can apply it. Understanding requires an ability to integrate disparate parts to create a whole. On line courses are akin to education in China and India. Memorize what the instructor said, feed it back exactly and you win. Then the challenge is to innovate. That comes from those who are "educated" by challenge at the US best universities. Not by online courses.

4. The smart phone: This is just a single step into a fully distributed world. The Apps explosion is really a simplified set of toy tools in many cases. The real challenge is embedding the measurement tools in people and things for beneficial purposes as well as economically profitable purposes. Just having an App to find a data is not adding much to our economic success. Having an implant to monitor and control caloric input and glucose levels is.

This one really got me:

MOTIVATORS *A lot of jobs will consist of making people feel either very good or very bad about themselves. Coaches, mentors and disciplinarians will spread to many areas of life, at least for those of us who can stand to listen to them. These people will cajole us, flatter us and shame us into improving our lives, our work habits and our consumption. That's why so many people go to yoga class instead of relying on the podcast. Managers who are motivators of first-rate talent will see their earnings continue to rise.*

What happened to the individual. Yes the world is filled with leaders and followers, and the rest who must just get out of the way. But the development of new ideas is often an individual like function. One frequently must ignore the others and lead by example. A good leader does so by example more often than my motivation. People often follow the successful person rather than just the nice one.

Then this one really shocked me:

PEOPLE WITH DELICATE FEELINGS *Computing and software will make it easier to measure performance and productivity. It will be harder to gloss over our failings and maintain self-deception. In essence everyone will suffer the fate of professional chess players, who always know when they have lost a game, have an exact numerical rating for their overall performance, and find excuses for failure hard to come by.* ***Individuals will have many measures of their proficiency.*** *They will have an* ***incentive to disclose that information to get the better job or social opportunity.*** *You'll assume the worst about those who keep secrets, and so openness will reign. Many of us will start to hate the idea of Big Data.*

I remember back in the early 70s I was working at a Lab at MIT and the Group Leader had just finished some "feelings" type seminar. He then decided that all in the group should learn from what he did and so he took it upon himself to have us go through a sensitivity type training session. We would share our feelings. That lasted but a brief time until the Air Force Security folks found that it may very well compromise many security clearances. His attempt at 70s feelings stopped abruptly. As to disclosing, try not to with a TS plus clearance. The world concerning disclosures to the appropriate authorities has always been there. But disclosing to the world is and should remain one's own choice. Individuals should not have to tell their boss all about their personal lives. I believe there are laws about that even now.

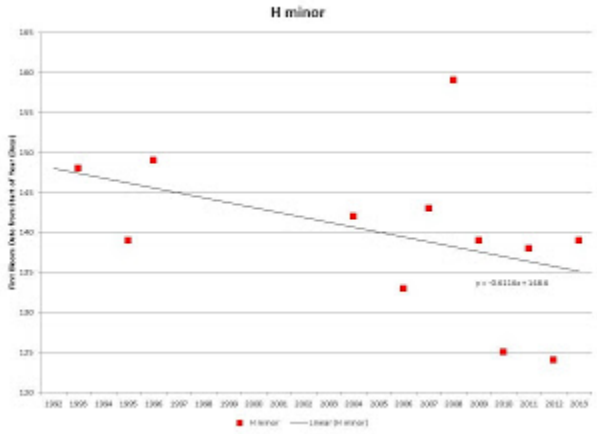
Thus in conclusion this was in my opinion one of the most incoherent and nonsensical articles I have ever read. But then it was written by one of those economists. No surprise there.
Labels: Economics

PIGOU: AGAIN AND AGAIN

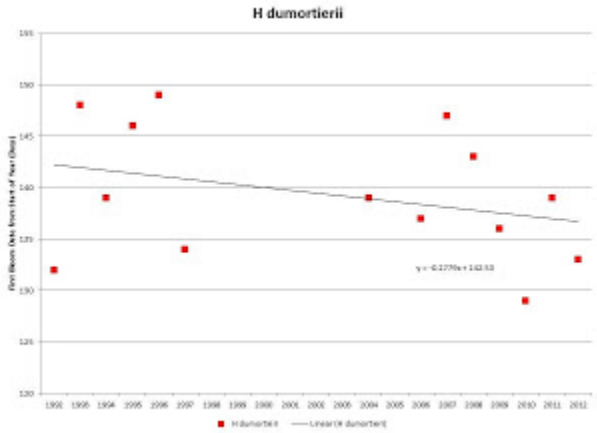
My "favorite" Harvard Economist is back with his rather socialistic approach to dealing with the alleged man-created carbon dioxide cause of global warming. Now permit me a few opening statement regarding this issue:

1. Unlike Harvard Economists, I have a second life as a Botanist and as such am attuned to the changes in Mother Nature. I have three Hemerocallis plants whose first bloom date, measured in days from the first of the new year, have demonstrated clear shortening. Namely they are blooming earlier each year. Why? Clearly after removing any confounding data it is the heating of the earth, at least the earth near these plants.

Now the first



Now for the second:



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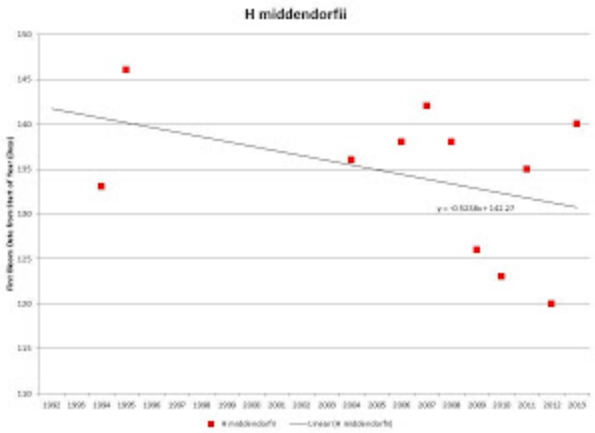


Thus what to believe, the facts and my eyes or what other people may be saying. The trend is clear and it is significant. Thus we have global warming. First bloom times are excellent integrators of total warmth.

2. Now for the cause. Carbon dioxide has been around for a while and the source and sink models are complex at best. More CO2 means more plant growth which means more O2. What is the stable balance? One really does not yet know. Then there is the oceans and their complex dynamics all too often poorly modeled in the global warming analysis. In the 1960s I did measurements of aerosols in the upper atmosphere. Then we had a growing amount and the fear was global cooling. Now we have reduced them and the opposite effect is occurring. Go figure.

3. The source of the cause is solely man. Well there are lots of things generating CO2 and methane etc. In fact methane is really a nasty source and Mother Nature generates tons of it.

So what can we conclude. The globe is warming. Which may or may not be a bad thing. The source may be CO2, but there is also other stuff. And the source of the sources are complex.

Now comes the Harvard Prof again with Pigou. He states:

The main question is how we, as a society, ensure that we all make the right decisions, taking into account both the personal impact of our actions and the externalities. There are three approaches. ...

Fortunately, a policy broader in scope is possible, which brings us to the third approach to dealing with climate externalities: putting a price on carbon emissions. If the government charged a fee for each emission of carbon, that fee would be built into the prices of products and lifestyles.

When making everyday decisions, people would naturally look at the prices they face and, in effect, take into account the global impact of their choices. In economics jargon, a price on carbon would induce people to "internalize the externality." A bill introduced this year by Representatives Henry A. Waxman and Earl Blumenauer and Senators Sheldon Whitehouse and Brian Schatz does exactly that. Their proposed carbon fee — or carbon tax, if you prefer — is

more effective and less invasive than the regulatory approach that the federal government has traditionally pursued.

Let us consider his logic a bit:

1. Economists are not engineers. Engineers see a problem and find a solution which is economical and works. Have a river and want to get to the other side, we build something called a bridge. We do not generate some additional and useless tax. Thus from an engineer's perspective we find ways to generate energy with less CO2 releases if that is the case or find ways to absorb and use the CO2 elsewhere. The result is more business and economic growth independent of Washington. But to an economist who appears to be ignorant of any engineering insight you just load on another tax.

2. Inherent in this third approach is that one has choices. In many cases in the lower middle class and lower classes there are fewer choices. They have to travel shop, live, work etc. Unlike the Harvard Prof they cannot afford the electric car route. Somehow the elite top 1% are lacking in observations of those underlings.

3. Then if we tax the poor folks the Government just gets more money, it is akin to giving Scotch to an alcoholic. Yet the good Prof states:

The crucial point is what is done with the revenue raised by the carbon fee. If it's used to finance larger government, Republicans would have every reason to balk. But if the Democratic sponsors conceded to using the new revenue to reduce personal and corporate income tax rates, a bipartisan compromise is possible to imagine.

Somehow I have never seen the Government reduce taxes especially this Government. Democrats conceding to lower taxes is akin to the Pope hiring the Devil to run the Curia. Never happen.

So what is the solution? Try technology. It is a word never mentioned by the socialistic Profs who promote Governmental interference.
Labels: Economics, Global Warming

FRIDAY, AUGUST 30, 2013

METFORMIN AND PCA

There was an interesting paper on the use of metformin and the reduction of prostate cancer. The article by Margel et al concludes:

Adjusted HR for PC-specific mortality was 0.76 (95% CI, 0.64 to 0.89) for each additional 6 months of metformin use. The association with all-cause mortality was also significant but declined over time from an HR of 0.76 in the first 6 months to 0.93 between 24 and 30 months. There was no relationship between cumulative use of other antidiabetic drugs and either outcome... Increased cumulative duration of metformin exposure after PC diagnosis was associated with decreases in both all-cause and PC-specific mortality among diabetic men.

Generally we know that metformin is used in Type 2 Diabetes and that in addition Type 2 Diabetics are obese. We also know that they generally consume high carbs and often have high oxidants resulting therefrom. Metformin increases insulin secretion somewhat and thus may drive down this process. This of course is speculation, logically somewhat correct, but of interest.
Labels: Cancer

CURIOUSER AND CURIOUSER

As Alice said:

'Curiouser and curiouser!' cried Alice (she was so much surprised, that for the moment she quite forgot how to speak good English); 'now I'm opening out like the largest telescope that ever was! Good-bye, feet!'

I have examined the negative votes on one star ratings on Crawford and it gets curiouser and curiouser.

As of this AM there are 3 reviews with exactly 4 positive and 415 negative for a total of 419. There is one with 4 of 420. There are 3 with 3 of 418. Close enough. Coincidence? Remember my writing on Groups vs Crowds. This is Group attack. It is too organized and exact.

This type of attack tells you two things. One is that the buyer should beware and always look at the bad reviews. The left wing technocrats only looked at what they saw as the "bad" parts of the negative reviews. There is no similar attack on the five star reviews.

The more I think of this the more I am convinced that the Internet Group think is potentially one of the most dangerous capabilities ever invented. The cost of starting a Group is small and the power it wields is great.
Labels: Books, Broadband, FCC

WEDNESDAY, AUGUST 28, 2013

IT IS JUST A LITTLE CANCER. DON'T WORRY.

In a recent JAMA article there is a discussion of the alleged problem of over-diagnosis of cancer. The authors are trying to make the point that we now discover malignancies quite early and that for the most part they will not kill the patient so we should not be treating them.

They start by saying:

Screening for breast cancer and prostate cancer appears to detect more cancers that are potentially clinically insignificant.

The operative word is potentially. The problem is that in PCa we still cannot differentiate between the 90% indolent and 10% deadly types of PCa. Ductal CIS of the breast has a similar

situation. Thus one errs on the side of caution and advises the patient accordingly. They ultimately make the decision, often based upon their mindset rather than medical evidence.

They continue:

Optimal screening frequency depends on the cancer's growth rate. If a cancer is fast growing, screening is rarely effective. If a cancer is slow growing but progressive, with a long latency and a precancerous lesion (eg, colonic polyps or cervical intraepithelial neoplasia), screening is ideal and less frequent screening (eg, 10 years for colonoscopy) may be effective. In the case of an indolent tumor, detection is potentially harmful because it can result in overtreatment. These observations provide an opportunity to refocus screening on reducing disease morbidity and mortality and lower the burden of cancer screening and treatments.

Again the issue of what is indolent. That is the operative phrase and that unfortunately is the problem. Now here is the operative position:

National Cancer Institute convened a meeting to evaluate the problem of "overdiagnosis," which occurs when tumors are detected that, if left unattended, would not become clinically apparent or cause death. Overdiagnosis, if not recognized, generally leads to overtreatment.

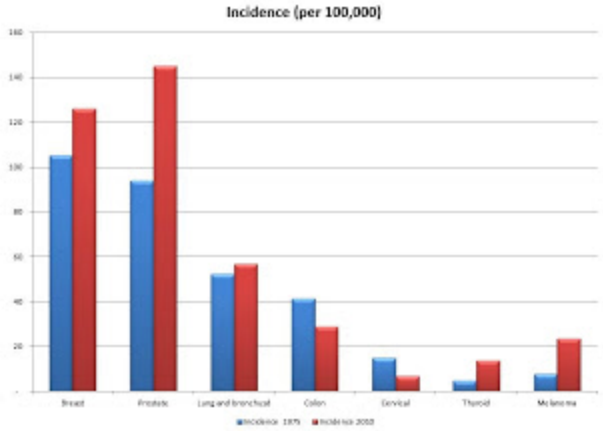
Do we have the tools at this point to determine what is capable of being left unattended and what is not. If we diagnose a melanoma, just a little melanoma, just a few clusters about the rete, some small spreading down to the dermis, should we just wait? But even to get there we had to excise. What of those few hundreds of thousands of cells in the prostate that have a Gleason 7 grade at biopsy. Do we say, "see you in a couple of years".

They conclude:

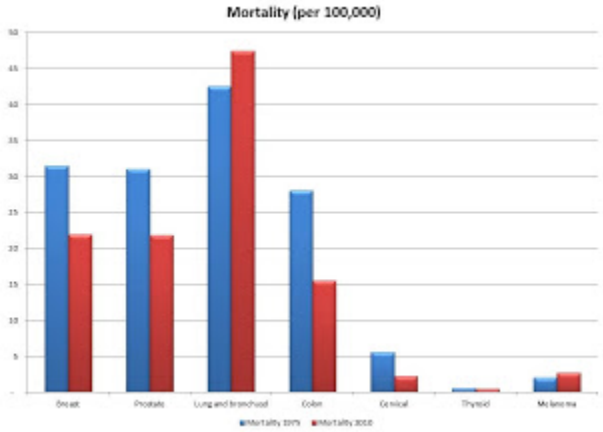
Physicians and patients should engage in open discussion about these complex issues. The media should better understand and communicate the message so that as a community the approach to screening can be improved.

Now the first part is often difficult. You tell a patient they have cancer and you can predict the result. Get rid of it. Worse the family finds out and you have the whole clan on your back, and then their lawyers. So you suggest, cajole, guide, and hope for the best. The Press on the other hand is often placing gasoline on the flames. Then add the glory docs who take to TV and have to tell a tale a day and you have a massive stew just boiling.

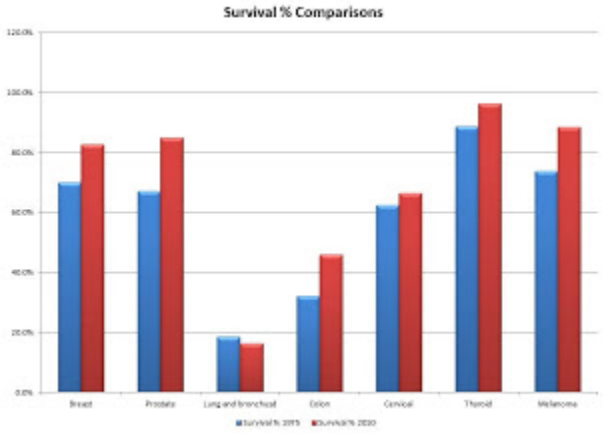
Now let us review some of their data:



First, the incidence. The argument is that incidence has increased because we are diagnosing earlier. This is true in prostate, breast and melanoma. That means that in all cases we are finding early stage cancers that would not change the ultimate end state. Namely the patient would never die from this cancer.



Now mortality as above. In breast and prostate we see a drop of mortality. That is due to better treatments. But melanoma is up, and up a lot percentage wise. But I thought we were diagnosing earlier, but more people are dying. Why? No answer given.



Finally I did a survival analysis. They did not do this. Survival of prostate and breast is up. But is that because of better treatment or because the numerator is enlarged due to the over diagnosis? In which case we may actually have worse survival despite all the improved treatments. There is a problem of logic here. The argument is far from compelling.

Finally look at melanoma. Survival is up but I thought we had over diagnosed here as well. Makes no sense.

The story is more complex that the authors seem to state it. We are still left with telling what we see and doing the best we can.

Labels: Cancer, Health Care

HOW MUCH IS 2+2?

I am really starting to hate these MOOCs. They requested the answer be in "prose". Prose is not poetry, that is all. So if one is asked:

"What is 2+2?"

The answer is 4. No, according to the other students one needs a paragraph to explain. But the directions said prose, not poetry. But the Peer, what an abuse of the word, Graders said it must be a "paragraph". So you lose all credit. No recourse.

I suspect that the desired answer should be:

"The questions asked what, and by what it means providing a numerical value to the terms which follow. Then the question poses the specifics. Namely the terms 2, +, and 2. The repetitive use of the symbol 2 may also imply a multiplicative operator as well as the given addition operator. Now we assume that the 2 chose is a numeral in the standard number system, and applying a Cantor set analysis one can determine by upward counting that the use of the addition operator one attains a total of 2 plus 1 or three then plus one that is 4 which is the equivalent of 2+2. Thus using this process one can obtained the desired answer of 4."

Are you out of you ever loving mind! The answer is 4. No paragraph, no subject, predicate, verb! Just 4! This appears to be an episode of Faulty Towers but in Australia!

This is why the MOOCs will never work as an academic performance system. Having thousands of untrained random folks deciding what the right answer is when they most likely never had the material or anything close is insane!

I suspect that the academics and politicians who push this nonsense have never tasted the medicine.

And yes, 4 is prose. It is not poetry. Poetry is:

I once had the answer as 4
But the grader lowered my score
So I write this long blog
To simmer and slog
And then go back no more

I have also recently heard that some new teachers are using this peer assessment approach. They do the following:

1. Assign the material to be read by the student

2. Have peer assessment in homework and exams

3. The instructor then sits in class and oversees the students arguing amongst each other who has the correct answer.

4. And this is at a $40,000 a year Prep School.

No wonder we are falling behind Uganda and Mongolia. Who allows such stuff. At least Socrates asked questions and had a method to his madness. I wonder what ever happened to teaching. At MIT I knew each of my students personally. I knew their performance, and when they were off top levels and when I was not performing. In this new world of teaching it appears we pay a fortune for at best being the school monitor.

Thus Peer Assessment is the worst idea I have ever heard of. Some of the peers are in my opinion just a bit short of being evil doers. There is no positive feedback and the basic premise of education has been removed. It appears as who can destroy more peers than anyone else. I guess Coursera is not alone, it include the real expensive schools as well. Too bad America!
Labels: Education

TUESDAY, AUGUST 27, 2013

THOU DOTH PROTEST TOO MUCH

The NY Times has a rebuttal of sorts by the gnome from the south alleging that economics is indeed a science despite all that we see in its performance related thereto.

The piece states:

Yet obviously something is deeply wrong with economics. While economists using textbook macro models got things mostly and impressively right, many famous economists refused to use those models, in fact, they made it clear in discussion that they didn't understand points that had been worked out generations ago. Moreover, it's hard to find any economists who changed their minds when their predictions, say of sharply higher inflation, turned out wrong.

Nor is this a new thing. My take on the history of macro is that the notion of equilibrium business cycles had, by the standards of any normal science, definitively failed by any normal scientific standard by 1990 at the latest. The original idea that money had real effects because people were surprised by monetary shocks fell apart in the face of evidence of business cycle persistence; the real business cycle view that nominal shocks didn't actually matter after all was refuted by decisive evidence that, in fact, it did.

Notwithstanding the cri de couer above, the fundamentals still remain. The models are speculations, they are gross assumptions of individual behavior and are based not upon fundamental physical facts but oftentimes based upon what the author believes are, or worse, should be facts. Those parts of economics which are accounting tautologies generally yield reliable results, as well they should by definition. Those parts which get involved into human interaction, demand curves and the like, often are the source of our troubles. Individuals really exist, not just crowds, or groups, and as a result oftentimes things just get in another direction.

One need look no farther that the above statement. One the one hand the gnome states that the truth is in the books but on the other hand the purveyors of the trade refuse to apply the very truths they espouse. In Medicine that would be per se malpractice and they would get sued. For an economist it is their opinion and non-actionable. Engineers get sued if the bridge collapses,

Architects if the building does not function properly, and even lawyers themselves can get in trouble. For all there are professional ethical standards. Again I ask, what economist has ever been sued? Never will it happen, it is NOT a science.
Labels: Economics

MONDAY, AUGUST 26, 2013

CROWDS ARE NOT ALWAYS THE ANSWER

There is an article in the Science News site commenting on the putative "crowd" behavior of ratings. They state:

The "wisdom of crowds" has become a mantra of the Internet age. Need to choose a new vacuum cleaner? Check out the reviews on Amazon. Is that restaurant any good? See what Yelp has to say. But a new study suggests that such online scores don't always reveal the best choice. A massive controlled experiment of Web users finds that such ratings are highly susceptible to irrational "herd behavior"—and that the herd can be manipulated.

As to Amazon and many other sites it is often not the crow that manipulates but the real manipulators manipulate. Shills are often used to praise a topic so it gets high points or to drive out a bad review if it detracts from the story to be pushed. I have argued and demonstrated that again and again. They are active "politically" driven sites.

The piece concludes:

The "wisdom of crowds" has become a mantra of the Internet age. Need to choose a new vacuum cleaner? Check out the reviews on Amazon. Is that restaurant any good? See what Yelp has to say. But a new study suggests that such online scores don't always reveal the best choice. A massive controlled experiment of Web users finds that such ratings are highly susceptible to irrational "herd behavior"—and that the herd can be manipulated.

I argue that all too often it is not this random crowd but deliberate groups pushing an agenda. I have seen several late. The first was the pro-Government controlled Internet crew who pushed a book by some contender for a FCC position. The group wrote dozens of positive reviews while voting down any negative reviews. The second is a review of a book about the HeLa cancer cells. This set of reviews slammed any negative comments as well.

The solution is simple. Always go for the most negative review and work upwards. The solution is that there should be no anonymous reviews at all and the identity of the reviewer and their bona fides should be available. Otherwise any character can praise of slam anything. Is there a crowd effect? Possibly, but many times it is a "group" rather than "crowd" effect.

Now for the purpose of this discussion let's define the two terms:

Crowd: A crowd is a collection of independent but manipulable individuals who have a propensity for commenting on some topic.

Group: A group is a collection of individuals who are bound in some manner by a common world view which they have a need to reaffirm or express to others.

Crowds just like to belong whereas Groups desire to influence and self affirm an a priori world view.

Crowds as contrast to Groups are malleable and tend to reaffirm an a posteriori consensus.

Now to the MIT researchers. How does one differentiate between a Crowd and a Group. Hint, timing and intensity. Groups have a semblance or organization. They tend to jump on an issue and they tend to be more clustered in intensity and position. In contrast the Crowd is more diffusion like, slowly building and following.

Given these general characteristics the interesting question is to apply some form of pattern recognition to the responses to ascertain whether the responses are Crowd or Group driven.This has been done in the intelligence world and one would suspect that the Amazons of the world would find this useful, Google certainly would.
Labels: Commentary

ECONOMICS AND REALITY

There is a piece today in the NY Times asking the existential question about Economics, What good it is? At the same time DeLong has a post with a quote which is the answer:

Larry Summers *(1983): "The first way to find a topic is to open Keynes's General Theory at random, read what's on that page, and math it up…"*

Now I do not have the reference to the quote but what I believe it says is to write something of merit to the economics community just go to Keynes and take a paragraph and set it to a massive set of incomprehensible equations.

Which oftentimes is what they do, and even more often without any thought to the reality of the situation.

Imagine, if you will, doing that to say the Bible. Take a paragraph, any paragraph, and then reduce it to equations. Take John Chapter 1:

He came unto his own, and his own received him not. But as many as received him, he gave them power to be made the sons of God, to them that believe in his name. Who are born, not of blood, nor of the will of the flesh, nor of the will of man, but of God. And the Word was made flesh, and dwelt among us, (and we saw his glory, the glory as it were of the only begotten of the Father,) full of grace and truth. John beareth witness of him, and crieth out, saying: This was he of whom I spoke: He that shall come after me, is preferred before me: because he was before me.

Well I tried but no luck. But then I am not an economist. But Summers had a point.

The Times article states:

The fact that the discipline of economics hasn't helped us improve our predictive abilities suggests it is still far from being a science, and may never be. Still, the misperceptions persist. A student who graduates with a degree in economics leaves college with a bachelor of science, but possesses nothing so firm as the student of the real world processes of chemistry or even agriculture. Before the 1970s, the discussion of how to make economics a science was left mostly to economists. But like war, which is too important to be left to the generals, economics was too important to be left to the Nobel-winning members of the University of Chicago faculty. Over time, the question of why economics has not (yet) qualified as a science has become an obsession among theorists, including philosophers of science like us.

As we have noted before so many times Economics is not only NOT a science, it is akin to a religion, a religion with many waring sects. Instead of just putting equations to Keynes, they have like the early Church various numbers of their Bishops meeting at various Synods trying to reach a consensus on say John 1: 11]-[16].
Labels: Economics

SATURDAY, AUGUST 24, 2013

COLLEGE AND SOME MORE POOR IDEAS

I read a piece in the WSJ regarding the costs of colleges. Now the dumbest statement I have ever read, in my opinion, is in this article, by of all people, an academic. It states:

A better idea, Mr. Vedder suggests, would be to implement a national exam like the GRE (Graduate Record Examination) to measure how much students learn in college. This is not on Mr. Obama's list.

Now imagine MIT EECS students being judged by a GRE exam! They learn hardware, software, mathematics, AI, networks, neuro-nets, and none of that would be on any GRE fit for all. Would we have to make certain the bio majors did the same as EECS, as History. It is clear that this individual has no clue as to the breath of the undergraduate curricula. Once one hears that statement one rejects all else coming from that neurocortex.

The reasons for escalating college costs are simple:

1. Government pays whatever is asked. Thus there is no real supply and demand. It is like public education and health care. But with a slight twist. In this case the student is stuck with the bill, sooner or later. And that bill becomes a drag on the total economy.

2. Buildings. This is the bane of higher Ed. They build again and again and for every dollar of capital spent there is $0.10 per year spent on maintenance, or even more. Thus if you have spent $1B in new buildings you face $100 million or more on just plain feeding the dragon you created. No one seems to figure that in.

3. More Government demands means more Deans and VPs. This has exploded over the past three decades. Behind each new Dean is an army of staff and they get paid, get benefits, get pensions. Worse they get more buildings, and the death spiral continues.

4. Salaries for Administrative folks is obscene. Take MIT. The new President I gather is paid almost $1.25 million. Now I can see someone getting a good salary but parity may have to be considered. Is this position, not person, worth that amount, and what are the conditions for getting rid of them? No one seems to consider that factor.

It is a systemic problem. It is not a GRE issue or an issue of graduates getting good jobs. It is that we have allowed and even supported expansive and expensive growth. The Government has been at the core of this.

Now the article continues:

Nor is the president addressing what Mr. Vedder believes is a fundamental problem: too many kids going to college. "Thirty-percent of the adult population has college degrees," he notes. "The Department of Labor tells us that only 20% or so of jobs require college degrees. We have 115,520 janitors in the United States with bachelor's degrees or more. Why are we encouraging more kids to go to college?"

Mr. Vedder sees similarities between the government's higher education and housing policies, which created a bubble and precipitated the last financial crisis. "In housing, we had artificially low interest rates. The government encouraged people with low qualifications to buy a house. Today, we have low interest rates on student loans. The government is encouraging kids to go to school who are unqualified just as it encouraged people to buy a home who are unqualified."

Yes indeed we have too many people going to colleges for degrees they will never use. We need plumbers, carpenters, electricians, but we have few places to train them and we have unions that make certain that they are NOT employed. And the Government supports that as well.

Yes there is a bubble, but unlike the housing bubble that broke and spewed forth its debris, this one unfortunately will become a chronic festering burden on our economy for decades. The

Government funds degrees in Fine Arts and Classic music and there frankly are few jobs. Even Oceanography has just so many openings.
Labels: Education

MDS AND METHYLATION

Introduction

Epigenetic factors are appearing to be more prevalent in our understanding of the causes of many cancers. These factors include such elements as methylation, long non-coding RNAs (lncRNA), micro RNAs and acetylation. None of these reflect a fundamental change in the DNA of the underlying genes, but they do reflect a complex process whereby the way the DNA is processed and presented functions. Unlike translocations and gene changes which are difficult to unravel, many of these epigenetic changes may be found to be reversible in part or in whole. We focus on methylation and methylation related disorders herein. The details are in a report we have just completed[37][1].

The MDS Therapeutic Paradigm

MDS, the myelodysplastic syndrome, is a multifaceted disease of the bone marrow cells which leads to the over-production of immature blood cells; erythrocytes, lymphocytes, platelets and others. It is often indolent in its early stages but then turns quite virulent and is often fatal, frequently due to the development of AML, acute myelogenous leukemia. However, recent understanding of a key driver of MDS, namely hypermethylation, has resulted in complex therapies which may have proven not only efficacious but curative.

We use this disorder as an example of how methylation causes potential cancers and further how it can be targeted and treated.

The therapeutic responses to MDS are representative to the multi-prong attack on various cancers. The fact that MDS is not per se a cancer but an artifact of a hypermethylation state, and that hypermethylation can be reversed, as compared to a genetic change such as found in CML, the Philadelphia chromosome translocation, and that we know how to deal with hypermethylation, lends MDS to some form of initial treatment. However demethylation does not always work.

Thus the second attack is more aggressive which is a modified hematologic stem cell transplant.

[37][1] See http://www.telmarc.com/Documents/White%20Papers/102%20MDS%20and%20Methylation.pdf

That further reduces the aberrant cell load to an almost miniscule amount. The final hit is using modified T cells called cytokine induced killer cells specifically targeted for the remaining hypermethylated cells.

This paradigm has been applied to other malignancies with substantial success. The classic cases are the childhood leukemias and Hodgkin's lymphoma. One would suspect that MDS being substantially of the same class would fit this paradigm. Our intent here is to examine the literature across the above spectrum and attempt to make an assessment of progress in this disease.

Historical Context

Methylation has been know of for decades but it has only been in the last fifteen years or so that the connection between methylation and cancers has been somewhat understood. In a 1997 paper by Jones and Gonzalgo the authors state[38][2]:

DNA methylation is a mechanism for changing the base sequence of DNA without altering its coding function. As a heritable, yet reversible, epigenetic change, it has the potential of altering gene expression and has profound developmental and genetic consequences. The methylation reaction itself is mechanistically complex and involves the flipping of the target cytosine out of the intact double helix, so that the transfer of the methyl group from S-adenosylmethionine can occur in a cleft in the enzyme.

Cytosine methylation is inherently mutagenic, which presumably has led to the 80% suppression of the CpG methyl acceptor site in eukaryotic organisms, which methylate their genomes. It contributes strongly to the generation of polymorphisms and germ-line mutations, and to transition mutations that inactivate tumor-suppressor genes. Despite a 10- to 40-fold increases in the rate of transitions.

This was somewhat of an opening salvo regarding methylation and cancers. One should remember that this was almost five years before the complete reading of human DNA and also at a time when actually reading the methylated states was complex at best.

The authors hypothesized a mechanism for uncontrolled growth using the methylation construct. They posited three ways in which methylation functioned.

First, it caused a gene change. This was the C to T mutation change.

Second they posited the promoter suppression via methylation of the promoter. This method is seen quite frequently in the process.

Third, there may be a chromosome instability resulting from methylation.

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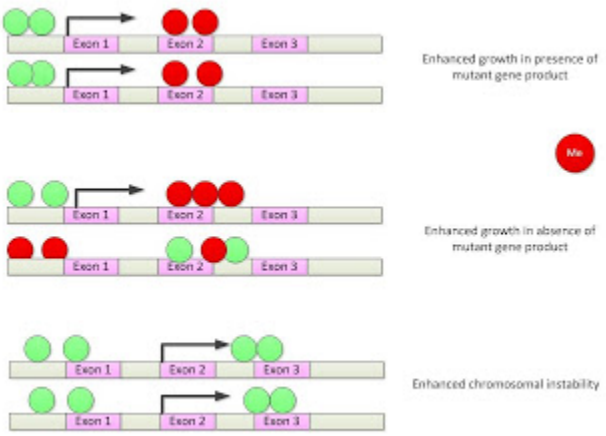
[38][2] Jones, P., M. Gonzalgo, Altered DNA methylation and genome instability: A new pathway to cancer?, Proc. Natl. Acad. Sci. USA Vol. 94, pp. 2103–2105, March 1997



At the same time Robertson and Jones wrote a paper on DNA methylation and its affects and they also suggested a strong link between that and cancer[39][3]. They stated:

As with the demethylation and de novo methylation observed during development, changes in methylation patterns during neoplasia have been recognized for some time. Initially it was shown that malignant cells have lower levels of methylation than do normal cells. This global hypomethylation accompanies a hypermethylation of CpG islands, DNA regions often associated with promoters of human genes that are normally protected from methylation.

The above statement is a clear description of what we now know to be correct; namely hypomethylation globally but hypermethylation of the CpG islands. The hypomethylation allows expression of a wide variety of proliferation genes while the CpG Island silencing via hypermethylation deactivates control genes. They continue:

The mechanism by which these regions remain unmethylated in the normal cell is not known, but it may be mediated by the binding of certain transcription factors. In malignant cells, these CpG-island regions become methylated and expression of the associated gene is silenced. In the case of a tumor-suppressor gene, this may result in a growth advantage for the cell.

DNA methylation– mediated transcriptional inhibition has thus been proposed as a mechanism that is alternative to mutation and deletion, in the removal of tumor suppressor– gene function. Examples of such genes include the two cell-cycle regulators p16 Ink4a and p15 Ink4b, the von Hippel–Lindau gene VHL in some renal carcinomas, the retinoblastoma gene product Rb, BRCA1, the angiogenesis inhibitor thrombospondin, and the metastasis-suppressor gene E-cadherin.

[39][3] Robertson, Jones, Dynamic Interrelationships between DNA Replication, Methylation, and Repair, Am. J. Hum. Genet. 61:1220–1224, 1997.

… Chuang et al. have shed new light on how methylation patterns are maintained and how they may of the associated gene is silenced. In the case of a tumor-suppressor gene, this may result in a growth advantage for the cell. DNA methylation– mediated transcriptional inhibition has thus been proposed as a mechanism that is alternative to mutation and deletion, in the removal of tumor suppressor– gene function.

Examples of such genes include the two cell-cycle regulators p16 Ink4a and p15 Ink4b, the von Hippel–Lindau gene VHL in some renal carcinomas, the retinoblastoma gene product Rb, BRCA1, the angiogenesis inhibitor thrombospondin, and the metastasis-suppressor gene E-cadherin (Graff et al. 1995). In a recent issue of Science …has shed new light on how methylation patterns are maintained and how they may become altered in cancer. It was shown that the DNA methyltransferase is targeted to newly replicated DNA by the replication associated protein PCNA (proliferating cell nuclear antigen).

PCNA is the polymerase-processivity factor for the d and e DNA polymerases, is homologous to the E. coli b subunit, and is required for DNA replication becomes altered in cancer. It was shown that the DNA methyltransferase is targeted to newly replicated DNA by the replication associated protein PCNA (proliferating cell nuclear antigen). PCNA is the polymerase-processivity factor for the d and e DNA polymerases, is homologous to the E. coli b subunit, and is required for DNA replication

Why Study MDS?

There are slightly more than 10,000 new cases of MDS each year. There may be a little difficulty in determine them because they can often go un-noticed until they convert to AML at which point the diagnosis would be clear. There may be a slight anemic, thrombocytopenia, and the presence of blasts, immature hematopoietic cells. A true diagnosis requires a bone marrow biopsy. The MDS patient may have one of many variants which we shall discuss latter.

However what seems common is the presence of hypermethylation resulting in the suppression of cell growth and proliferation control genes on the lineage of hematopoietic cells first affected. Thus the thrombocytes may be the initial ones affected and we see a drop in platelets and a presence of blasts. But in all cases it is the hypermethylation. There is as of yet in the process no genetic change, the excess immature growth is due solely to hypermethylation. Thus the control is simply control of hypermethylation via drugs which block the process. It is a somewhat simple model for developing a therapeutic.

Thus why study MDS? The answers are:

1. MDS is not a full blown cancer. It lacks the genetic breakdown.

2. MDS is a hypermethylation disease. Hypermethylation can be reversed. Thus there is an opportunity to seek a “cure”.

3. MDS does lead to cancer, most likely AML. The process that results in that change is worth of study as a means to seek both prevention and cure.

4. MDS can be monitored both genetically as well as via hypermethylation measurements.

Overview

In this report we examine several factors in depth. Specifically:

MDS: We present an overview of MDS and its various forms. This is a complex disease and it is almost as if no one patient is identical to any other patient. We consider the cause of methylation at the DNA level but we can at best speculate on the ultimate initiator. We know that many MDS patient had pre-existing malignancies for which the received both chemotherapy and radiation therapy. The nexus there seems to somewhat clear. However, many, if not most, MDS patients have no clearly defined initiating event.

Methylation: We explore methylation and examine how it occurs, and what it does to the functioning of the DNA expression. In many of our cancer models we often just look at gene, RNA and protein flow. As we have indicated before we often look at the epigenetic factors as noise. However it has become clear that the epigenetic elements are integral parts of a cells expression of its genetic capabilities and thus should be included in any model.

Demethylating Therapies: We examine the various demethylating therapies. The specifics are discussed in some detail as well as the efficacy of the therapeutics.

Acetylation: The histones around which the DNA is wound also exhibit acetylation. We examine this phenomenon and relate it to methylation.

Immunotherapy: We discuss immunotherapy focusing on the use of CIKs, cytokine induced killer cells, primed T cells directed at the remaining methylated hematopoietic cells.

We conclude with observations relevant to combined therapies.

Now the histones may also be acetylated and drawn together. When histones are drawn closer the genes in between cannot be read and thus they are not expressed. Now we can summarize this as follows:

	Hypermethylated	Hypomethylated
Benign	Suppresses Proliferation Gene	Activates Suppressor Gene
Cancer	Suppresses Control Gene	Activates Proliferation Gene

The third general step is the use of CIK, or cytokine induced killer cells. These are somewhat akin to NK cells and have been developed specifically for cancers of these type. We briefly discuss how they are prepared. The efficacy is yet to be fully determined but there is a large base of Phase I and II Trials demonstrating efficacy

Lin and Hui provide a definition for CIK cells[40][4]:

Cytokine-induced killer (CIK) cells are polyclonal T effector cells generated when cultured under cytokine stimulation. CIK cells exhibit potent, non-MHC-restricted cytolytic activities against susceptible tumor cells of both autologous and allogeneic origins. Over the past 20 years, CIK cells have evolved from experimental observations into early clinical studies with encouraging preliminary efficacy towards susceptible autologous and allogeneic tumor cells in both therapeutic and adjuvant settings. ...

we anticipate that the continuous therapeutic application of CIK cells will likely be developed along two major directions: overcoming the challenge to organize large prospective randomized clinical trials to define the roles of CIK cells in cancer immunotherapy and expanding its spectrum of cytotoxicity towards resistant tumor cells through experimental manipulations.

Jiang et al add to this description as follows[41][5]:

The number of immune cells, especially dendritic cells and cytotoxic tumor infiltrating lymphocytes (TIL), particularly Th1 cells, CD8 T cells, and NK cells is associated with increased survival of cancer patients. Such antitumor cellular immune responses can be greatly enhanced by adoptive transfer of activated type 1 lymphocytes.

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[40][4] Linn, Y., K. Hui, Cytokine-Induced NK-Like T Cells: From Bench to Bedside, Journal of Biomedicine and Biotechnology, Volume 2010.

[41][5] Jiang, J., et al, Cytokine-induced killer cells promote antitumor immunity, Journal of Translational Medicine 2013, 11:83.

Recently, adoptive cell therapy based on infusion of ex vivo expanded TILs has achieved substantial clinical success. Cytokine-induced killer (CIK) cells are a heterogeneous population of effector CD8 T cells with diverse TCR specificities, possessing non-MHC-restricted cytolytic activities against tumor cells. Preclinical studies of CIK cells in murine tumor models demonstrate significant antitumor effects against a number of hematopoietic and solid tumors. Clinical studies have confirmed benefit and safety of CIK cell-based therapy for patients with comparable malignancies.

Enhancing the potency and specificity of CIK therapy via immunological and genetic engineering approaches and identifying robust biomarkers of response will significantly improve this therapy.

The preparation and creation of CIK cells is done as described by Jakel et al[42][6]:

*CIK cells are generated by culturing **peripheral blood lymphocytes (PBL)** with*

1. *interferon-γ (**INF-γ**) monoclonal*
2. ***antibody against CD3 (anti-CD3)** and*
3. ***IL-2** in a particular time schedule.*

*The **cytokines INF-γ and IL-2 are crucial for the cytotoxicity** of the cells and anti-CD3 provides mitogenic signals to T cells for proliferation. Most of these CIK cells (87%) are positive for CD3 and for one of the T-cell coreceptor molecules CD4 (37.4%) or CD8 (64.2%), respectively.*

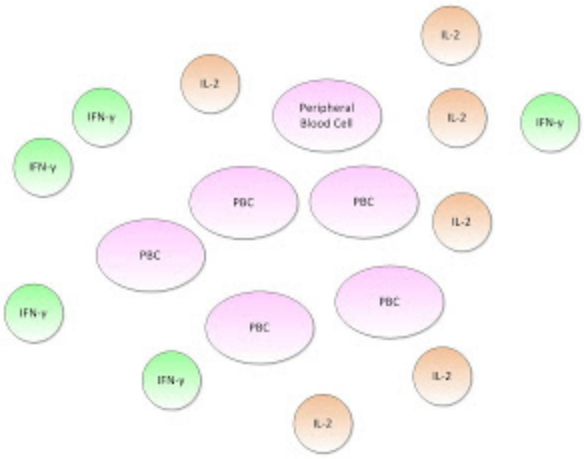
IFN-γ, added at day 0, activates monocytes providing crucial signals to T cells via interleukin-12 (IL-12) and CD58 (LFA-3) to expand CD56+ cells.

After 14 days of culture, 37.7% of cells are CD3+CD8+CD56+. These cells are referred to as natural killer T (NK-T) cells and represent the cell type with the greatest cytotoxicity in the CIK cell population.

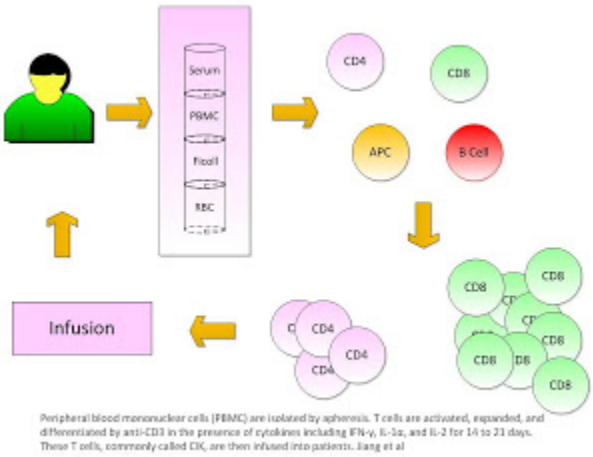
Interestingly, these CD3+CD56+ double positive CD8+ T cells do not derive from the rare CD3+CD56+ cells in the starting culture but from proliferating CD3+CD8+CD56− T cells.

Their cytotoxicity is nonmajor histocompatibility complex (MHC)-restricted and they are able to lyse a variety of solid and hematologic tumors. Cell lysis is not mediated through FasL but through perforin release. CIK cell cytotoxicity depends on NKG2D recognition and signaling.

[42][6] Jakel, C., et al, Clinical Studies Applying Cytokine-Induced Killer Cells for the Treatment of Renal Cell Carcinoma, Clinical and Developmental Immunology, Volume 2012.



Jiang et al propose the following:



Peripheral blood mononuclear cells (PBMC) are isolated by apheresis. T cells are activated, expanded, and differentiated by anti-CD3 in the presence of cytokines including IFN-γ, IL-1α, and IL-2 for 14 to 21 days. These T cells, commonly called CIK, are then infused into patients. Jiang et al

Jiang et al prepare their cells as follows:

CIK cells have been evaluated as an adoptive cell immunotherapy for cancer patients in a number of clinical trials.

Peripheral blood mononuclear cells (PBMC) were isolated by apheresis.

T cells were then activated, expanded, and differentiated by

1. ***anti-CD3*** *in the presence of cytokines including*
2. ***IFN-γ,***
3. ***IL-1α, and***
4. ***IL-2***

for ***14 to 21*** *days to generate CIK, which were subsequently infused into patients.*

There are no significant clinical results for this in MDS but there are many Trials underway. One could suppose that this is a substantial third step after a BMT procedure. Logically it could be curative.

Observations

We now want to make some general and specific observations. WE shall discuss each as a separate topic.

Complexities of Epigenetics

Epigenetics has become as significant a factor in cancer as the pathway and immunological approaches. The impact of miRNA, lncRNA, methylation, acetylation, and other epigenetic elements are now understood as causative. However the drivers initiating many of these are not clearly understood. The methylation in MDS for example is understood as a cause but what leads to the methylation is still speculative. For example in melanoma one could speculate that backscatter X-rays in full body airport scans provide just the driver for methylation if it is applied at the right time. However that is also speculative and no studies have been done. It is speculated that excess radiation, excess CAT scans or radiation for cancers can cause the methylation seen in MDS. Clinical proof is lacking however.

Downside of Methylation

Methylation treatment with DNMT suppressors is known to drive down the blast percentage. However it is a broad based therapeutic and demethylates many other cell. This may also give rise to secondary neoplasia, by activating proliferation genes in other cells in the body. It is not known how significant this is. It might result in sequelae as is found in Hodgkin's lymphoma but the sequelae there are often found 20-30 years later. Thus since MDS occurs at 70 years of age that well exceeds any life expectancy.

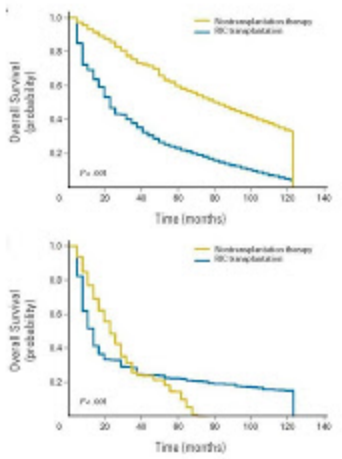
Hypo vs Hyper Methylation

The problem with MDS is known to be hypermethylation. But there are many cases of hypomethylation as well. One then wonders if the approach taken herein applies to those cases as well.

Efficacy; Remission or Cure

Limited survival data is clinically available using the CIK approach. Koreth et al present data based upon a Markov model but we have considerable concerns about the approach[43][7]. The results are shown below.

[43][7] Koreth J., et al, Role of Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem-Cell Transplantation in Older Patients With De Novo Myelodysplastic Syndromes: An International Collaborative Decision Analysis, JOURNAL OF CLINICAL ONCOLOGY, June 2013.



It should be noted that the top graph is for low to low intermediate and the bottom graph is high intermediate to high, using IPSS scoring. These Kaplan Meir curves show that for the high case we have a rapid drop and then a slow decline with about 20% at 10 years. Since the average age is about 70, the average life expectancy is 14 years and so 20% seem to have reached average life expectancy. In contrast the opposite is the case for the more indolent forms.

The problem that we see is the initial conditions. Perhaps one would expect most patients have initial health conditions which would bias them against a BMT survival. Perhaps other health conditions are also a concern. The problem is that MDS is so complex and given the patients initial health status conditions it is expected that any case is different and thus any generalized result is problematic.

Labels: Cancer

FRIDAY, AUGUST 23, 2013

MORE ON THE MOOC PROBLEM

Again I have been reading the Discussions on the MOOC I have finished. The Peer Graded final was in my opinion a total disaster. There was, in my opinion, one arrogant student who decided not just to grade 4 exams but some 17 if memory serves me correctly. His grades were atrocious. He posted them all, I guess to boost his ego, which of course backfired.

Then another student, this one I would hire, looked at the students bios and did a calculation and found that more than a third had PhDs or MDs or both. Oops I guess I was found out. Then he checked their bios and publications and found that many had written extensively in the area. He then concluded that perhaps this one third might know something, something more than the other student who had given his rather arrogant grade. Then he took it one step further and calculated the probability that of the 17 or so grades given what number were true experts, even better that the teacher in Australia! Brilliant. Then he concluded that the arrogant guy most likely made a blunder.

Then what happened. The foolish student, in my opinion, went and regraded all 17 or so! Upwards of course without any basis. So what were the first grades and even more so what good were the second! So Coursera had, in my opinion, this moronic way to get peer grades with a system which is fatally flawed. Namely cultural troglodytes who push their egos but with a modicum of intellect. I could have told them that. In running my companies across some 20 plus countries my greatest concern was cultural mollification, keeping everyone happy while minding local cultural norms. Had I tried something like this, well you understand.

Whoever came up with this approach just missed the mark. It sets a bad taste in people mouths especially as to the integrity of the process. They just ought drop this approach and return to multiple choice questions. Otherwise you have the Facebook generation mindset that whatever I think is as good if not better than whatever you think because I thought it.

Fools all too often get in trouble whenever they try to use the thought process.
Labels: Education

FRIDAY, AUGUST 23, 2013

OPEN ACCESS

Science has a piece this week stating that now more than 50% of "published" papers are open access and in the biotech world it exceeds 60%. The lowest number is in engineering. They state:

Efforts to give the public free access to peer-reviewed papers have reached a milestone: One-half of all papers are now freely available within a year or two of publication, concludes a new study sponsored by the European Commission. That means so called open-access publishing has reached a "tipping point" and will now accelerate, suggests Éric Archambault, the lead author of the study and president of Science-Metrix Inc. in Montreal, Canada. "Things are likely to move much faster now." But some open access observers have been quick to criticize the study, which yielded a number twice as high as other analyses.

This is a most interesting indication of several things. First the biotech world is fast moving and having the ability to get results from a broad base of sources makes it move quicker. Engineering is a slow plodding field. Just look at IEEE publications most of which are recast papers written by a mass of faculty and students rehashing what a single person did decades ago. So who cares. In contrast having access to the latest papers can result in the conversation and ideas spreading at the speed of light, literally.

The next issue is the whole question of peer reviewed papers. Peer review is time consuming and does not always do what was intended, for at heart it is all too often a political process. Open non-anonymous commentaries would be more effective, not the type that one finds after some blog post, but well though out "letter" replying to the papers. I suspect we may very well see a change in that direction, and as PLOS and others move forward perhaps a web site can combine rapid publications with credible named reviews written to be informative not just snarky bits which we all too often see.

Labels: Commentary

THURSDAY, AUGUST 22, 2013

NOW LET'S DESTROY HIGHER ED

In a brief piece in today's NY Times the article previews the proposal of the current Administration to get its hands into the higher education system, even further that it has.

The article states:

A draft of the proposal, obtained by The New York Times and likely to cause some consternation among colleges, shows a plan to rate colleges before the 2015 school year based on measures like tuition, graduation rates, debt and earnings of graduates, and the percentage of lower-income students who attend. The ratings would compare colleges against their peer institutions.

This means that the schools will most likely add a new Dean or even VP to oversee the collection, analysis, comparison, of this information, just adding to the already overburdened overhead at American Universities.

Now I did not need the Federal Government to have accomplish this task for me some fifty plus years ago. I gathered the information myself, no Internet, no iPhone, no Facebook. Just a set of paper catalogs, which I really liked, and some hard work. I went through a process of beginning life on my own and never once assumed to rely on the Government.

The piece continues:

... proposal urges colleges to experiment with approaches that reduce costs. The plan mentions so-called competency-based degrees, in which college credits are based not on the hours students spend in classrooms, but on how much they can show they know.

Another approach mentioned in the plan is online education through what have become known as "massive open online courses," or MOOCs, which are mostly free.

Competency? No grade? What is the difference. When I taught electronics some 40 plus years ago the circuit worked or it did not. Try med school, dead or alive. Then we also see them grabbing onto the MOOCs. They are not ready for prime time, and I would guess that not a one in the current Administration has actually take a few to understand their deficiencies. And back to competence, are we having the Administration define what a student must learn? It sounds a lot like that one. Does that means that MIT and Country College of Morris will be measured pari passu, they must teach at the same competency level?

If so then we will create just an extension of our existing Public School system and we know where that got us.

The solution is simple, but now near impossible. Get Government out of higher education, and that means even taking the student money away. Why, because that was the driver for allowing schools to ramp up tuition. The article clearly states:

Almost all of the federal government's $150 billion in annual student aid is distributed based on the number of students a college enrolls, regardless of how many graduate or how much debt they incur.

We know we have more than a trillion in Government backed student debt and we are adding to it at the rate of $150 billion a year. That in my opinion is a major driver for escalating student costs. Adding the Government in the mix even more will just send that higher and the quality lower.
Labels: Education, Politics

WEDNESDAY, AUGUST 21, 2013

MORE OBSERVATIONS ON MOOCS

I just finished a MOOC course and it included a peer grading exercise. What chaos! Imagine several thousands of people of varying degrees of competence in hundreds of countries grading other people whom they have no knowledge of. It is interesting but it becomes uncontrolled chaos.

For example:

There were N questions and of course one looks for N answers. Without exception not one sample I saw linked an answer to a question. You had to read a complex paragraph to try to intuit where the question was answered. If I were teaching the course they all would have failed. But that was not to be.

What is an answer? If you ask a question then one or two words may suffice. Why write the great American novel for an answer. But alas they just rambles on.

Plagiarism, some students who wrote on the Discussion Group went looking for it anywhere. Frankly the "rules" are so loose and it was open book that if you found the answer somewhere,

anywhere, let it be, this is not for real folks, it is a free course and you will not be judged by anyone except yourself.

Rambling Discussions. Not being a Twitter or Facebook user perhaps I am deficient in understanding run of the thumbs discussions. But they go on all over the place. I wonder if any of these people have a life.

Culture does come through. I should not have been surprised but one can see cultural factors coming through in judgmental statements.

You have the Twitter generation, the Facebook crowd, people just mouthing off as if each person is equal, no matter what they know or what they achieved. Every person has their opinion and they throw this into the mix. This is intellectual chaos. Frankly the system is rigged for chaos.

I had never seen this type of back stage discussions in my years of teaching but I guess it must have existed. But I suspect that it presents a treasure trove for sociologists and anthropologists.Peer grading in my opinion is a disaster. It brings forth the total cultural confusion of our world. Black and white multiple choice keeps those forces under control. But the cat is now out of the bag!

One wonders what all the hype is about. Some Mongolian teenager gets 100% on MIT electronics? Praiseworthy indeed, akin to some backwater American doing the same, if we knew the ancestry. Details do count. Again the reason people go to MIT is not to ace an online test. They most likely did that in Secondary School. The reason they go is to understand how to understand. How to pose the question, how to use a plethora of tools to come up with the right answer, or at least a good one, and recognizing good from bad. If the goal is just doing well on a test, then we become India and China, masses of test takers, all prepping to score high. Frankly we already have that in the SATs, and we see masses of prepping. True education is thinking differently, questioning the common and extending the mind to new areas. Manipulating on line courses is at best a means to an end, never the end in itself.
Labels: Education

SATURDAY, AUGUST 17, 2013

ECONOMICS VERSUS MEDICINE

There is a piece in the WSJ, a paper which now appears as some pop publications with all sorts of things other than the financial news, which was written by an economist bemoaning medicine. The article was written by a female economist. She bemoans all the advice that is given women as to how to care for themselves during pregnancy. Her main gripe appear to be that there is little if an evidence behind any of this advice.

Now she complains about coffee as follows:

A far bigger issue for me was coffee. I love coffee. The thought of giving it up during pregnancy struck fear into my heart. Of course, for the baby, I'd do anything. But I didn't want to do it for no reason.

The big concern with consuming caffeine during pregnancy is that it might lead to higher rates of miscarriage. Caffeine can cross the placenta, entering the fetus's bloodstream, and it isn't clear how the fetus processes it. In addition, researchers have speculated that caffeine can inhibit fetal development by limiting blood flow to the placenta.

Still, these effects have not been proven. In the end, randomized experiments are difficult or impossible, and women who drink coffee tend to be different from those who don't. One big issue is that older women tend to drink more coffee, and age and miscarriage are closely linked.

Now I know little about obstetrics, I did deliver a baby or two, but that was decades ago. It may be like riding a bike but I dare not try that. However, mothers are given tons of advice which may or may not be scientifically based. She further bemoans that:

I'm hardly alone. Pregnant women are clamoring for better information about everything from exercise to hair dye to bed rest and delivery. They don't want categorical limits based on fuzzy science and half-baked research. They want to assess risks for themselves and make their own best decisions.

Now let me deal with a few facts:

Physicians have a ton of data regarding smoking, drug use, excess alcohol, preexisting conditions, age related birth issues, genetic complications and the like. I have a few old obstetrics books on my shelves that relate those warning and even way back then there were clinical studies and true science backing up the claims. But a cup or two of coffee or a glass of wine may be a bit too over-bearing, except that in today's legal mess of malpractice what is a physician to do.

On the other hand did an economist ever get sued for malpractice? Hardly! Did an economist ever do a double blind study? Never. They can even do a study in macroeconomics with their eyes fully open. Thus I see this bemoaning the failures of medicine as a complete admission of the real total failure of economics. There is no body of science akin to physiology, genetics, and the like in economics. No economist can do an experiment. They only play with numbers after the fact and when they try to predict, diagnose, prognosticate, the seem to end up in screaming matches where no one even comes close to the right answer.

So we have a female economist bemoaning the issue of whether two or four cups of coffee will do fetal damage. I do not know, I have read the literature. I can do some good guesses on clinically based results in several fields of cancer, but telling a person whether a glass or two of red wine at dinner is bad for the fetus may be difficult unless some study has been done, but I suspect that there are hundreds.

Perhaps Economists who live in glass castles should not throw stones.

Oh yes, I just checked my NEJM looking for caffeine and pregnancy and got a few dozen hits. The latest is worth a look. The NEJM article states:

Obesity, cigarette smoking, alcohol use, and moderate-to-heavy caffeine use may be associated with sporadic miscarriage, but relationships between these conditions and recurrent miscarriage have not been extensively studied and are uncertain. There is no good evidence that physical activity, including sexual activity and exercise, causes miscarriage.

References:

1. The ESHRE Capri Workshop Group. Nutrition and reproduction in women. Hum Reprod Update 2006;12:193-207
2. Mishra GD, Dobson AJ, Schofield MJ. Cigarette smoking, menstrual symptoms and miscarriage among young women. Aust N Z J Public Health 2000;24:413-420
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4. Weng X, Odouli R, Li DK. **Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study**. Am J Obstet Gynecol 2008;198(3):279.e1-279.e8.

Hope the facts help out here!
Labels: Economics, Medicine

THURSDAY, AUGUST 15, 2013

LONG NON-CODING RNA (LNCRNA) AND PROSTATE CANCER

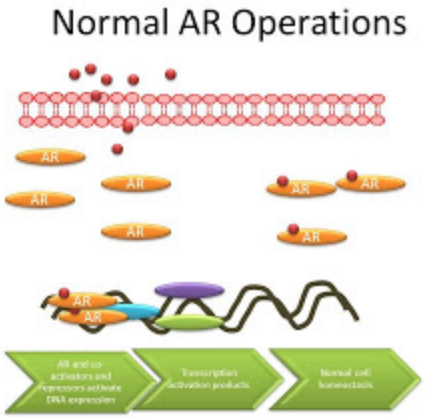
Introduction

A recent paper on the understanding of several long non-coding RNAs in the case of androgen resistant prostate cancer has raised the hopes of many to begin understanding the function of these epigenetic players in the control of malignant cells. To date, very few lncRNAs have been determined no less understood functionally. This brief note focuses on them in the context of PCa. We examine the AR case of PCa, then the basics of lncRNAs, and then spend some time examining the recent work and its implications. Finally we present some overall observations.

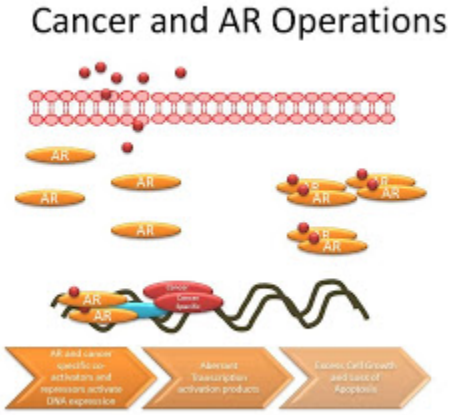
Androgen Pathway

Prostate cancer can be controlled if not cured if the cancer is detected and removed in a controlled area. However when the cancer begins to spread it lives off of androgens for a long while, and by eliminating the androgens we can in turn “starve” the cancer cells. However the cells manage to find alternative paths to existing without the androgens and this becomes what is termed androgen resistant (AR) prostate cancer, PCa, or ARPCa.

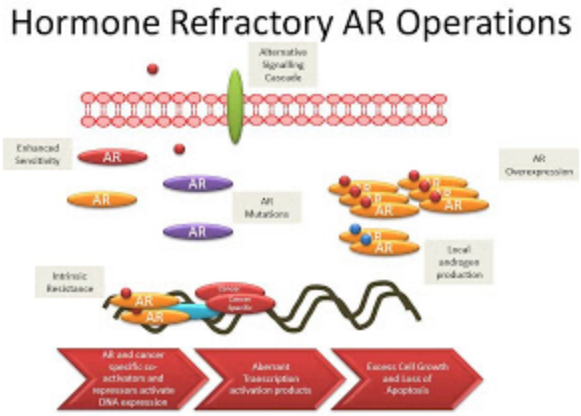
Normal operations of the prostate cell are shown in the Figure below. They result in normal cell homeostasis, namely basal and luminal cells reproducing as needed and in a normal manner.



The next step is a cell becoming cancerous. This we depict below. The result is excess cell growth and loss of apoptosis. Yet the driver is still the androgens entering the cell and driving the process through the AR.



Finally we have the AR independent growth as shown below. The assumption is that mutations occur that result in the ability to activate the AR functions leading to uncontrolled cell growth without the androgen exogenously being provided. In the recent paper in Nature that we shall discuss the growth change and control is now linked to epigenetic elements, namely the lncRNAs.



Long non-coding RNA

Long non-coding RNA, lncRNA, are the long RNAs recently discovered, most of which whose function is yet unknown, which can actually control gene transcription. The lncRNAs range from 200 to well over 100,000 nucleotides. In Weinberg's latest edition of Cancer he presents about one page only to lncRNAs, and such is an example of their newness and lack of understanding[44[1]].

Kovalchuks state that lncRNA have several functions:

1. Regulation of expression of neighboring genes
2. Blocking of splicing proteins-coding genes using antisense transcripts
3. Interaction with proteins making them more or less capable of fulfilling specific functions
4. Serving as precursors for smaller ncRNAs.

Kornienko et al present an excellent overview of these functions and we summarize here in their words some key elements of them:

Regulation of transcription is considered to be interplay of tissue and developmental-specific transcription factors (TFs) and chromatin modifying factors acting on enhancer and promoter sequences to facilitate the assembly of the transcription machinery at gene promoters. With a growing number of lncRNAs implicated in transcriptional gene regulation, this view may need refinement to include networks of tissue and developmental-stage specific lncRNAs that complement known regulators to tightly control gene expression and thereby organism complexity.

Transcriptional regulation by lncRNAs could work either in cis or in trans, and could negatively or positively control pc gene expression. lncRNAs work in cis when their effects are restricted to the chromosome from which they are transcribed, and work in trans when they affect genes on other chromosomes.

[44[1]] Weinberg, 2013, p 26.

They continue:

lncRNAs can inhibit general protein-coding (pc) gene expression in trans

(a) by preventing transcription factor (TF) activity (7SK lncRNA) or

(b) by inhibiting RNAPII binding to DNA (B2 lncRNA). Xist lncRNA is transcribed from the X inactivation center (XIC) and inactivates a whole chromosome in cis

(c) by recruiting epigenetic modifiers (EM). lncRNAs can regulate specific genes, acting in trans like HOTAIR

(d) or in cis like HOTTIP

(e) by directly recruiting epigenetic modifiers to certain genomic loci.

In both cases the lncRNA binds EMs via a specific sequence or structure and targets them to promoter regions via DNA/RNA interaction elements to affect expression of the respective pc gene. Transcription of a lncRNA through a pc gene promoter or a cis-regulatory element (RE) affects pc gene expression in cis independent of the lncRNA product (f) by mechanisms discussed in the text. Both DNA strands are shown as separate boxes to indicate lncRNA transcription over the pc gene promoter in the antisense orientation.

Thus the lncRNAs have become an interesting target for examination especially as we learn more about why certain cancers return after targeted pathway control. lncRNAs are one of the many epigenetic elements which make understanding the process of cancer development and metastasis so complex.

PCa and lncRNA

There is a recent paper in Nature describing how lncRNA acts in an interesting manner of providing ongoing growth capability in the case of androgen resistant prostate cancer, ARPCa. From the overview in Eureka we have:

...the study shows that two long non-coding RNAs (PRNCR1 and PCGEM1) activate androgen receptors, circumventing androgen-deprivation therapy. In their active state, these receptors turn on genes that spur growth and metastasis, making these cancers highly treatment-resistant. The study illustrates how prostate cancer can thrive, even when deprived of hormones, and provides tempting targets for new therapies.

"Androgen-deprivation therapy will often put cancer in remission, but tumors come back, even without testosterone," said contributor Christopher Evans, professor and chair of the Department of Urology at the UC Davis School of Medicine. "We found that these long non-coding RNAs were activating the androgen receptor. When we knocked them out, cancer growth decreased in both cell lines and tumors in animals."

…These prostate cancers are very aggressive and usually fatal, but their continued growth, despite being deprived of hormones, is just now being better understood. It's not unlike removing the key from a car ignition, only to have the vehicle re-start on its own. In this case, the aberrant starting mechanisms are long non-coding RNAs, a class of genetic material that regulates gene expression but does not code for proteins. Using patient samples from UC Davis, the group determined that both PRNCR1 and PCGEM1 are highly expressed in aggressive tumors…

Further investigation determined that one of these long non-coding RNAs is turning on androgen receptors by an alternate switching mechanism, like a car with a second ignition. This is critically important because many prostate cancer treatments work by blocking a part of the androgen receptor called the C-terminus. However, PCGEM1 activates another part of the receptor, called the N-terminus, which also turns on genes — with bad results. "The androgen receptor is unique, if you knock out the C-terminus, that remaining part still has the ability to transcribe genes," said Evans.

In addition, about 25 percent of these cancers have a mutated version of the androgen receptor that has no C-terminus. These receptors are locked in the "on" position, activating genes associated with tumor aggression.

Regardless of the receptor's status, PRNCR1 and PCGEM1 are crucial to prostate cancer growth. In turn, knocking out these RNAs has a profound impact on gene expression, both in cell lines and animal models. The team used complementary genetic material, called antisense, to knock out the RNAs and observe how the tumors and cells responded. In each case, there was a direct relationship between RNA activity, gene expression and cancer growth. "These long non-coding RNAs are a required component for these castration-resistant cancers to keep growing," said Evans. "Now we have preclinical proof of principle that if we knock them out, we decrease cancer growth."

Now we consider the work directly. Ling et al report:

Although recent studies have indicated roles of long non-coding RNAs (lncRNAs) in physiological aspects of cell-type determination and tissue homeostasis1, their potential involvement in regulated gene transcription programs remains rather poorly understood. The androgen receptor regulates a large repertoire of genes central to the identity and behavior of prostate cancer cells2, and functions in a ligand-independent fashion in many prostate cancers when they become hormone refractory after initial androgen deprivation therapy3. Here we report that two lncRNAs highly overexpressed in aggressive prostate cancer, PRNCR1 (also known as PCAT8) and PCGEM1, bind successively to the androgen receptor and strongly enhance both ligand-dependent and ligand-independent androgen-receptor mediated gene activation programs and proliferation in prostate cancer cells.

They continue:

In addition to their relevance to disease, the current results illuminate several fundamental molecular mechanisms. PRNCR1 and PCGEM1 underscore a new role of RNA interaction with

sequence-specific DNA-binding proteins — modification of transcription factor activity. The liaisons between lncRNAs and transcription factors can program stepwise chemical modifications on transcription factors, gating the successive flow of information from enhancer engagement to target-gene activation. The insights that these findings provide into how lncRNAs can mediate enhancer–promoter looping are also intriguing. The RNA-mediated recruitment of a protein with intrinsic avidity for a promoter-associated histone mark to distantly located enhancer elements could stabilize DNA looping and promote communication over three-dimensional space. This would mean that, rather than being simple scaffolds, lncRNAs are more akin to a complex computer circuit board, linking together various disparate molecular components and dictating the logical operation of the system.

In a Nature commentary on the paper the authors Schmitt and Change state:

Yang et al. report that two long non-coding RNAs (lncRNAs) — PRNCR1 and PCGEM1 — activate the androgen receptor. Interaction of PRNCR1 with this receptor at androgen-response genomic elements allows recruitment of DOT1L, an enzyme that methylates and so activates the receptor. PCGEM1 can now bind to the active androgen receptor and recruit the enzyme Pygo2, which allows communication between this receptor and its target genes by binding to H3K4me3 chromatin marks in the genes' promoter sequences. Many androgen receptor target genes have been implicated in prostate-cancer growth.

This discovery is quite useful and insightful. It represents a powerful argument for more aggressively examining the epigenetic factors of the lncRNA. We have seen the impact of miRNA and of methylation and now this opens another powerful area.

Observations

This is one of the first papers to lay out a complete story for how the lncRNAs may control metastatic growth. This also is a key element in our growing body of knowledge of epigenetic factors and cancer.

There are several observations worth noting:

1. Classic pathway analysis totally neglects epigenetic factors. This miRNA, lncRNA, and methylation have almost been considered as noise. Must we now expand the model to directly and expressly include these factors and if so how.

2. There is a reference to dealing with the lncRNAs via a therapeutic. There are two questions here; first, what therapeutic and second as we learn from BRAF inhibitors on melanoma and in hypomethylation therapeutics in MDS there are unintended consequences. What may they be as we expand to lncRNA?

3. As we have just begun to touch the edge of the complex and as yet indeterminate number of lncRNAs, how can we deal with them holistically?

4. As one may suspect these may add to our ever growing markers for cancer diagnosis and prognosis. How will these be added?

5. Exosomes are one way to determine what is in a cell. They have been used for prostate cancer staging. Can we now target these lncRNAs in such an exosome test?

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Labels: Cancer

POWER, POWER EVERYWHERE BUT NOT A WATT TO DRINKL!

The NY Times has a piece regarding wind power. Namely they seem to present the argument that the wind power generating companies spend too much time idle because of how the grid is managed.

Let us briefly consider how power works. Let us assume that instead of electricity we assume we have a water system to lots of homes. We need to guarantee say 20 lbs/sq in pressure from any hose that is turned on. Now with no load on the system we need very little pump power to keep up that pressure. There is some loss along the pipes but very little. Now assume we have a very hot day and everyone turns on their hoses. Thus we need to turn on the pumps to force more water through the pipes and ensure the pressure.

Actually one way the town deals with the constant pressure is to use the water tower as primary source. They fill it up and then as it is drawn down, they pump more water into it. If it gets drawn down too quickly they turn on more pumps to keep the pressure up. The tower is a check on pressure and levels the load, the pumps can be made variable to keep the tower at a minimal level. Unfortunately we have no such analog for electricity in our current world, except batteries, which are quite costly. It is cheaper to modulate demand with generators.

This is generally done with little effort. However the water company must deal with low and high loads. But as many of us know if we were to open the fire hydrants then the water pressure may drop, and if we were to have to fight a fire somewhere we may not have enough pressure and thus have a problem.

This is akin to the problem of the power companies except compounded by wind. If it is a still hot day, lots of power and no wind. So the grid must get power from some reliable source. Unlike a water system which can pump some water into the towns water tower one cannot do so with electricity. Thus an expensive but reliable source is better than a cheap green one.

Now the Times states:

Except when they aren't allowed to spin at their fastest. That has been the case several times in the farm's short existence, including during the record July heat wave when it could have produced enough much-needed energy to fuel a small town. Instead, the grid system operator held it at times to just one-third of what it could have produced.

"We were being told to turn on diesel-fired units that are very expensive and dirty and told to ramp down what is renewable, cost-effective energy for our customers," said Mary Powell, chief executive of Green Mountain Power, the utility that owns and operates the wind plant. "We should go with the sources that can have the highest value, especially during peak times."

The argument falls on deaf ears. Reliability is essential. Wind power may work if the grid is widely connected and over the connection area power can be redirected at low to zero marginal costs. But remember it is unreliable power and not easily controllable.

They continue:

Indeed, in New England in recent months, the grid system operator has cut back power from wind and hydroelectric plants several times, generally, its representatives say, because they were making too much electricity. New wind farms are frequently located in sparsely populated areas or along mountain ridges where there has not been a need for transmission lines with a robust carrying capacity, officials say.

I see this all too often in New Hampshire. Dozens of wind towers sit idle on the mountain tops like giant dinosaurs, frozen in time, generating neither power or money.

This is a complex systems problem, and the stuffing of this green energy into a half thought out system will just waste more of our taxpayers money. But it is again our Government, not the brightest bulbs on the block.
Labels: Government

WEDNESDAY, AUGUST 14, 2013

ANONYMOUS: THE BANE OF THE INTERNET

Science has an interesting piece on the web site pubpeer.com. This is a web site where people can in total anonymity publish comments on peer reviewed published papers. The article states:

What does it take to run a website where scientists can chat freely about published papers? Anonymous e-mail addresses. Temporary phone numbers. Undisclosed locales. Jitters that one day, your cover will be blown, your career destroyed, and your family's finances depleted. It sounds like a John le Carré novel. But no, the protagonists here are a handful of biologists who last fall unveiled PubPeer, which bills itself as "an online community that uses the publication of scientific results as an opening for fruitful discussion." The goal is something of a free-for-all journal club, welcoming comments from readers and authors across disciplines.

I am not a fan of anonymous anything. If one wants to judge and value a comment then tell me who made it and I can check their bona fides and see what they have produced. Anonymous posts have become the bane of the Internet. I can see this in a few MOOCs I have examined. There are endless non-sensical and some outright defamatory remarks made by unknowns. Now we open it up to peer reviewed papers as well. This will just feed the mill of the on line press.

The article continues:

But many who participate in these discussions sit at a tense nexus: They long for more unfettered conversation about science, yet insist on doing so anonymously, fearful that their words will come back to haunt them. One of PubPeer's founders, who describes himself as a tenured professor, says that even a senior scientist "very rarely, myself included, wants to take the risk" of criticizing fellow scientists under their own names. The professor and his shadowy brethren—another founder tells Science that he is finishing up his Ph.D. somewhere in the United States—have gone to great lengths to protect their identities. "I don't want it to impact my scientific life or my personal life," says the professor of his site, adding that the phone number from which he was calling "probably won't work after a few days."

One must use their own name, because then and only then will one confront reality. If you are right then take the stand. If you have an issue but perhaps are not fully certain then say as much. Discussions in science and frankly in all fields requires open discussion. This is not Hamilton and Madison thrashing through the Constitution while at risk for their lives from the British.

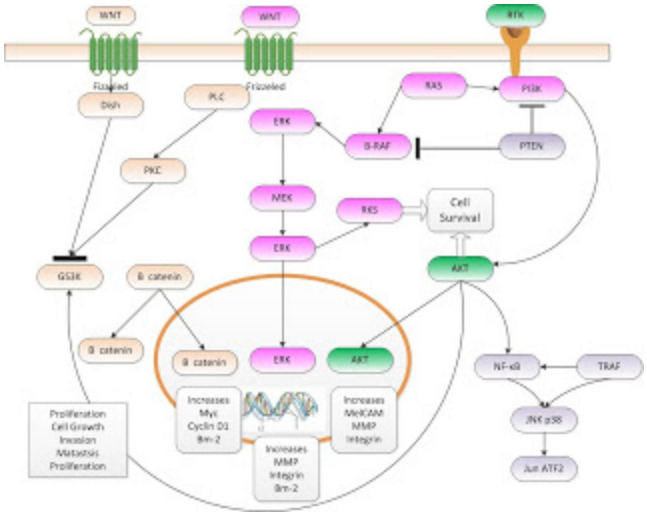
In addition the anonymous writer tends to often time be just nasty, thus accumulating a side conversation based on at best High School banter.The article continues:

A big reason for staying hidden, many scientists suggest, is that despite all the talk of honest discussion in their community, there's little reward for engaging in it. "If the system was much more open and much more tolerant of dissent then this would not be needed," says Raphael Levy, who studies cell imaging at the University of Liverpool in the United Kingdom. He has left both anonymous and named comments on PubPeer.

Discussions and disagreements amongst scientists has been rampant in the past, and it is not new. On the other hand I have seen many peer reviewed papers as just a collection of clique published similitudes with no content. But all too often that is what people need for tenure. The paper may be correct but of little if any new value.
Labels: Commentary

BRAF, MELANOMA, AND UNINTENDED CONSEQUENCES

The introduction of the BRAF inhibitors has been lauded as a significant breakthrough in melanoma treatment. Of the 40-50% of patients with the BRAF V600 mutation it has prolonged life, albeit for a limited amount on average. However there has been observed secondary cancers putatively resulting from the use of the therapeutic. Logically RAF and specifically BRAF are common in many cells and one would expect even a mutated form elsewhere.



Recent Results

Now Gibney et al state:

The clinical benefits of BRAF inhibition in patients with advanced-stage BRAF-mutant melanoma are now well established. Although the emergence of cutaneous squamous-cell carcinomas (SCCs) and secondary melanomas in patients on BRAF-inhibitor therapy have been well described, reports are emerging of additional secondary premalignant and malignant events, including RAS-mutant leukaemia, the metastatic recurrence of RAS-mutant colorectal cancer and the development of gastric and colonic polyps.In most cases, paradoxical MAPK activation—resulting from the BRAF-inhibitor-mediated homodimerization and heterodimerization of nonmutant RAF isoforms—seems to underlie the development of these

secondary tumours. Although evidence supports that therapy with the simultaneous administration of BRAF and MEK inhibitors abrogates the onset of treatment-induced SCCs, whether combination treatment will limit the emergence of all BRAF-inhibitor-driven pathologies is unclear.In this Review, we describe the clinical and mechanistic manifestations of secondary cancers that have thus far been observed to arise as a consequence of BRAF inhibition. We discuss the concept of pre-existing populations of partly transformed cells with malignant potential that might be present in various organ systems, and the rationale for novel therapeutic strategies for the management of BRAF-inhibitor-induced neoplasia.

These observations are a warning which should be heeded in therapeutics which albeit targeted are still broad based.

Newswire states:

However, a type of cellular signaling caused by the BRAF inhibitors may leave patients susceptible to secondary malignancies, such as squamous cell carcinoma and RAS-mutant leukemia. "These secondary cancers emerge because BRAF inhibitors can activate tumor growth pathways in cells with genetic changes," explained co-author Keiran S. Smalley, Ph.D., assistant member of the Cancer Biology and Evolution Program at Moffitt. "When the BRAF inhibitor signaling activates a biological pathway called MAPK (mitogen-activated protein kinases), secondary cancers can emerge." The researchers call the development of secondary cancers a case of paradoxical activation."The paradoxical activation of MAPK signaling was an unexpected observation that emerged as BRAF inhibitors were being developed," said co-author Geoffrey T. Gibney, M.D., assistant member of the Chemical Biology and Molecular Medicine Program at Moffitt. "Combination therapies using BRAF inhibitors and other inhibitors are being considered to prevent paradoxical activation of MAPK pathways." A possible combination therapy to lessen the risk of paradoxical activation and the emergence of secondary malignancies is combining BRAF inhibitors with other inhibitors. One option is an MEK inhibitor, which inhibits the mitogen-activated protein kinase enzymes used to therapeutically affect the MAPK pathway that is often overactive in cancers. However, this combination does not eliminate all secondary cancers. The researchers note that extended follow-up for patients showing long-term responses to BRAF inhibitors has often been lacking. They also added that BRAF-mutant melanoma patients with a family history of colorectal cancer may require more than the usual screening if BRAF-inhibitor therapy is necessary.

This clearly demonstrates the need for better pathway dynamics models and prediction. We arguably know the key parts but there are other parts whose activation we yet understand.

Observations

Unintended consequences are quite common. These are useful in several ways.

First, they help better understand the pathways dynamics and perhaps extend the therapeutic methodology to track the unintended consequences and head them off at the pass.

Second, and here I think specifically of azacytidine and MDS, using a hypomethylation therapeutic to attack a hypermethylated cell, to restore normal homeostasis may have systemic effects. The use of hypomethylation therapeutics will not only attack the aberrant cells but frankly everything else. Thus the unintended consequences may be delays but could be substantial.

Third, in a sense these become in vivo petri dishes for examining pathway aberrations. Thus it is imperative to think about the consequences ab initio and just as importantly be prepared to understand the consequences a posteriori.

Fourth, have a set of therapeutics targeted to counter the possible negative consequences would be imperative.

Fifth, using the secondary cancers one has the opportunity to examine pathway induced cancers. Thus capture of the genetic as well as epigenetic information is critical.

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Newswire:, http://www.newswise.com/articles/enhanced-treatment-surveillance-needed-for-certain-melanoma-patients-to-prevent-secondary-cancers-moffitt-cancer-center-researchers-say

Labels: Cancer

DEATH OF THE BOOKSTORE? NOT REALLY

There is a letter in the NY Times bemoaning the death of the bookstore. The writer notes:

I was an independent bookseller in the early 1990s during the rise of the book "superstore," so

the showrooming phenomenon was nothing new to me. When a superstore moved nearby, customers started "shopping" in our store, browsing, seeking advice, then leaving without making a purchase. Suspicious, we started following them on their beeline to Barnes & Noble, where they inevitably bought the book we had recommended at a discount we couldn't afford to give. Dispirited, we closed our store. Now Barnes & Noble and all brick-and-mortar bookstores face the same circumstance.Your local bookstore can't survive as a showroom. The Justice Department apparently wants you to have cheap book prices above all else. But isn't there a bigger picture? We vote at the polls, but also with our wallets. What is the value of the best book you've ever read? Can you even put a price on it?

Creative Destruction. It happens all the time. Welcome to the free market. People are still buying books, some are getting them free. I have posted a few draft books on the web and am amazed how they get found and downloaded. My one on Obesity and Type 2 Diabetes has been downloaded tens of thousands of times. Is it worth publishing and monetizing? Not for me. Like Paine who profited naught from his publications I felt that getting ideas out there was important. It worked, as small and isolated as the island of ideas is the system now works.

Back to bookstores. I love old used book stores, they harbor ideas oftentimes forgotten. One can stroll and for a reasonable price get a new light on old thoughts. My Amazon purchases are more targeted for professional purposes. But the old style bookstore may have become a thing of the past if it fails to reinvent itself. The complaints of the letter will fall upon deaf ears, things change, and the writers allusion to more Government control is both uncalled for an ineffective.
Labels: Books

MONDAY, AUGUST 12, 2013

WHAT TO WATCH FOR; I THINK

The FED Bank in San Francisco issued an interesting report, first reported on Zero Hedge, which states:

Conclusion: Asset purchase programs like QE2 appear to have, at best, moderate effects on economic growth and inflation. Research suggests that the key reason these effects are limited is that bond market segmentation is small. Moreover, the magnitude of LSAP effects depends greatly on expectations for interest rate policy, but those effects are weaker and more uncertain than conventional interest rate policy. This suggests that communication about the beginning of federal funds rate increases will have stronger effects than guidance about the end of asset purchases.

This is kind of like saying; you can pour on as much gasoline as you want to but just beware of lighting the match.

Namely QE has little effect but once the FED says they are increasing the Funds Rate all hell will break out. As it is the collapse of the bond market is the canary in the coal mine, the market is already anticipating this. The key question will be:

1. If the FED readjusts the FED rates will they be adjusted towards inflation, or pushed ahead of

inflation?

2. Will the push to higher rates drive market perceptions and result in higher equities?

3. Will this result in inflation?

I am reminded of the Rowe conjecture, that balance between reality and perception. I suspect we may very well be in for a rocky ride.
Labels: Economy

THE MIND OF AN ECONOMIST

I have little love for economists. Mostly because they have foggy thinking processes, all too often driven by their political world view rather than any form of reality.

Take for example the comments of a left wing economists in the NY Times today. He states:

Rather than deal purposefully with this changing economic landscape with useful policies encouraging the growth of other industries, our government spent decades papering over the growing weaknesses by allowing the financial sector to run amok, creating "growth" based on bubbles. We didn't just let the market run its course. We made an active choice to embrace short-term profits and large-scale inefficiency.

The first sentence is telling. It effectively states that the Government should be the chooser of winners and loser in the market place, establishing policies to support winning economic and technological developments and enhancing their chance of success. Surprise, the Government has no single individual who can make such a choice. The Market does this.

In the real world, the entrepreneur comes up with an idea, seeks capital, starts a venture, brings it to market and if the dogs eat the dog food, he wins and so does society. If not he and his investors lose and start all over again. What Government can do is just get out of the way.

The source of many of our problems is Government getting in the way.

However another source of our problems is the classic Norbert Wiener warning that machines would replace people. Well, that was in 1948. This is 2013. Almost 70 years later. So why are we surprised.
Labels: Economics

ELECTRICITY: SPEND WISELY NOT WIDELY

The White House just issued a report on the power system in the US and the assumption that climate change will bring more sever weather and that Government must do something massive to assure that power is not interrupted by the weather.

The report states:

Smart grid investments made by the U.S. Department of Energy's Smart Grid Investment Grant (SGIG) in some of the states hit by Sandy lessened the impact for thousands of electric customers. For example, In Philadelphia, roughly 186,000 smart meters were up and running by the time Sandy hit. The Philadelphia Electric Company (PECO) estimated that about 50,000 customers experienced shorter outages due to its new smart grid systems, which also included

upgrades to its Outage Management System (OMS). PECO observed more than 4,000 instances where smart meters were able to remotely determine when power was restored, saving PECO and its customers time and money.

Frankly the most significant part of the problem is not the grid, it is the last 500 feet. Sandy did not hit Philly. It his the New Jersey Shore from Island Beach north to Staten Island in New York Harbor. The loss of power was dominated by down local trees. Does a smart grid solve this problem, most likely not. Unless we rebuild the system to be multiply redundant, which is foolish.

What is the problem for 90% or more of the outages. Trees, like the example above, which have not been fixed. Foot after foot of line is covered by fragile branches. So why not cut them? Simple, the environmental groups want to keep the "green" look. So they wait until Mother Nature "cuts" the tree and we all lose power for a week!

Tree after tree should be trimmed or removed. Before we lose power, and the costs are orders of magnitude higher. You do not need a grid to solve this problem, just a saw and some common sense.

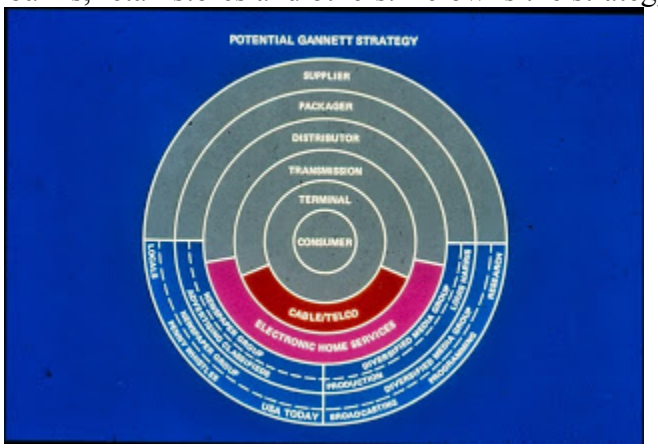
But I forgot who we have in Washington. Sorry, we will just waste the money and still lose power. Who or what will we blame the next time?
Labels: Economics, Politics

MONDAY, AUGUST 12, 2013

NEWSPAPERS: THERE WAS NO SURPRISE

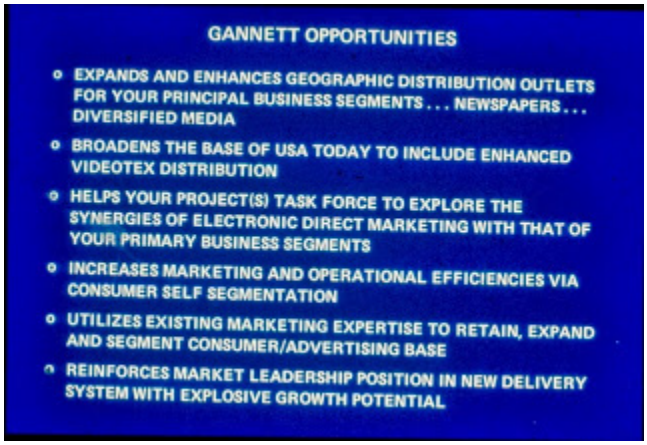
In 1980 and through 1983 I had responsibility as President of the Warner Electronic Home Services Group to develop what was then called Videotext. This was the immediate predecessor of the Internet. We used two way CATV systems and also integrated telco networks with cable and provided video on demand.

The newspapers in those days saw this as a threat. We met with the Washington Post, the NY Times, the Boston Globe, Gannett and others. Each had their "teams" preparing for the new electronic world, as did banks, retail stores and others. Below is the strategy slide for Gannett.



Thus in discussions at that time there was a clear understanding of how the new electronic distribution channel would disrupt their business and moreover what could be doe to thwart it. Specifically we stated to them the following:

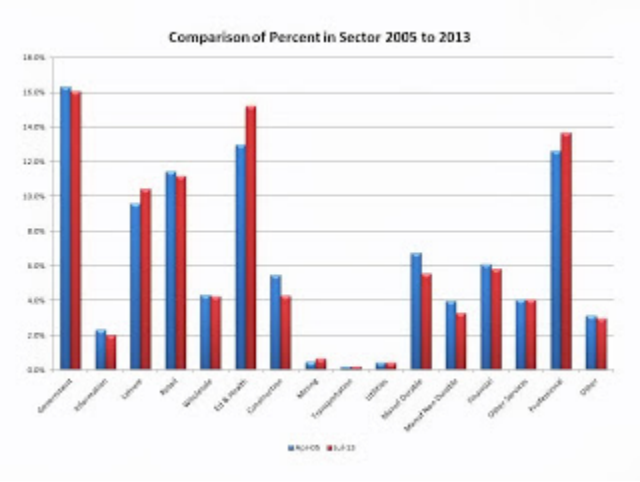
Namely there were strategies they could follow which would protect them in the long term. The opportunities were:



Did any of them do anything? Some did but they did so to align themselves with the old way of doing things. They all too often just missed the point. I recall a meeting with the Boston Globe team, old newspaper types, who just did not see what was happening. The recent sale of the Globe and Post are just first steps of a new generation trying to adapt. The problem may be more systemic and not solvable. After all we told them thirty years ago and they did not listen then.
Labels: Innovation, Internet, Press

FRIDAY, AUGUST 9, 2013

MORE OBSERVATIONS ON EMPLOYMENT



The above charts is of interest. Let me make a few observations:

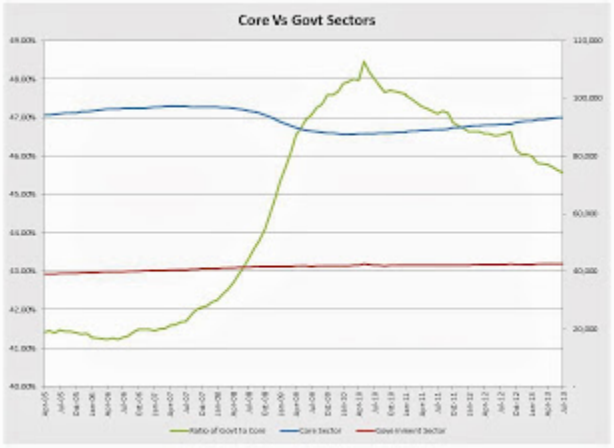
1. Construction, Manufacturing have dropped as a percent of labor force.

2. Education and Health has exploded.

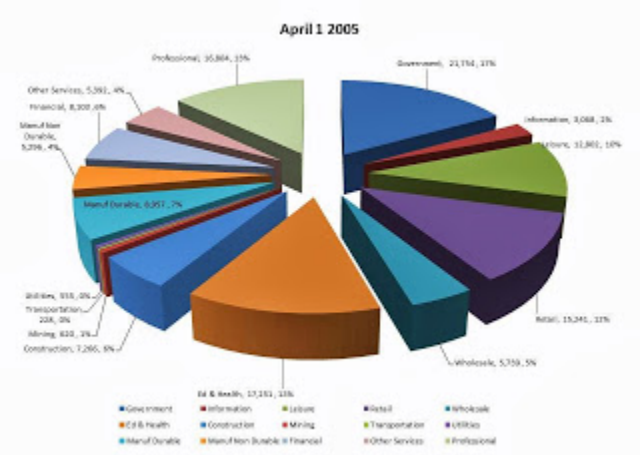
3. Professional and Leisure have increased.

Thus the nature of our economy is substantially changing. Just think of this as an inflection point!
Labels: Economy

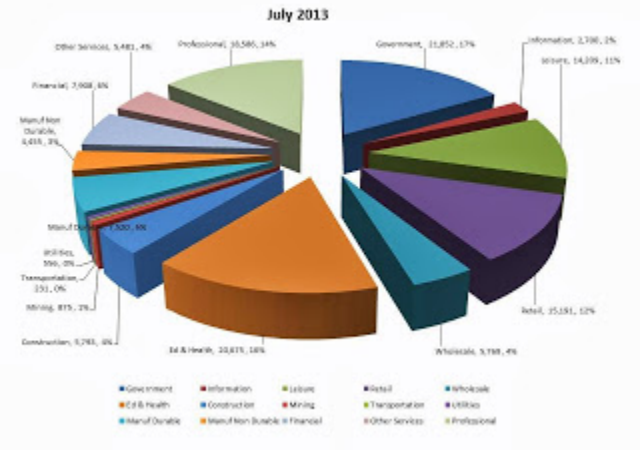
ANOTHER LOOK AT EMPLOYMENT



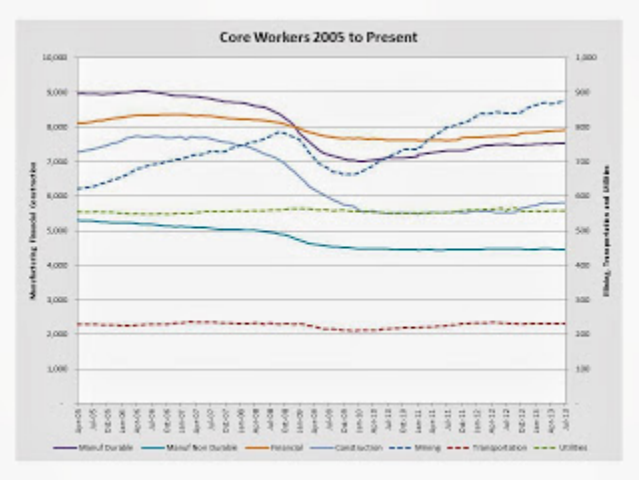
The above is another look at the employment data. Note that Core employment as a percent of total and as related to Government is increasing. The ratio of Government to Core has dropped from a peak of 48.5%to 45.5%. However the baseline was 41.25%. We still have too many non-productive Government workers and they are supported by far too few Core workers.



The above is April 2005 split of workers which gives the detail. The following is July data.

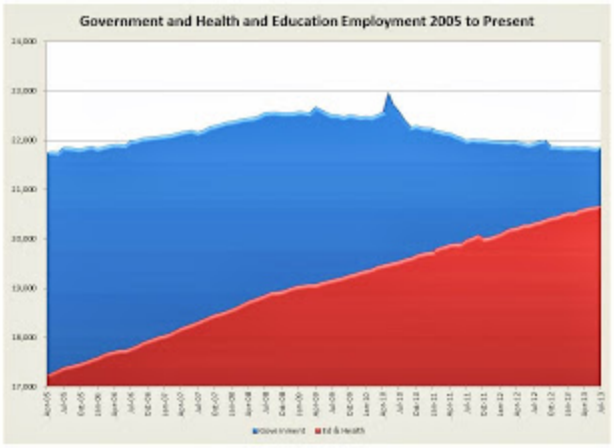


Now we have also the following which is Core sector details.

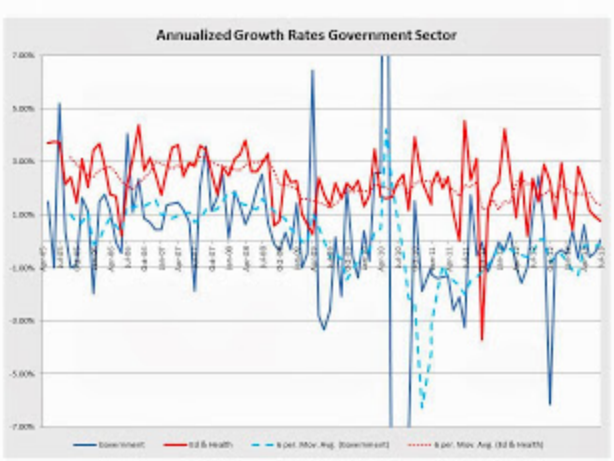


Most elements are growing with Mining returning to a strong growth. Durable Manufacturing is increasing whereas Non Durable Manufacturing still declines.

Now we show the Government sector below.



Note that core Government is slowly declining at the State and Local levels whereas Ed and Health Care is continuing to explode. This is a critical issue. We will NOT be able to support this sector.



The above depicts the rate of change and as noted above we have an unsustainable Health sector.
Labels: Economy

MANNERS AND THE ACADEMY

Rajan has an interesting and polite piece in Project Syndicate, the generally left wing blog for various issues. His discussion is with regards to the "manners" of various economists in dealing with their peers. Now to start, economics is not a science, and there is at this stage in its development no possible way that it can become one. It is a two fold body of intellectual study: first, it is a body of study which collects data and tries to connect parts of the data albeit generally in a tautological manner, second, it is a political voice, which tries to express one's political world view in the way people and the government should act to achieve certain goals.

One cannot do experiments in economics, economics does not allow predictions, it does not permit verification or validation, in essence it is merely a bystander body of ideas where at best we can record the past and hope that we can learn from it, but alas it is a human endeavor subject to the stochastic rhythms of change.

Rajan begins:

Why do high-profile economic tussles turn so quickly to ad hominem attacks? Perhaps the most

well-known recent example has been the Nobel laureate Paul Krugman's campaign against the economists Carmen Reinhart and Kenneth Rogoff, in which he moved quickly from criticism of an error in one of their papers to charges about their commitment to academic transparency.

This is the snarky little boy syndrome, and we all too often have seen it before. He ends by saying:

In fairness, given Krugman's strong and public positions, he has been subject to immense personal criticism by many on the right. Perhaps the paranoid style in public debate, focusing on motives rather than substance, is a useful defensive tactic against rabid critics. Unfortunately, it spills over into countering more reasoned differences of opinion as well. Perhaps respectful debate in economics is possible only in academia. The public discourse is poorer for this.

The point he seems to be making is that within the walls of the Academy there are rules of debate. Outside the walls there is a free for all. Perhaps Rajan believe that those who participate in the snarky public debate should rethink their motives. Indeed Krugman is a prolific poster on his NY Times blog, snapping here and there against any perceived opponent of his political view. The reality of the situation is that the Romer Plan was a disaster, and the recovery of the Recession has also been a mitigated mess. The FED has stumbled post Bretton Woods to attempt to stabilize world currencies. Yet the FEDs Balance Sheet continues to expand with no real end in sight.
Labels: Academy, Economics

THURSDAY, AUGUST 1, 2013

MORE ON AMAZON REVIEWS

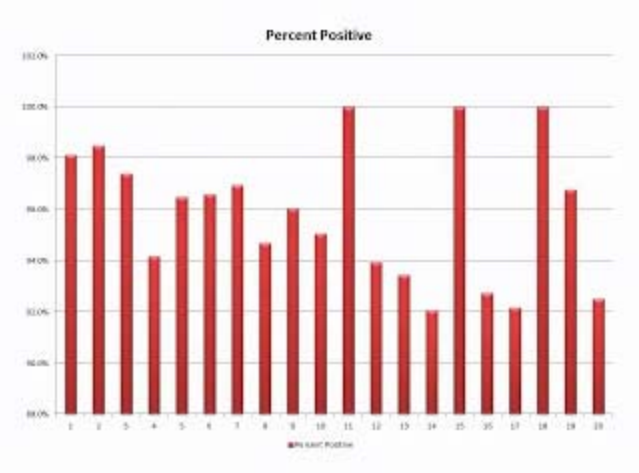
I spent a few minutes examining the five star reviews of Crawford's book as described by Tech Dirt. Some interesting observations:

1. Of the top 20 reviews only 31% used a Real Name.

2. Of the top 20 only one had a bio of sorts and he was a truck driver.

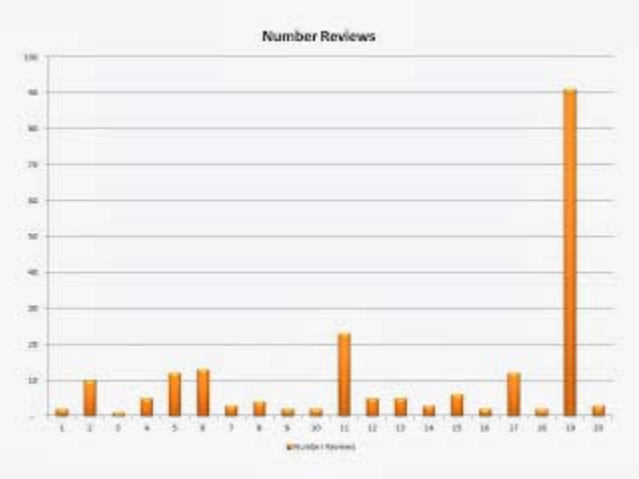
3. Of the top 20 there were in excess of 2,300 positive votes, often for reviews that just complained about negative reviews.

4. Of the top 20 the average number of prior reviews was 10, excluding one outlier, and 70% had less than 5 reviews and of them no had reviewed a book.



5. Of the top 20 the average positive was 95.9%.

6. Of the top 20 reviews the average time for the review from the date of publishing was 35 days with one review posted 11 days PRIOR to publishing. 45% of the positive top reviews were published on February 11, 2013 by mostly no real names.



7. Of the 20 top reviews the number of prior reviews average 10 and frequently was substantial less. In addition may of the reviews by the reviewers were about electronics and video games.

This is just a summary of the data.

In contrast to Tech Dirt's praise of the top reviewers, my analysis of the data seems to lead one to believe that there is something quite disturbing about these reviews. Yes those which are negative but equally those which are positive. This book is one of two items I have seen where outside influences prevail. Truth is lost. Perhaps that may reflect directly upon the author and her ideas. I do not know.
Labels: CATV, FCC

GOOD INTRO TO EPIGENETICS

Epigenetics in Health and Disease is a good introduction to the field. I make a few comments which hopefully make this an attractive read.

Epigenetics is an ever growing field of research demonstrating that although genes themselves still follow the Watson-Crick paradigm, that there are many complex factors which can distort their actions. Namely things are not necessarily as straightforward as they look. The book by the Kovalchuks is an excellent introduction to this field. It benefits from the fact that it is written by a single set of authors and thus does not suffer from the repetition, changes in style, and levels of coverage many of the multi-author texts have.

The authors provide a review of the chromosome and its structure and the importance of the histones in the overall expression of genes.

They then provide an excellent discussion of methylation, one of the key elements in epigenetic control. Methylation of the C element in DNA has been found to provide a broad set of changes in gene expression. The authors introduce the reader to these in a straightforward and understandable manner. As such this can be used as a good first introduction to this area.

The author then goes into non-coding RNAs including the miRNA and lncRNAs. The authors provide a broad discussion of these areas across many kingdoms, plants, animals, fungi etc. This coverage is well done and allows the reader to see how these effects impact many areas. All too often the focus may be upon the human, but seeing this in other kingdoms as well is extremely informative.

The authors conclude with several chapters on the impact of these epigenetic factors; methylation and ncRNAs. The classic set, cancer, behavioral, and environmental are discussed.

On the positive side the authors have kept the level of presentation understandable and consistent. The level and depth is adequate for a good initial introduction to the literature. The book is not an in depth reference text but then again there is none that I am aware of. In addition the knowledge in this field is changing on an almost daily basis.

I would strongly recommend this book to anyone wanting to take the first steps into this exciting area. There are some additions that I would like to have seen:

1. In the cancer area, the Myelodysplastic Syndrome, MDS, is an interesting hypermethylation pre-cancer often resulting in AML. It is treated with drugs targeting this hypermethylation. I believe that this would be an excellent case study for many cancers. In addition there is the cause or effect element regarding the methylation states of many cancers. This is still a work in progress.

2. Flower colors and patterning is an interesting area for the use of epigenetic analysis. I would like to see some discussion here. For example is there a relationship to the X chromosome issue as in calico cats or is this a pathway control issue often found in other patterning areas.

3. Figure can be dramatically improved. The black and white ones are barely readable and the colored versions are in the rear of the text and are not of great quality. The figure lend a great deal.

4. Agouti mouse issues regarding a way to measure methylation effects may be a useful tool and should be considered for inclusion. Just a thought

Overall the authors have done a superb job and the book is worth being on the shelf of all involved in this area.
Labels: Cancer, Genetics

WEDNESDAY, JULY 31, 2013

MOOCS AND MISSING THE POINT

I am not a fan of MOOCs, especially as the next step in higher education. My latest test is that I am finishing a course taught by some Aussie. I diligently followed all the lectures through number 4. It was a frustrating waste. So were the handouts. So I changed strategies. All I did was look at the exam for the week and then do what I would normally do, search the literature and prepare an answer. Instant best grade and no wast of time trying to understand Aussie or the lecture notes which rambled.

So perhaps all we need to do is set out exams. Let the students find out how to answer the questions and then you have solved the problem? Yes? No. You have not shown the student the other ways of thinking. You just reinforce the way they do it now, which may not be bad, but the Ah Ha moments all too often do not come from such intellectual inbreeding.

Now the Chronicle of Higher Education notes:

Last year, a former Princeton University president, William G. Bowen, delivered the Tanner

Lectures at Stanford, continuing a long tradition of college leaders' using the top floors of the ivory tower to speak difficult truths about academe.

When the dot-com craze was sweeping the nation, back in 2000, Bowen—an author in the 1960s of the original "cost disease" diagnosis of labor-intensive industries—kept his eyes on the evidence. He didn't yet see reason to believe that colleges could use technology to save money. But another decade of progress changed his mind. "I am today a convert," he said. (The lectures were published this year by Princeton University Press as Higher Education in the Digital Age.) Bowen's random-trial-based research suggests that "online learning, in many of its manifestations, can lead to at least comparable learning outcomes relative to face-to-face instruction at a lower cost."

I would suspect the good former president may never have taken one of these courses. There is nothing more important than the interaction in a class where one gets a glimpse of a different direction. MOOCs for the most part are canned lectures with no feedback, no way to ask a question, other than a time delayed discussion forum, which all too often become an ersatz Facebook blather page. One can evaluate the value of a posting simply by seeing if the person identifies themselves. All too often they are Anonymous.

Thus unlike the esteemed president, I am totally unimpressed. However, the questions were good and helped focu
s me on questions I would not have asked. However, many of the questions I would never have asked anyhow!
Labels: Education

TUESDAY, JULY 30, 2013

AMAZON SHILLS

There are certain books which attract reviewers who push one side or another. The Crawford book on cable companies is a prime example. The one star reviews are clearly cable shills. The five star reviews are clearly the Progressive left wing lobby who want the Government to control everything, that is until they do not control the Government.

In Tech Dirt there is a somewhat reasonable albeit poorly researched and a bit one sided piece commenting on the one star reviews. The negative hits on my review were clearly the result of the Tech Dirt article. There is a cadre of left wing (wing-nuts) who believe that the Government should supply everyone with 1 Tera bps link no matter where they are at no cost. Frankly these are the folks who may in my opinion represent the core that leads to destruction of the United States.

The Tech Dirt article states:

Astroturfing -- the process of a faux "grassroots" effort, often set up by cynical and soulless DC lobbyists pretending to create a "grassroots" campaign around some subject -- is certainly nothing new. It's been around for quite some time, and it's rarely successful. Most people can

sniff out an astroturfing campaign a mile away because it lacks all the hallmarks of authenticity. A separate nefarious practice is fake Amazon reviews -- which have also been around for ages -- amusingly revealed when Amazon once accidentally reassociated real names with reviewers' names to show authors giving themselves great reviews. Over time, Amazon has tried to crack down on the practice, but it's not easy.

So what happens when you combine incompetent astroturfing and fake Amazon reviews? Check out the reviews on Susan Crawford's book, Captive Audience: The Telecom Industry and Monopoly Power in the New Gilded Age. Now, I should be clear: while I respect Crawford quite a bit, and often find her arguments compelling and interesting, I found Captive Audience to go a bit too far at points, and felt that the book lost a lot of its persuasive power in really overstating the case. We agree that the broadband market is not even remotely competitive, but we disagree on the solution to that. Still, I think the book is very much worth reading, and an important contribution to the discussion on broadband/telco policy.

Now from a previous post I reviewed the book. The review was up for some four months and generally got 80-90% useful indications. Then someone must have read it in the pro Crawford or pro-Cable camp and they went to work giving it dozens of negative help indications in hours. It is clear that the action was coordinated and deliberate to cram down the review.

This book in my opinion is of poor quality. I indicated as such why I felt it to be so. I am no fan of the cable companies, Comcast in particular. I was a Group President at Warner Cable a few decades ago so I have had a seat on both sides. I was also a Senior VP at NYNEX and now Verizon so I understand the telcos, and I also in my own company built one of the largest fiber networks in the world. But expertise seems to have no value in the cyber world of game playing. The anonymous reviewers and critics are useless shills in the world of information.
Labels: Books

ATTACKS ON AMAZON REVIEWS: THE PROGRESSIVE BROWN SHIRTS

Crawford wrote a book entitled, Captive Audience: The Telecom Industry and Monopoly Power in the New Gilded Age. This is a difficult book to review. Not because of some of its conclusions, which I am hearty agreement with based upon hands on experience, but because the author all too often steps well outside her area of expertise and opines on things which are just wrong.

Before continuing there is one other observation that it appears that anyone who disagrees with this author seems to get slammed with unhelpful reviews in what appears to be a blatant attempt to push any negatives out of view of a potential reader. I initially noticed this happened to this review within the first few hours. Thus the reader should be advised as regards to the comments. Just an observation. After a few months of positive reviews I have noticed the dozens of negative hits coming fast and furious, and rather than commenting on facts this is a way to push the facts off the table. Perhaps one should examine the historical precedents for this technique and thus weigh the votes. After an deliberate attack by the book's followers on Amazon I removed the book review and let it stand here.

However her conclusions are of merit despite, in my opinion, the confusion of her argument.

1. "Cable Companies are bad". She has some very valid points here as she demonstrates through the vehicle of the Comcast and NBC merger. She argues that such a merger should never have happened. One could provide substantial grounds for preventing it, most on antitrust issues, but they were never truly approached by the current administration. The reasons why is a tale unto itself.

2. "Fiber is the only way." Here I argue she is clearly wrong and is so since she does not understand the technology. Since this is a key point in her argument one wonders why she did not at least reach out to find better support and understanding.

3. "Government is the best market regulator." This is an extreme position which has mixed, at best, results. In fact it has been clear in the technology space that the Government is the worst regulator.

Let me address the above points and relate them to the text itself:

1. Wireless has substantially more capacity than the author understands.

2. The cost of fiber is dominated by local costs such as franchise acquisition, costs of pole attachments, and the delay costs of laying the fiber.

3. There exists a significant body of law the antitrust laws which can and should be used to manage the industry not just regulation.

4. Cable companies are monopolies for the most part and should be regulated as such.

Let me now provide some details contained within the book specifically supporting the above:

On p 78 the author speaks of the abandonment by Verizon of fiber deployment. Why did Verizon abandon its buildout? Frankly there are two. First there were the exploding legal costs and delays in getting local franchises. These were exasperated by the local cable companies but facilitated by the local towns who often did not understand the economics of competition, they just asked for more as they were advised by the incumbent cable operators. Second, and this is a critical element, was the success of wireless in expanding bandwidth efficiency. Namely with only a 1 bps/Hz a decade earlier they now were at almost 10 bps/Hz and they could see ultimately even another order of magnitude increase. This focus on wireless was most evident with the succession to the CEO position with the wireless head taking the helm. Thus it was to some degree a problem with the incumbent but it also was an understanding that the wireless alternative was more than viable.

On p 90 there is an interesting discussion regarding the "interstate access charges". In fact these were the interconnect fees. The author refers to the Prodigy effort, but such an effort was doomed from the start by the massive overhead put on it by IBM, yet at the same time they were facing the overhead of AT&T. The access charge issue is a simple one. There were local phone

companies and long distance ones, at that time.

The local companies demanded and received a fee for interconnecting to the local company. Even though the local companies were separately paid by the customer, they were allowed by the FCC to impose this charge to third parties such as an AOL or Prodigy. Fortunately the FCC abandoned this stance. The author seems to have not fully understood this issue.

On p 95 the author tries to outline the history of on line capabilities using the AOL and Time Warner as an example. In fact it began in 1978 with Warner Cable and the QUBE system. This was the first two way cable system that allowed interaction and online purchasing. This Warner, and perforce Time Warner, had been developing this for almost two decades. In the early 1980s Warner Cable developed the first "Electronic Shopping Mall" a two way video on demand d system in a joint venture between Warner, Bank of America and GTE, with Bell Atlantic and DEC participating. That effort collapsed when Warner ran into financial difficulties. Chase Bank and others did the same during the videotex period. The author appears to posit this sudden even with Time Warner and AOL when in reality there had been many trials, tests, and attempts.

On p 125 the author states that Edison invented the telegraph. What of Morse? Perhaps some fact checking of simple facts would help.

On p 129 and on the author refers to Sen Franken so many times one wonders why? The book was not written by Franken and based upon his public record he was both new and definitely not an expert in regulatory issues and technology. This continual referencing becomes a distraction.

On p 133 there is a discussion of the new channels being cash cows. However there is a very serious issue here. The cable companies bundle up packages of programs which they also own and demand that anyone providing one provide the full package and at premium prices. The consumer gets the full sports package and pays for it no matter if they have ever seen a single sports event. This is the major failing of the FCC and the FTC. Legally this is akin to bundling, a practice clearly prohibited by the antitrust laws. But to data the DoJ has never acted upon this, nor has the FTC.

On p 156 on the author delves into the cable versus wireless issue and here she is well out of her depth. It is a pity because this area is a significant one for possibilities. Let me first outline the wireless argument and then return to the text:

1. Wireless capacity can be measured by the number of bits per second, bps; it can deliver to a user.

2. The user demands bps depending on the application and the number of them the user may have. For example HDTV had been a bid user of bandwidth.

3. Now two things have occurred technically over the past ten years. First bandwidth efficiency, measured in bps/HZ, has increased from 1 bps/Hz to now 10 bps/Hz. Yet at the same time the data rate required for video has collapsed, going from 100 Mbps down to 4 Mbps. Thus supply, that is bps/Hz, has exceeded the demand, such as Mbps. Namely we can now easily use wireless

for HDTV.

4. The acquisition of bandwidth by the wireless companies has continued and now provides almost universal service. Wireless does not require franchises or pole attachments, and can be delivered in a short order.

5. Wireless efficiency now at 10 bps/Hz is anticipated to increase to 100 bps/Hz. That means that a 20 MHz spectrum could provide a 2 Gbps channel to a single user, and with multibeam antennas it can to so to a plethora of users. This backs up directly to a competitor of fiber. And at a tenth the cost!

On p 160 the author again reinforces her lack of technical understanding and capabilities. She states:

"When people want to download a lot of data, say to make a video call, they overwhelmingly opt for high speed wired connections."

Perhaps she has not been made aware of the iPad.

This distortion continues throughout this chapter. She does it again on p. 161,

On p 251 she states:

"Will wireless help America reach the president's goal of one gigabit to every community? No."

The answer is yes, and since the wireless companies have hundreds of MHz not the 20 above, they can well exceed that.

On p 258 she describes the franchises being exclusive. In fact almost all were no-exclusive. The problem was the cost of overbuild.

On p 263 she demands "For starters most Americans should have access to reasonable priced 1-Gb symmetric." Now I assume she means 1 Gbps not 1 Gb. it is rate not totality, and she

On p 265 she begins her argument of moving to a utility model. She states "To do this though American needs to move to a utility model." Frankly the issue should be one of bundling or tying in and the control is the existing antitrust laws. The problem with the utility model is all too well known. The FCC controlled and was controlled by AT&T before divestiture. The result was very slow development of technology and capability. The utility model sets prices based on a return on investment, namely the provider is guaranteed a profit based on invested capital, and their costs are covered no matter how inefficient. The result is a capital intensive and bloated system. Better would be a real competitive market where the barriers to entry are not enforced by the Government but the Government enforces the antitrust laws already on the books.

On p 267 she also makes statements regarding the costs of fiber. Based upon my experience doing this her numbers are categorically wrong. The most significant costs not included is the

franchise acquisition costs, often in excess of $1,000 per sub, plus the costs of pole attachments and the delay costs associated with dealing with local regulators.

On p 267 she further states "The government standardizes, regulates, provides tax subsidies, and puts price supports in place every day." One could just imagine the Government standardizing wireless or broadband structures. They have no technical depth and furthermore the politics that would encompass such would be unimaginable. The Government should just stand apart from any standards. Let the technical people deal with that, and live or die by their decisions.

On p 269 she gets into the Internet discussion. Again for some reason she uses Franken as a foil but they are a distraction. The fact is that indeed ARPA, specifically IPTO, developed the early Internet deployment in the 1970s. In fact I ended up with the task of deploying the international circuits for IPTO. Then through the early 1980s it somewhat slowed but with the help of Kahn and Cerf the IETF was formed and began an open source development of what could be called standards, albeit very flexible one. Then the DOD abandoned it and spun off a separate network and the result almost went nowhere but at the end of the 80s we saw such academic networks such as NYSERNET evolve and the NREN come forth. Thus the Internet history is a mixed bag of public and private parentage and the bright line alluded to by the author is without merit.

The book is worth reading but only, in my opinion, if one can work through the mire of the author's statements for which she has no basis or those which are just outright technically in error.

The classic book on telephone change is the Coll book, Deal of the Century, outlining the breakup of ATT. Coll is a brilliant writer and deals with facts he both understands and can explain. The author of this book had such an opportunity but she clearly went well beyond her ken and the result is that between the facts and opinions are prognostications based on fact-less presumptions. The issue she is focusing on is truly an important issues and needs as much public understanding as possible. The cable companies have secured for themselves a protected niche and have further vertically integrated in a manner which later 19th century antitrust minds would find abhorrent. This is ever so true in view of the channels they control; information and communications.
Labels: FCC

MONDAY, JULY 29, 2013

OVERDIAGNOSIS AND DEATH

A recent focus on the "over diagnosis" of cancer has been highlighted in JAMA and the NY Times. The Times states:

The concern, however, is that since doctors do not yet have a clear way to tell the difference between benign or slow-growing tumors and aggressive diseases with many of these conditions, they treat everything as if it might become aggressive. As a result, doctors are finding and treating scores of seemingly precancerous lesions and early-stage cancers — like ductal carcinoma in situ, a condition called Barrett's esophagus, small thyroid tumors and early prostate cancer. But even after aggressively treating those conditions for years, there has not

been a commensurate reduction in invasive cancer, suggesting that overdiagnosis and overtreatment are occurring on a large scale.

That is a simple way to say that we know only after the fact what is aggressive and what is indolent and not before the fact. The classic example is prostate cancer. Of course we do not want to treat indolent prostate cancer and of course we do want to treat aggressive prostate cancer. But how do we tell. There are new tests which purport to assit tyhat process but in my opinion in a wek manner.

The JAMA piece states:

An ideal screening intervention focuses on detection of disease that will ultimately cause harm, that is
more likely to be cured if detected early, and for which curative treatments are more effective in early-stage disease. Going forward, the ability to design better screening programs will depend on the ability to better characterize the biology of the disease detected and to use disease dynamics (behavior over time)and molecular diagnostics that determine whether cancer will be aggressive or indolent to avoid over treatment. Understanding the biology of individual cancers is necessary to optimize early detection programs and tailor treatments accordingly. The following recommendations were made to the National Cancer Institute for consideration and dissemination.

Yet we are not there yet. We understand what genes may cause aggressive disease but we are at a loss of epigenetic characteristics, at least now.

JAMA continues:

The original intent of screening was to detect cancer at the earliest stages to improve outcomes;however,detection of cancers with better biology contributes to better outcomes. Screening always results in identifying more indolent disease. Although non-physician has the intention to over treat or over diagnose cancer, screening and patient awareness have increased the chance of identifying a spectrum of cancers,some of which are not life threatening.Policies that prevent or reduce the chance of over diagnosis and avoid over treatment are needed, while maintaining those gains by which early detection is a major contributor to decreasing mortality and locally advanced disease. The recommendations of the task force are intended as initial approaches. Physicians and patients should engage in open discussion about these complex issues.The media should better understand and communicate the message so that as a community the approach to screening can be improved.

The recommendation should be to better understand what the true tell tale imprints of cancer are. DIC may or may not be bad, HG PIN may also be so, and melanoma in situ may just be a wandering melanocyte. At what point do we jump to attention and attack?
Labels: Cancer

SUNDAY, JULY 28, 2013

AD HOC PROPITER HOC

There is a recent paper lauded by the left which in essence states:

"People who have money have offspring who succeed financially disproportionately to those whose parents are not that well off and thus to equalize the outcomes we should tax those who have succeeded so as to enable the offspring of those who have not to get an equal chance."

The paper's conclusion is:

In this paper, we explore the possibility that equalizing individuals' economic outcomes may help to equalize their children's opportunities: that is, when poor parents have more disposable income, their children's performance improves and they have greater opportunity to succeed.

We study the effect that this intergenerational connection has on optimal tax policy, which will take advantage of this relationship to shape the ability distribution over time. But exactly how it will do so depends on complex interactions between natural ability and the returns to investment in human capital. Ours is the ...first paper we know of to model this complexity and derive policy implications.

We characterize conditions describing optimal tax policy when children's abilities depend on both inherited characteristics and parental (...nancial) resources. On the intratemporal margin, we highlight competing effects of this endogeneity. If parental resources have greater marginal effects on the children of low-skilled parents, then optimal distortions may be smaller at low incomes because of their positive effects on overall tax revenues and the incentives of high-skilled parents.

On the other hand, larger distortions at low incomes have a bene...fit in encouraging preceding generations to invest in their children's ability pushes in the other direction. In the end, the implications for optimal marginal distortions are ambiguous. On the intertemporal margin, we show that optimality requires a more sophisticated understanding of the cost of raising social welfare through transfers across generations, in particular including the effects of one generation's resources on future generations'tax payments and utilities....

Of course, future research may be able to improve our understanding of the tax policy studied in this paper. For example, when a panel dataset of suffcient duration allows us to link data on parents'and children's wages, this will allow estimates of the intergenerational effect of parental income on parent-child wage transitions. Incorporating other dimensions of parental influence is another natural next step.

We have shown (in the Appendix) that parental leisure versus work time does not seem to exert an important infl‡uence in this case, but one might study how the composition of parents'available resources (i.e., as disposable income or in-kind, such as education) affects the results. Such analyses may have implications for a broader class of policies that, like the taxes in this paper, could be used to affect –rather than merely respond to–the dynamics of the ability

distribution.

Somehow they have left out the genetic facts that dumb parents often give rise to dumb offspring, and that drug addicted parents no matter what the gene pool is will not provide an equal opportunity tor the offspring, and that single parent offspring are disadvantaged by the loss of income, and the list goes on. As one who deals in genetics, that is often the dominant factor and success is all to often delimited by that factor. But the authors seem ignorant of that issue.

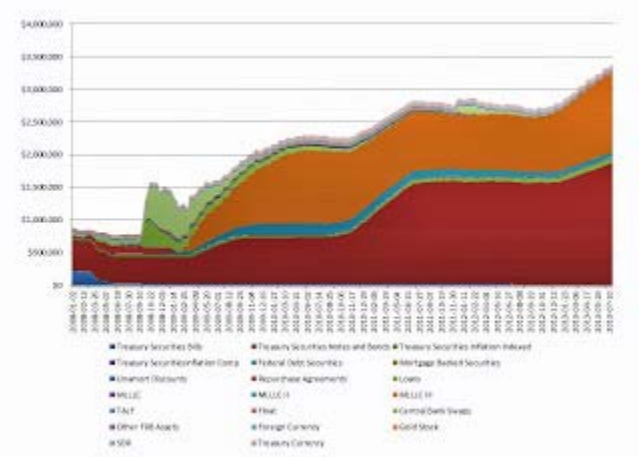
One can state a counter example for every such success. Take the Koch brothers, MIT grads but with a father who set them up. Then take O'Malley, no rich father, a Manhattan College grad, and just as successful. Was parental income redistribution the determinant? Hardly, it was competence and drive. I can think of dozens of my MIT MITES minority students, all successful, despite in many cases low income parentage. Then again one can think of the generation who made it, the generation who spent it, and the generation who lost it. Genes go just so far.

But taxing those who achieve to redistribute it to those who do not is not the answer.

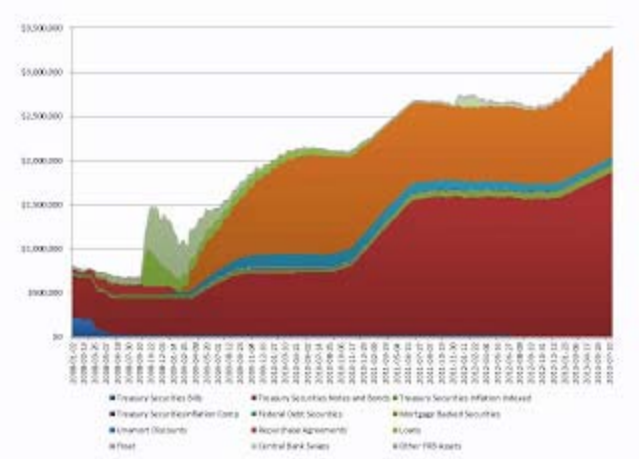
The answer is simple. Scholarships based solely upon academic performance. The old NY State Regents Scholarships. You take a test and your grade determines whether you get it or not. No issues regarding your volunteer work, class projects, advanced placement exams. Just one test, anyone can try it, if you are in the top, say 10%, you get a free ride to college. And the college must accept you. That is the answer. Hang out the gold ring, make it fair, simple, and independent of anything else. Even rich kids can apply.
Labels: Economy

SATURDAY, JULY 27, 2013

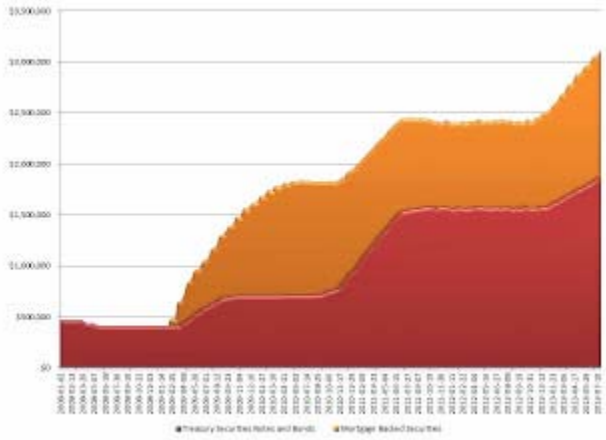
MORE THOUGHTS ON THE FED'S BALANCE SHEET



The above is the FED's Assets as of July 26, 2013. Still ramping up and for some serious reasons. Let us take a look at the most significant elements below:



Clearly we have really only two to deal with so let's look at them. Namely the Treasury holdings and the Mortgage Backed Securities.



This shows that the FED continues to buy tons of this stuff now amounting to over $4 trillion. This is the most significant part of the Asset Base. Now when this starts to unwind we will have significant problems. The new FED Chair should be asked what to do about this mess. Are we to stop it and if so when do we unwind it and at what cost.

This will be the challenge for the next decade!
Labels: Economy

THURSDAY, JULY 25, 2013

CORRELATION AND CAUSATION

The Cancer Epidemiology journal reports on a correlation between a woman's height and her risk of post-menopausal cancer. They state:

Height was significantly positively associated with risk of all cancers (HR = 1.13; 95% CI, 1.11–1.16), as well as with cancers of the thyroid, rectum, kidney, endometrium, colorectum, colon, ovary, and breast, and with multiple myeloma and melanoma (range of HRs: 1.13 for breast

cancer to 1.29 for multiple myeloma and thyroid cancer). These associations were generally insensitive to adjustment for confounders, and there was little evidence of effect modification.This study confirms the positive association of height with risk of all cancers and a substantial number of cancer sites.

The causal argument is that height means more active growth factors and more active growth factor means a higher chance for cancer.

Boy is that a stretch. Take melanoma, something for which I have a modicum of understanding (see my Draft book on Melanoma Genomics). Is height a causative agent? That in my opinion goes beyond being just a stretch. Frankly I cannot think of a single pathway, epigenetic, ECM, or other factor for which that works.

The problem all too often is correlation is not causation. They both may have a similar cause, but that is left as an exercise for the reader. Although it gets great play from the Press (See NY Times):

Height can be influenced by a number of factors beyond genetics. The amount and type of foods consumed in childhood can influence height, and childhood nutrition may also play some role in cancer risk. A higher circulating level of a protein called insulin-like growth factor, which can be influenced by factors like exercise, stress, body mass index and nutrition, is also associated with both increased height and an increased cancer risk.

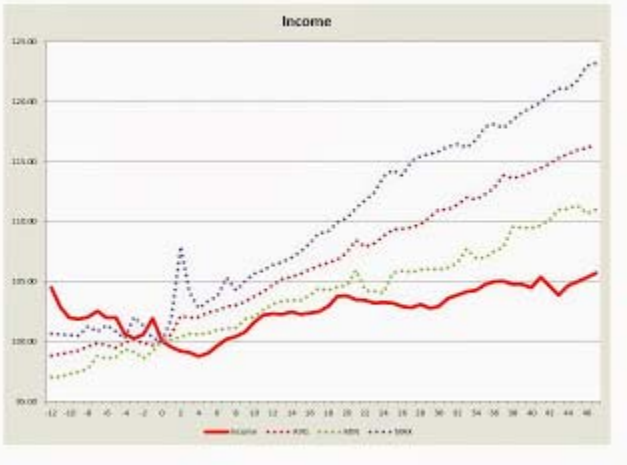
They found that for every 4-inch change in height, there was a 13 percent increase in risk for developing any type of cancer. The cancers most strongly associated with height were cancers of the kidney, rectum, thyroid and blood. Risk for those cancers increased by 23 to 29 percent for every 4-inch increase in height.

I would not worry too much about this issue. You see I am 6'3".
Labels: Cancer

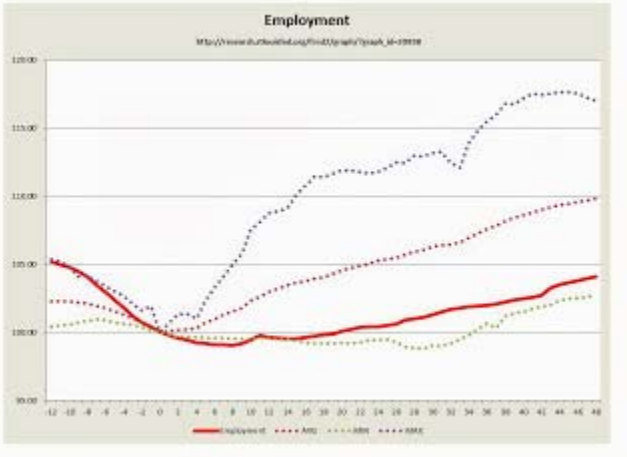
RECESSION STATISTICS UPDATE 2013

From time to time we examine the Recession Stats from the St Louis Fed. They are not too heart warming.

First, Industrial Production is lagging from the average.

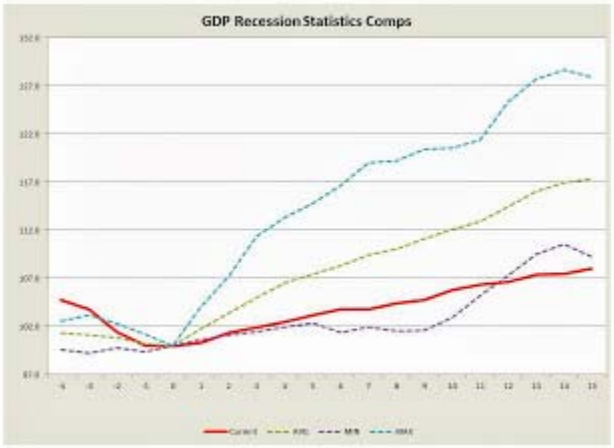


Second, Income is the worst factor. People are not being paid. This is clearly the worse recovery from this perspective.

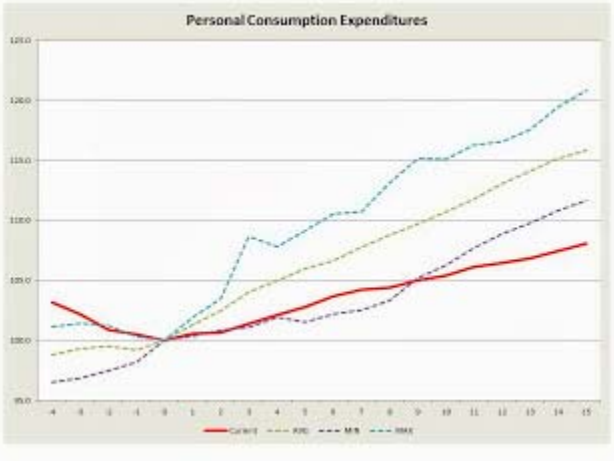


Then as we look at Employment it too is slow. Nothing new here except it is defining a new bottom.

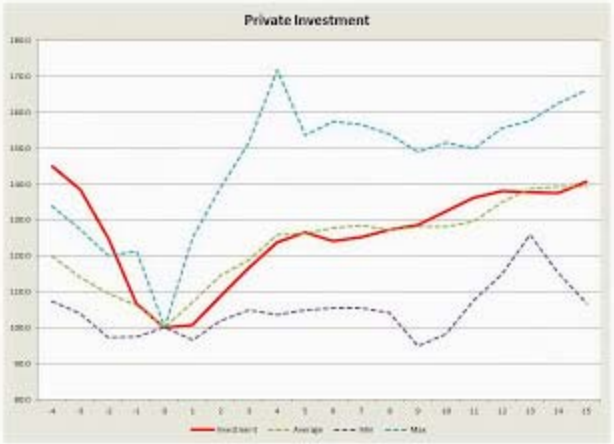
Retail sales is on par, which means people are spending but not investing.



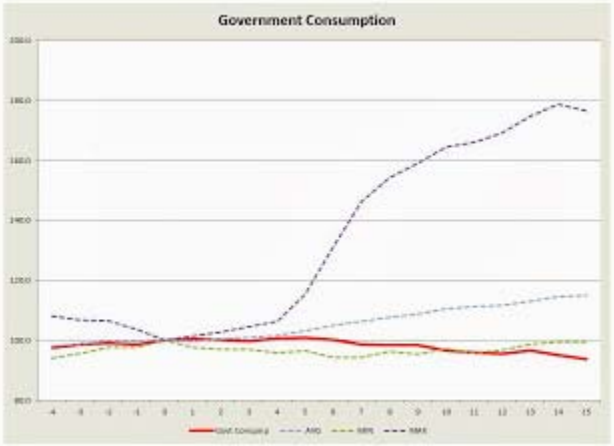
The GDP is defining a new bottom as we have seen. Now let us examine the elements of the GDP:



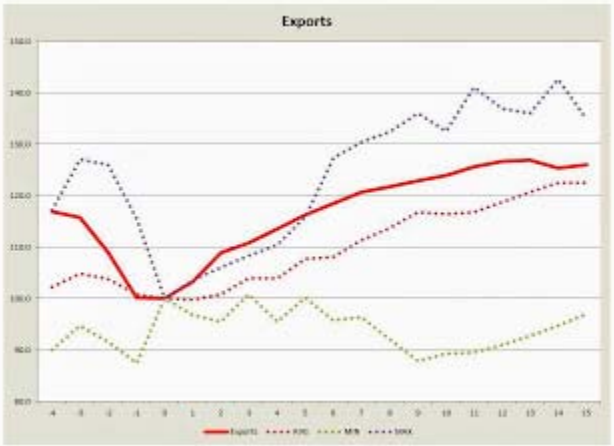
Personal consumption is low, also defining a bottom.



Private Investment is on par.



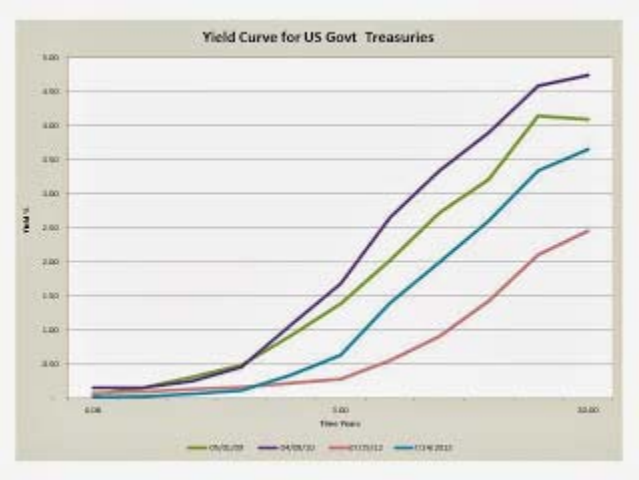
Government spending is the lowest yet. One wonders what is happening here. Then we have Exports:



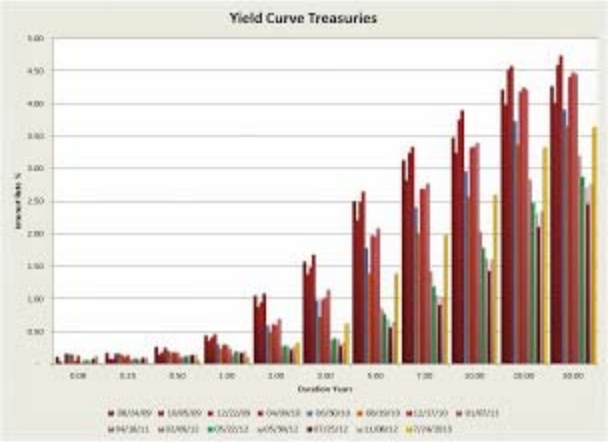
And finally Imports:

The news is not good some five years after the bottom. Then again there were no real expectations from the team in place.
Labels: Economy

YIELD DATA



The steepest yield curve was back in 2010. We see it creeping up again, low short term and growing long term. This will hit bonds a bit.



Here is a summary across time and one can see the increase.

Here is the spread and it is starting to back to where it was a few years ago. Still lots of room but there is substantial movement.

Labels: Economy

SUNDAY, JULY 21, 2013

THE MOOCS: REAL OR A PASSING FAD?

The Economist has a piece on the MOOCs, those on line university like courses.

The article states:

But Anant Agarwal, the boss of EdX, reckons the MOOC providers will be more like online airline-booking services, expanding the market by improving the customer experience. Sebastian Thrun, Udacity's co-founder, thinks the effect will be similar in magnitude to what the creation of cinema did to demand for staged fiction: he predicts a tenfold increase in the market for higher education.

Sceptics point to the MOOCs' high drop-out rates, which in some cases exceed 90%. But Coursera and Udacity both insist that this reflects the different expectations of consumers of free products, who can browse costlessly. Both firms have now studied drop-out rates for those students who start with the stated intention of finishing, and found that the vast majority of them complete the courses.

I have tried, and am still trying, some of these courses, both Coursera and EdX. I have now four under my belt, I finished one, dropped two and are in process with another. My experience can be summarized as follows:

1. They have a lot to learn about teaching. Edx has a system which is reminiscent of software circa 1975. It is inflexible and if you have any question about what they are asking you have no way to find out how to answer it. They have a lot to learn from Google. Edx appears to have been designated by Microsoft.

2. I have done two Coursera courses; one taught by a Scot and the second an Aussie. Frankly I cannot understand at least half of what is said. They speak as if they were in class with local students and not dealing with a global class.

3. Coursera is now trying to monetize itself by charging for a certificate. If you just want to learn it is still free. Would I pay for any of these, not yet. I pay for professional courses from Mass Med Society and HMS but they are real and frankly better than any of the MOOCs.

4. EdX does not have a business model but it has a following. My problem is that the software must be much more adaptive. Strange to say this since it was originated from MIT CS group, but then again these folks in my experience often have the arrogance of the Chosen. If your mission is the world one should and must adapt.

5. One of the most interesting parts of these courses is the Discussion fora. I am not a user of Facebook, frankly it is too intrusive, so this is as close as I get. The comments are written by ego driven and arrogant and mindless morons. I have never seen such blather. They snipe at each other and make senseless remarks. One wonder what benefit they are. On the other hand it is a window to the minds of those who follow the material. I have also seen the classic "teacher's pet" writing how wonderful the instructor is. What good is this, there are issues to be remedied and if one remarks about such the anti-bodies surround you and the cells consume you in blather.

Thus the MOOCs need focus, they need professionalism, they need control, and they need a great deal of software improvement, especially EdX. I would not worry about MIT or Harvard, yet.
Labels: Education

FRIDAY, JULY 19, 2013

THE HEAT AND HISTORY

The NY Times has a short piece on the hottest summer on record, not now but in 1953. They state:

In 1953, New York baked for 12 all-but-unbearable days in a row. From Aug. 24 to Sept. 4, the high temperature in Central Park was never less than 90 degrees, and the nights seemed almost as warm. Consolidated Edison, which prepared a PowerPoint presentation on past heat waves in anticipation for this one, calculated that the average temperature for those 12 days was 95 degrees. The peak was a scalding, scorching 102 on Sept. 2.

I remember that summer quite well. We lived in our new post WW II Cape Cod house and I had the bedroom on the second floor with the window open to the garage next door, about 4" or so, and thus there was no circulation of air. I spent nights sleeping on the concrete in the back yard on WW II cots. There was no air conditioning and we had no car at the time, we went everywhere by bus. Or we walked. No one on Staten Island went to the beaches, they were polluted daily by New Jersey sewerage.

In 1953 there was no place to get away from the heat, you just sat there an by day twelve or so you just started to wilt. Unlike Thailand where it hits 90 in the day time but drops to 70 at night in this New York Heat Wave it just sat there, and stayed 90 all the time.

What amazed me was one of the comments:

Fascinating to look at old photos like the one accompanying this one. People were so thin in the olden days.

Those were the days when we did not have a McDonald's, no Starbucks, no Twinkies, because we had little extra cash. Pizza was a once a summer treat. Yes, people were thinner. It was not genetic then, nor genetic now. People just ate less then and more now. That is what amazes me about the obesity debate, it is just consumption. Global warming not withstanding.

Finally, one should remember also that during the same period of the early 1950s we have multiple hurricanes. The heat wave heats the ocean and in turn sets up conditions for north east hurricanes. So perhaps Sandy was just a prelude. Hope not but history sets a precedent.
Labels: Commentary

WEDNESDAY, JULY 17, 2013

MY EARLY MORNING JOB

Just for information here is a sample of my fields of lilies. I have well over 4,000 crosses and 600 named hybrids. Summer has been hot and we are reaching 500 crosses as of today. Hopefully make it to 600+. The daylilies love the heat, but even at 4 AM this morning it was worse than a bad day in Bangkok. Enjoy looking at the Garden if you want.

Labels: Commentary

TUESDAY, JULY 16, 2013

CLINICAL TRIALS AND CONFUSION

In a recent article in the NY Times the author states in discussing a recent ASCO meeting and a presentation on a specific drug:

The centerpiece of the country's drug-testing system — the randomized, controlled trial — had worked. Except in one respect: doctors had no more clarity after the trial about how to treat brain cancer patients than they had before. Some patients did do better on the drug, and indeed, doctors and patients insist that some who take Avastin significantly beat the average. But the trial was unable to discover these "responders" along the way, much less examine what might have accounted for the difference... Indeed, even after some 400 completed clinical trials in various cancers, it's not clear why Avastin works (or doesn't work) in any single patient. "Despite looking at hundreds of potential predictive biomarkers, we do not currently have a way to predict who is most likely to respond to Avastin and who is not," says a spokesperson for Genentech, a division of the Swiss pharmaceutical giant Roche, which makes the drug.

The author concludes, and I wonder if he knows what he is concludoing:

Part of the novelty lies in a statistical technique called Bayesian analysis that lets doctors quickly glean information about which therapies are working best. There's no certainty in the assessment, but doctors get to learn during the process and then incorporate that knowledge into the ongoing trial.

We have argued that again and again. BRAF inhibitors are Bayesian in a sense. Namely we understand one of the deficiencies in a melanoma for a class of patients. We can then address that deficiency. That is in essence Bayesian, namely P[Outcome|Patient Genomic Condition].

In fact the development of our understanding of cancer pathways, inter-cellular matrices and their interactions, and the immune system and its control mechanism, will allow for patient, and even tumor cell, specific therapeutics.

The problem we have faced in therapeutics is that they have been meat cleaver approaches, cell cycle inhibitors which inhibited all cell cycles thus eliminating hair and other debilitating effects.

Now we can understand what genetic pathways have broken down and we can address that specific problem.

The Times author also states:

In a famous 2005 paper published in The Journal of the American Medical Association, Dr. Ioannidis, an authority on statistical analysis, examined nearly four dozen high-profile trials that found a specific medical intervention to be effective. Of the 26 randomized, controlled studies that were followed up by larger trials (examining the same therapy in a bigger pool of patients), the initial finding was wholly contradicted in three cases (12 percent). And in another 6 cases (23 percent), the later trials found the benefit to be less than half of what was first reported.

In JAMA that article by Ioannidis states:

Clinical research on important questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones

This paper has received a great deal of criticism. Yet the biggest concern in my opinion is that it lumps all trials together. Many trials are truly gross guesses. They are in effect meat cleaver therapeutics. The newer genetic based therapeutics totally change that perspective.
Labels: Health Care

NCI DATA BASE FOR CANCER CELL LINES

The NCI has published a pare in Cancer Research. The paper states:

The NCI-60 cell lines are the most frequently studied human tumor cell lines in cancer research. This panel has generated the most extensive cancer pharmacology database worldwide. In addition, these cell lines have been intensely investigated, providing a unique platform for hypothesis-driven research focused on enhancing our understanding of tumor biology. Here, we report a comprehensive analysis of coding variants in the NCI-60 panel of cell lines identified by whole exome sequencing, providing a list of possible cancer specific variants for the community.

Furthermore, we identify pharmacogenomic correlations between specific variants in genes such as TP53, BRAF, ERBBs, and ATAD5 and anticancer agents such as nutlin, vemurafenib, erlotinib, and bleomycin showing one of many ways the data could be used to validate and generate novel hypotheses for further investigation. As new cancer genes are identified through large-scale sequencing studies, the data presented here for the NCI-60 will be an invaluable resource for identifying cell lines with mutations in such genes for hypothesis-driven research. To enhance the utility of the data for the greater research community, the genomic variants are freely available in different formats and from multiple sources including the CellMiner and Ingenuity websites.

On the NCI web site they state:

NCI scientists have developed a comprehensive list of genetic variants for each of the types of cells that comprise what is known as the NCI-60 cell line collection. This new list adds depth to the most frequently studied human tumor cell lines in cancer research, molecular pharmacology, and drug discovery. The NCI-60 cancer cell panel represents nine different types of cancer: breast, ovary, prostate, colon, lung, kidney, brain, leukemia, and melanoma. In this study, the investigators sequenced the whole exomes, or DNA coding regions, of each of NCI-60 cell lines, to define novel cancer variants and aberrant patterns of gene expression in tumor cells and to relate such patterns and variants to those that occur during the development of cancer. They also found correlations between specific variants in genes such as TP53, BRAF, ERBBs, and ATAD5 and the activity of anticancer agents such as nutlin, vemurafenib, erlotinib, and bleomycin.

NIH introduced the tools such as CellMiner a year ago and it was in the following release:

Genomic sequencing and analysis have become increasingly important in biomedicine, but they are yielding data sets so vast that researchers may find it difficult to access and compare them. As new technologies emerge and more data are generated, tools to facilitate the comparative study of genes and potentially promising drugs will be of even greater importance. With the new tools, available at http://discover.nci.nih.gov/cellminer, researchers can compare patterns of drug activity and gene expression, not only to each other but also to other patterns of interest. CellMiner allows the input of large quantities of genomic and drug data, calculates correlations between genes and drug activity profiles, and identifies correlations that are statistically significant. Its data integration capacities are easier, faster, and more flexible than other available methods, and these tools can be adapted for use with other collections of data.

CellMiner is accessible at NCI.

Labels: Cancer

TUESDAY, JULY 9, 2013

"EWE WHEY" OR YES IN QUEBEC

Learning a language is often a difficult task, but understanding English is near impossible. I started to understand the difference in three separate events. Once in Florence I tried my Staten Island Italian with a vendor. They stopped me and asked where I learned Italian. I told them on State Island. They told me I was speaking almost perfect Sicilian, a dialect not well accepted in Florence. Then there is French. I speak French, but would never be accepted in Paris, Normandy and Savoy is fine, but never Paris. I once had an investor from Quebec and had the good fortune to listen to his speak with those in Paris. Then it became clear. My next visit to Quebec I started to more clearly hear the differences.

Then of course there is England. Now once I met a colleague in a hotel near Buckingham palace, down from Victoria Station. Well it was Faulty Towers redux. Not only incomprehensible but

the staff was just bumping into one another.

Now where does this take us, well to the MOOCs. I have been trying out a few and one was taught by a woman from Edinburgh. She was somewhat understandable except for the vitamin work where it was not v-eye-tah-mihn but vit-teh-men. Try that on for size. Now I am trying one with a woman from Melbourne. Now I really do not understand Australian. I have a better grasp of Thai. This woman speaks so quickly, uses a strong Aussie accent, and has zero ability to "teach". She clearly understands her material, and she is trying, but this is why MOOCS will never make it, no feedback. No one to ask. "What the hell did you just say!" That's New York for we really do not get your accent. Now being in New York it is not that we do not have accents, why I can take a cab ride and yet still communicate. Thank God we do not have any Ausssie cab drivers, no one would ever get to where they want.
Labels: Commentary, Education

MONDAY, JULY 8, 2013

GLOBAL WARMING: HAVE A CONTEST

For some reason I have seen several blog discussions again on taxing carbon emissions. Let us assume that there is global warming, I see it in my early blooming daylily species, so I have to believe my own eyes. So set that part of the argument aside. Now is that good or bad, well for me it has allowed better hybridizing and perhaps a benefit. I have over fifty new hybrids ready this year, thanks in part to global warming.

Now Posner goes on suggesting

As long as global warming is gradual, and catastrophic effects are not felt for the next 50 to 100 years, there is room for hope that geoengineering will limit or even reverse global warming. Ways of trapping the carbon dioxide produced by burning oil, coal, natural gas, and forests may be developed or sunlight may be blocked by injecting sulfur compounds into the atmosphere, which would reduce the amount of sunlight that reaches the earth (though could create other forms of pollution—sulfur dioxide, for example, creates acid rain). Or safe means of piping carbon dioxide emitted from electrical generating plants underground might be developed. There are even suggestions for "whitening" roofs (on a very large scale) to increase earth's reflection of the sun's rays.

But there is no guaranty that global warming will be gradual. It may turn abrupt; there are a number of examples in earth's geological history when this happened. For example, a period called the "Younger Dryas" at the end of the last ice age is believed to have seen an increase in the average global temperature by 7 degrees centigrade, which is 12.6 degrees fahrenheit, in only 10 years. Were that to happen again, it would be an unbelievable catastrophe. The probability of abrupt global warming cannot be estimated; but heading off even catastrophic events that are uncertain can make good economic sense if the resources required to do so are modest.

It is always good to see a lawyer prognosticate on science, so let that stand. How fast is the climate changing? No one really knows. Is it for better or for worse? Again net of the equation

no one knows. I suspect the Polar Bears will adapt and eat what the Black Bear around my house does. But that is a tale for another day. Now Posner proposes:

A more efficient method of limiting global warming than regulatory controls such as proposed by the President (and that as described promise to be a bureaucratic nightmare) would be a tax on carbon emissions, which I advocated in my 2005 book and which a number of countries have adopted.

Frankly that in my opinion is total nonsense. You see we need electricity, we need to commute to work, we need the results of the infrastructure that create carbon dioxide. I have made that argument against Mankiw time and again. The poor schlub who has to commute to his job in Cambridge cleaning the halls of Harvard must drive at night with a few others in a broken down care from some distance. He has no choice. The same in most cities. There is no elasticity of demand for the poor folks, so tax them?

Even more so, why in God's name tax anything, it just feeds the Government monster, more Government useless workers getting higher salaries bigger benefits and treated to great parties and big bonuses.

My favorite Economist, Frances Woolley makes several good points in her recent post.

Then I tried the economic freedom line: "A carbon tax makes fossil fuels more expensive, so people have an incentive to consume less. The great thing about them, though, is that people have a choice about how to cut their consumption."

"Think about the alternative," I said, "Do you really want a bunch of new regulations, people saying what you can and cannot do? This way there's no need for a big government bureaucracy, and people decide what's best for them."

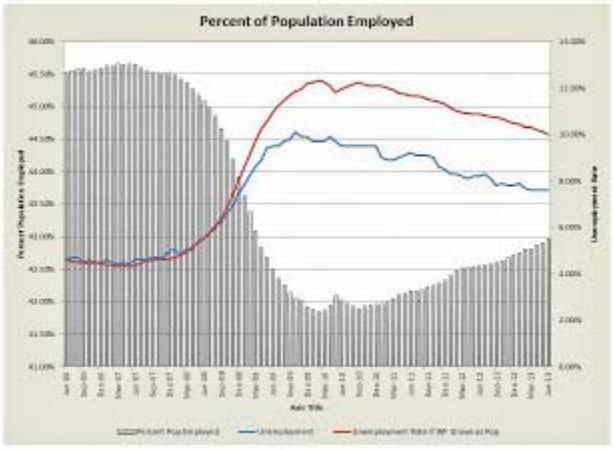
Neither of these arguments made the slightest impression on my cousin. "I don't believe this talk about revenue neutrality," he said, "there won't be cuts to other taxes. The government will just take the money and spend it on useless things like your salary."

Now I really like the insight Frances has, it is a rare form, keen insight into the obvious. Rare amongst economists. But the real point is that this is an engineering problem. Engineers face this all the time. Get rid of some byproduct, efficiently. Chem Es do this for a living. So why not solve the problem, not tax it. Even more so I propose a contest. The Government give a prize of say a billion dollars to the first entity to demonstrate an cost effective way to eliminate carbon dioxide. Make them rich. This combines all the key elements of a free market. It solves a problem, it rewards success, it does not tax, and it does NOT add a single Government employee. They did stuff like this when airplanes were new. Why not give it a try?
Labels: Global Warming

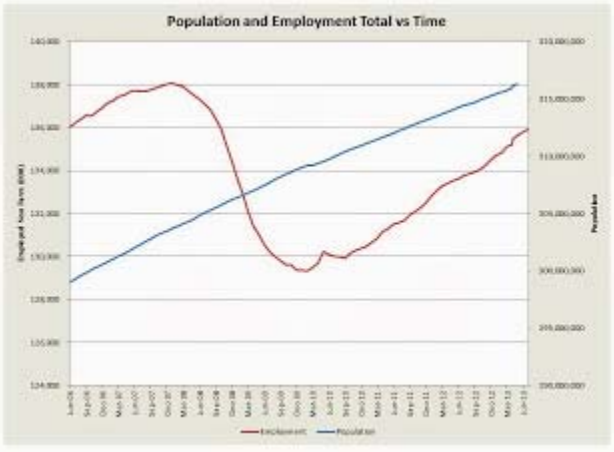
FRIDAY, JULY 5, 2013

EMPLOYMENT: BAD NEWS AND GOOD NEWS

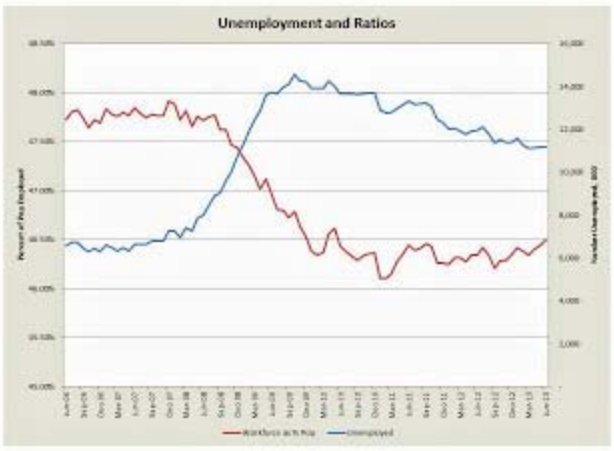
Who would have thought when I started this Blog some five years ago that we would still be in the woods. Well I did given the folks who were taking charge. So no surprises, just a lost decade or two.



Now 7.6% is not good. Not good at all. But the percent of the population employed has increased, not to where it should be but more than what it was. And then increase is sustained at a positive level. It took 3 years to go from 42% to 43%. We need to be at 45%. That means another six years at this rate! Unless we find another Reagan.



We see a gap but a narrowing gap in the above. Again another six years to close at this rate.



The same as the above. Well just sit back and watch the corn grow.

Labels: Economy

WEDNESDAY, JULY 3, 2013

HOW DOES IT MAKE ME FEEL?

NEJM has an interesting piece on patient input. They state:

As an oncologist, when I sit with patients to discuss starting a new chemotherapy regimen, their first questions are often "How will it make me feel?" and "How did patients like me feel with this treatment?" Regrettably, this information is generally missing from U.S. drug labels and from published reports of clinical trials — the two information sources most commonly available to people trying to understand the clinical effects of cancer drugs.

This is a serious issue not only with oncologists. The challenge is to meet the anticipated needs of the patient. Patients respond much better when what they are told matches what happens. Then there are no surprises. They can often deal with a great amount of discomfort much better than lesser amounts of uncertainty.

They continue:

The FDA has taken several recent steps toward encouraging inclusion of the patient perspective in drug development. It issued highly influential guidance on the use of patient-reported outcomes (PROs) in drug development, collaborated with the Critical Path Institute and industry to form the PRO Consortium with the aim of developing robust symptom-measurement tools, and obtained support from Congress in the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) to expand its internal expertise on the methodology of measuring PROs. (Unfortunately, allocated PDUFA funds have been withheld, which substantially impairs the FDA's ability to implement planned patient-centered programs.)

These FDA efforts are evident in the ruxolitinib label and in the label for abiraterone acetate, approved this year for metastatic prostate cancer, which describes beneficial delays in time to the development of pain and the need for opioid use. Yet in preapproval trials in patients with cancer, symptom or functional-status evaluations that meet the FDA's standards remain rare.

The FDA should clearly expand on this effort. In a sense the patient should have a peer reviewed assessment of what to expect.
Labels: Government, Health Care

WEDNESDAY, JULY 3, 2013

THESE ARE THE FOLKS WHO GAVE YOU THE ACA

Arrogance is a human fault. Arrogance when combined with ignorance can be truly dangerous. Many who gave us the ACA were and are truly arrogant, even more so they have a hubris that exceeds what the gods would ever allow a human.

In today's NY Times one of those characters, in my opinion, states:

The employer mandate was included in the Affordable Care Act — which I helped design as an adviser to the Obama administration — in order to ensure the continuation of employer-sponsored insurance after the creation of state-sponsored health care exchanges. We didn't want every employer to simply drop its coverage and send all its workers to the exchanges.

But complying is proving to be more difficult than expected for employers. The act requires businesses with more than 50 employees to provide coverage to their full-time workers or face a penalty of $2,000 per employee. A full-time worker is defined as someone who is paid for 30 or more hours of service a week or 130 hours a month. It sounds simple, but determining who should be counted turned out to be a nightmare.

Just read this. Sentence one boasts of his involvement. Sentence two says its implementation is a nightmare. I wrote extensively about this when it was going through the Congressional intestines. I wrote against it, spoke to my useless Senators, and to no avail.

This is merely a gimmick as a hope to save the 2014 elections. Most Americans are just ignorant, that is until it hits them personally. But this delay is just a delay of the inevitable. This plan is a disaster. Then again you voted for it folks!
Labels: Health Care

FRIDAY, JUNE 28, 2013

AM I GONNA MAKE IT DOC?

Patients almost always want to know what will happen if they have some disease where their demise is imminent. The classic big guys remark about "Am I gonna make it doc?" often is the

bravado covering abject terror.

In a recent NEJM article there is an interesting piece on prognostics in medicine. Namely we are all now seeing more and more survival curves, conjoined with prognostic tests which contain genetic information.

The patient wants to know but unfortunately the physician really does not have a clue. The article states:

We believe that at least as much attention should be paid to clinicians' communication about the uncertainty associated with prognostication as to the search for better prognostic models. We propose a framework of three central tasks that clinicians can perform to help patients and families manage uncertainty. Physicians should tailor this framework to the core values of the patient. Some patients will value quality of life more than quantity of life, and for these patients uncertainty about future well-being may be of greater concern than life expectancy.

My concern about better prognostics fall in the following categories:

1. Prognostic data on survival work only for large groups not for a single patient. When I look at the Kaplan Meir survival data for such therapeutics as those new ones for melanoma and even for transplants for MDS I see a 20-30% survival at the tails. To me that tells me something, besides the patient who hope to be the tail. I ask why that group, what happened there? Unfortunately we all too often do not have an answer.

2. Prognostic data is now being used by the Government, namely CMS and under the ACA, for treatment directives and physician control and compensation. Just look at the prostate cancer debacle. The "Committees" making the decisions have decided that PSA tests are useless so they will soon disallow them. They may be useless for some but not all. Yet to the "Committee" they apply to all, a classic Soviet style prognostic decision process.

3. Genetic Tests Yield Prognostic Data: With the ability to collect massive genetic data from genes to SNPs we now have researchers announcing new prognostic tests which at best are problematic and at worst harm the patients. The problem is that all too often one can statistically get "prognostic" data from any correlation, meaningless as it may be.

4. Prognostic Data on Survival Applies to Only Some: I read a recent paper on MDS survival and was truly disappointed by what was in my opinion poor statistical analyses. It compared low risk and high risk patients undergoing bone marrow transplants. It showed the higher risks with better survival. It also showed the higher risk having initially a faster drop in Kaplan Meir at the beginning and then a sustained flattening at 30%. Why? One reason may be that the one who died early had poor HLA matches while those who survived had better, say 10 point match to a 5 point match. But such an analysis was not to be,

The article then states:

Prognosis, and prognostic uncertainty, have a profound influence on physicians, as well as on

patients and families. Physicians' generally optimistic bias is well documented. In one study, physicians overestimated the likely duration of survival of terminally ill patients by a factor of five, and the longer the duration of the patient–physician relationship, the more optimistic the estimate. Clinicians may also have trouble with prognostic uncertainty. Some react with an unwillingness to talk to the patient about the future at all (but commonly express this unwillingness in terms such as "we have to wait and see" or "no one can tell"). Others, ignoring the uncertainty inherent in prognostication, do more and more tests in the futile hope of improving their prediction. We believe that physicians need to recognize their reaction to uncertainty and how these reactions may influence their conversations with patients.

The question of what is going to happen is always on the mind of a patient and their family when a severe diagnosis is made. All too often the physician just does not know. The lung cancer patient who on average is supposed to be dead in three months but lasts three years. The pancreatic cancer patient who also was to last three months but dies of old age. They may be the exceptions but our prognostic capabilities are still quite weak, except on the average. Yet we have never seen an "average" patient.
Labels: Cancer, Health Care

MONDAY, JUNE 24, 2013

OBESITY AND CONGRESS

There is a letter today in the NY Times from Congressional members applauding the AMA panel decision on obesity and then recommending expanding Medicare coverage for drugs and therapy. They state:

We recently introduced a bipartisan, bicameral bill to lift the ban on obesity drug reimbursement under Medicare and encourage intensive behavioral counseling. This would open doors to examine different approaches to obesity treatment.

If the costs of obesity drugs and new treatments are covered, large research studies can examine what treatments have the most effective patient outcomes. Better understanding these outcomes would foster a healthier population and lead to significant health cost savings.

Now try and follow the logic here.

First, this is Medicare, those over 65, with a lifetime of obesity in almost all cases.

Second, the damage is already done; diabetes, kidney damage, atherosclerosis, retinal damage, nerve damage, etc. Most likely they are already on chronic care regimens.

Third, research, research on what? They are fat, they ate too much. And now at 65+ we want to add this to Medicare? For what benefit?

This is one of the dumbest statements I have ever read! And two are Republicans! No wonder we are collapsing as a nation.
Labels: Health Care

SATURDAY, JUNE 22, 2013

IMAGINE IF A CHEMICAL ENGINEER WERE A NYC EMPLOYEE

The NY Times today discussed the collapse of the Regents grading system. The quote by one of the Officials is as follows:

"We anticipated there to be bumps," Ms. Hughes said, noting that the city had originally set a deadline of this coming Monday to have all tests graded. "Things are moving more slowly than we had hoped."

So hundreds of students, if not thousands, for who believes any Government spokesperson in my opinion, did not graduate or get their grades. Could you imaging some Chemical Engineer saying, "We expected some small explosions" or a surgeon saying "{We expected a few dead patients". Bumps in the road are all too common in Government projects, just look at the new 911 System in NYC as well. Now this is 2013, software has been developed for sixty plus years, testing is a sophisticated science, so why all these mistakes. I would guess because it is the Government. You see if this were some commercial enterprise it would lose customers and go out of existence. One suspects the folks involved will get a bonus.
Labels: Education

FRIDAY, JUNE 21, 2013

HEALTH CARE COSTS: WHOSE FAULT?

In a recent article in Becker's one of the current contenders for Governor in the Commonwealth of Massachusetts makes some rather extreme statements in my opinion.

They state:

The failure of the healthcare system stems from six main areas of waste, Dr. Berwick said: overtreatment, failures to coordinate care, failures in care delivery, excessive administrative costs, excessive healthcare prices and fraud and abuse.

Now let us examine this a bit.

1. At no time does he put any blame on the patient. Obesity, smoking, diet, sexually transmitted diseases, drug abuse, and the list goes on are all self inflicted causes of chronic and costly disease. We can estimate the costs quite well but in the mind of this person in my opinion only Government can remedy this with more care not better behavior and personal responsibility.

2. Excessive health care costs are a bit confusing since 20% of health care is Medicare which as a monopsonist sets the price. Insurance companies also have such power. No physician ever collects what they say the costs are.

3. Failures are perhaps a human condition, but through better process are controllable. So what does he suggest? Never seem to get an answer.

4. Administrative costs? Ever try to deal with they Government, they are the cause NOT the solution.

The article also states:

"We live in a civilized and wealthy country," Dr. Berwick said. "We should make healthcare a human right."

A right? A costly right. Perhaps a right to privacy should come first. Also when rights like this are mandated by such as on high they often not only miss the mark but have very negative consequences, intended or not.
Labels: Health Care

WEDNESDAY, JUNE 19, 2013

AMA AND OBESITY

The AMA has declared obesity a disease, says Medpage. They state:

Obesity should be called a disease and not simply a condition, the American Medical Association's policy-making House of Delegates voted on Tuesday. The vote -- approved by roughly 60% of the AMA's full House -- goes against the recommendation of its Council on Science and Public Health, which issued a report earlier this week saying that calling obesity a disease would be problematic.

"Problematic" is an understatement. In almost all cases obesity is self inflicted. Again it is simply input less output is net accumulation. Too much input and at 3500 kcal per pound you get fat. In almost all cases that is the rule.

The NY Times states:

"The suggestion that obesity is not a disease but rather a consequence of a chosen lifestyle exemplified by overeating and/or inactivity is equivalent to suggesting that lung cancer is not a disease because it was brought about by individual choice to smoke cigarettes," the resolution said.

Now just parse this statement. Lung cancer caused by smoking is a self induced disease, why, because it cannot be reversed by lifestyle change and will kill you. It is still self induced and preventable. Obesity is self induced and absolutely reversible. The revers can also often stop and reverse the underlying Type 2 Diabetes. This may make the physicians job easier by not demanding the patient do something but it explodes the costs on those of us who watch our weight.

The Times also states:

One reason in favor, it said, was that it would reduce the stigma of obesity that stems from the widespread perception that it is simply the result of eating too much or exercising too little. Some doctors say that people do not have full control over their weight.Supporters of the disease classification also say it fits some medical criteria of a disease, such as impairing body function.

This creates a broad definition of disease. This is in my opinion one of the most ill conceived things ever done in the field of medicine. People who cause the problem should face the consequences. They burden those who do not inflict their own lack of will on others.

The AMAs statement is as follows:

Today, the AMA adopted policy that recognizes obesity as a disease requiring a range of medical interventions to advance obesity treatment and prevention. "Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans," said AMA board member Patrice Harris, M.D. "The AMA is committed to improving health outcomes and is working to reduce the incidence of cardiovascular disease and type 2 diabetes, which are often linked to obesity."

The statement makes it even worse. It states it is a disease and require "medical intervention". It just requires shutting one's mouth. All one must do it look around a physicians office and see most of the staff morbidly obese and then look behind the screen and see food just lying all about with continual consumption. The solution is simple, get physicians to start the process by denying any food in the office, and seeking non-obese help, if at all possible.
Labels: Health Care

TUESDAY, JUNE 18, 2013

ARE TERRORISTS THAT DUMB?

Terrorists are most likely like spies. At least one would think they would or should be. Spies have been around for a real long time, a real long time. The Persians had spies in Greece some 2500 years ago. So it is nothing new. Spies, and one would suspect Terrorists, communicate

amongst one another and they would most likely do so in some secure manner, not say sending emails on some well known site or planning in an open "chat room". But perhaps they are really that dumb.

There is an article in Science which has alleged "experts" applauding the current administrations massive tactics of seeking these folks by examining what is in plain sight. In fact they state:

"I can tell you that this kind of thing is extremely effective," says Alex Pentland, a computational social scientist at the Massachusetts Institute of Technology in Cambridge who has studied phone networks.

Now being told by someone from the Media Lab is not really that comforting to me but perhaps it may be somewhat truthful. I would not know what their basis is. The article continues:

The first step, Uzzi says, would be to map who calls whom—with each person represented by a point or "node" and each person-to-person link represented by a line or "edge"—to create a simple communication network. Next, the analyst would study details of calls—their frequency, duration, and timing—to determine how closely connected each pair of people is. This step breaks the communication network into smaller, overlapping social networks. The third step would be to study the dynamics of a social network, to see how activity ebbs and wanes and the network evolves. The fourth step would be to try to correlate the dynamics of the network with external events,

This assumes the "plain sight" scenario. If we take spies as the example, they have two options; hide in plain sight and be totally covert. When in plain sight you must be transparent, not attract attention, and be as if you were a sleeper. You could not stand out, you don't communicate, and you must fit in with everyone else. If you are covert than you stand apart and in this case you must use secure and covert means of communicating. Thus codes, secure comm links, such as wireless HF digital links, so that no one knows just who you are calling.

The use of the above techniques work well in commercial applications where people volunteer their information and have no desire to "hide". We can find that people say on Staten Island order more Pizza deliveries per 1,000 HH than any other area in the US and further that they have the greatest BMI in the US as well. But if we had some Chinese espionage agent I doubt that they would call the Embassy to transmit data. I would think.

I can recall all the means and methods of WW II and those in the Cold War, so why would they not be employed? Can we really detect those hiding in plain sight. Perhaps, but the Fort Hood terrorist was shouting out his plans and no one ever paid attention? What happened there. He apparently even gave presentations that should have alerted a Mall Guard.

Thus the issue is less the value than the very rights we would expect. As for Congress and its overview, I have found that all too often those providing oversight just do not have a clue technically so what good does it do.

I am still in favor of human intel, people, people where the action is. Again, just sitting in that

bar in Istanbul, the coffee shop in Algiers, the shops in Islamabad. Words, accents, clothing, shoes, packages, hair cuts, people meeting, those are the tools of intel, and the ability to have a keen insight into the obvious.
Labels: Commentary

THE PHILADELPHIA CHROMOSOME

The book by Wapner, The Philadelphia Chromosome, is simply perfect. It is a wonderful balance of science, personalities, inventions and medicine. It flows smoothly, giving the reader the opportunity to catch up each time a new step is taken. The topic is simply the best example of how we are beginning to understand cancer in a detailed manner, thus allowing us to develop therapeutics to treat cancer, turning many from death sentences to chronic disease. The focus of Wapner's book is CML, chronic myelogenous leukemia. This is a blood cancer where the white cells start changing and slowly increase and then in a blast crisis cause total collapse and death. This is the story of how it was understood what caused it and how to stop it.

She takes the discovery of the Philadelphia chromosome and walks the reader step by step to the acceptance and use of imatinib. I remember a colleague in Vienna, Austria, who in 2002 came down with CML, at a young age, and I had been following the imatinib development and after a few calls it was possible to get him on the therapeutic and he survived. This tale has some many coincidences, most positive, that makes its telling almost mandatory to best understand where cancer therapeutics is progressing today.

The tale presented by Wapner is fairly straightforward; it is a mixture of science, luck, coincidence, and human nature.

The first part of the book takes us from the early 1950s through the mid-1980s, where we go from not understanding to having a somewhat clear scientific comprehension of both the problem and a remedy. The first part moves through the following:

1. Using an innovative way to look at chromosomes the 1959 discovery of a chromosomal alteration indicates that a hematological cancer, CML, presents with this abnormality. A short end on one chromosome and longer end on another were observed. This is just six years after the Watson and Crick paper.

2. Recognition of a cancer generating gene.

3. Recognition of the fusion of two chromosomes

4. The understanding of how protein kinases work via the src gene from chicken sarcomas. In fact on p 47 the author describes this process and she does a superb job in highlighting what will become a significant key in the overall development of imatinib.

5. The discovery of the Abelson gene, abl, and its relationship to cancer. On p 63 the author relates how Abelson was berated in 1969 by physicians and the president of AACR, the cancer

research society. Frankly at that time cancer was the realm of the surgeon, who often just cut as much as possible and often doing more damage than good.

6. The new Gag/Abl protein, namely the fusion seen on chromosomes is identified as the fusion of two genes. The author on p 72 has a wonderful description of this insight.

7. Gag/Abl causes cancer. On p 83 the author discusses the work in David Baltimore's lab in the early 80s. At the same time they found abl had come from chromosome 9 and was transported to chromosome 22 attached to gag.

8. The tale of Drucker and his persistence and dealings with Ciba Giga, eventually to be Novartis starts at this point. Here we see the drive of pushing, connecting, developing, and frankly persevering with a positive result. It was recognized that the Gag/Abl fusion product was the driver of CML and that the driver of that was ATP and ATP found a connection point on the protein. Then if a new molecule could bind and block the ATP the gene effects, namely cancer, could be blocked. Thus starts the second part of the book.

The second part of the book is much less linear and shows the complexity afoot in the pharma world. Even though Drucker, and at this point many others, saw the path forward, it was necessary to engage the pharmas and their massive powers as well as their bureaucracies. Thus, we have the tale of this part. The author does a superb job of giving some light on the development and testing of therapeutics. One walks away seeing the most bureaucratic part the pharma and the FDA and Government entities almost acting as sideline players at best.

The infighting in the pharmas, the conflicts between development, marketing, toxicology, and management is a wonderful tale, typical of so many large institutions. The lesson from part one is the brilliance of the dedicated researchers, that from part two is one wonders how any therapeutic is ever developed. In today's world it would take fifty years to approve aspirin!

Wapner's book presents great history but it begs the question of the future progress. Although that was not the intent of Wapner, she sets up the question quite nicely. She shows how research and development proceeded from the 1950s through the end of the century. I would argue that we are at the beginning of a new paradigm of development, and it is not clear if the institutions are all that prepared to deal with it.

There are several drivers which make the future even more interesting.

First the communications over the period of 1959 through 2002 were driven most often by personal contact, journals and conferences. Today the Internet spreads results and data around the world instantaneously. The chance occurrences are increased orders of magnitude.

Second, as we look at kinases we now understand them first as intracellular networks and pathways and secondly as distributed spatio-temporal systems. This means that we are moving from the world of bench researchers and their singular focus to the "engineer" and their systematic approaches. Cancer is viewed as an unstable multidimensional system. Fortunately there are many tools and expertise to deal with such a paradigm.

Third, and this is an exceptionally critical change, we have multi-national participation, with explosions from countries like China.

One is starting to see more and more of the fundamental work arising from not just the US and Europe but Asia. These three factors will most likely be accelerators for the tale told by Wapner. However she also contains the cautionary tale of the Pharmas and the regulatory bodies, oftentimes the brakes on progress. That will most likely be the challenge to realizing true progress on cancer.

The future may very well be driven by the observations of Eddington and Einstein:

"It is also a good rule not to put too much confidence in the observational results that are put forward until they are confirmed by theory." Arthur Eddington

"It is quite wrong to try founding a theory on observable magnitudes alone. It is the theory which decides what we can observe." Albert Einstein

The two quotes frame the changes which are occurring in the understanding of cancer. The tale by Wapner was initially data driven, there was not model, it had to be constructed. Now, we have models, we understand pathways, we understand where they fail, and thus result in cancers. We have the models and thus hopefully we can make better and faster sense of the data. Wapner sets the path to best understand that progress.
Labels: Books, Cancer

FRIDAY, JUNE 14, 2013

GENES AND THE LEFT WING

Apparently the left wing bloggers have determined that Justice Scalia does not "believe" in evolution. One of the left wing bloggers, who in my opinion is all too often a bit over snarky states:

The text goes on just like that: simply summarizing molecular biology. That's right, Justice Scalia can't confirm these details with his knowledge (valid) or his belief (um, what?).

Can't he hire a clerk to teach him molecular biology?

Now let us examine just what this complaint seems to be.

Justice Scalia states:

I join the judgment of the Court, and all of its opinion except Part I–A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. It suffices for me to affirm, having studied the opinions below and the expert briefs presented here, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and

*that **complementary DNA** (cDNA) is a synthetic creation not normally present in nature.*

Now one should note several things. First belief is a legal term of art, and before commenting the Justice indicated that this is a complex issue which may not have been fully illuminated. Second, and this is critical, Scalia unlike the one who crafted the opinion, uses the correct term for cDNA, complementary DNA, not what we have commented in before. Thus Justice Scalia is spot on in both delimiting his knowledge in the complexity of the issue and secondly in using the correct term.

Thus unlike the left wing bloggers he appears as is so often the case to be correct, and the left wing bloggers just wrong. So what else is new?
Labels: Commentary

THURSDAY, JUNE 13, 2013

WOMEN AND LUNCH

Some day I must cross the border and visit one of my former students who is in Ottawa and at the same time visit Frances Woolley. Today she writes a long blog about men and women having lunch together. Now since I am old enough to be her father perhaps I may be able to shed some light on the situation. That man and woman thing.

You see when I grew up it was during WW II and there were few men around. The world as I saw it was controlled and managed by women, mother, grandmother, aunts, cousins. The men I intuited were sent off to war and some never returned. I even envisioned that the women made all these choices, after all even all my teachers were women and the girls often got the best grades. There were indeed very few men. I was the minority, and there always was that concern about what happened when you grew up. Bit perhaps an observation may also be useful. The "Baby Boomers" came along after our "Silent Generation" and the key difference was that the men were home, during perhaps some Freudian key period in their lives. For us them men came home after we had been imprinted, for them the imprinting was dramatically different. Just an observation.

Now segue to the late sixties, I am teaching at MIT, my first major assignment, the Sophomore Electronics course. Never saw a woman in class, and then there in the front row was a real woman. Yes, I made the mistake of asking if perhaps she was in the wrong class. Today that question would have you drawn and quartered but then it was trying to be polite. No, she replied, she was a Biology major and she wanted to learn electronics, a laudable goal I thought. From that point I never asked again and the numbers grew exponentially.

By the late 1980s I had accumulated a few female students, and I would travel back and forth, but the thought that there could be any issues never crossed my mind, nor my wife's. You see I still had my WW II memories, and now their were colleague, not students. I knew their families, their spouses, and eventually even their children. They were professionals and after years still are. I have even assembled cribs for my student's children, and perhaps they may be told later in life of such a heroic event. Namely my doing anything really mechanical!

Now Frances writes:

As a person becomes professionally more established, too, new challenges arise. Is it okay to go out to for dinner with a co-author in another city? To go out drinking with a former supervisee? Nick Rowe, in his position as Associate Dean, will go out for drinks with the (male) Dean. But is it appropriate for a female Associate Dean and a male Dean to go out drinking?

Drinks and dinner, well it all depends. In the context of normal professional relationships I see no problem, in the context of how it "looks" it all depends. Are there predatory individuals, yes and I have seen them, but I suspect that it is they that often look askew at others. In New York today there are no second glances, no issues with such meetings. Then again I feel safe with age, there being nothing more disarming than being perceived as grandfather.

So Frances, whenever I get to Ottawa I would love to have a drink, and I will bring my wife and my former student, of course assuming she can get a baby sitter.
Labels: Commentary

THE MYRIAD DECISION AND CDNA

The Supreme Court states:

They can also synthetically create exons-only strands of nucleotides known as composite DNA (cDNA). cDNA contains only the exons that occur in DNA, omitting the intervening introns.

As NCI states:

The next step is to convert the mRNA back into a DNA molecule in the test tube. This can be thought of simply as reversing what went on in the cell when the gene DNA was switched on and mRNA was made by base pairing. This is a two-stage process. First, each mRNA is copied into a new DNA strand using base pairing to form a mRNA-DNA duplex. Next, the mRNA is chopped up and removed, and the DNA strand is used to make a second DNA strand. This double-stranded DNA is called complementary DNA or cDNA. Thus, each cDNA in the test tube originally came from a specific mRNA in the cell.

But in the MIT cDNA course they call it ***complementary DNA***, NOT "composite DNA (sic)" Even Wikipedia uses that term. It is amazing this is on page 1 they make this massive fundamental mistake. Any AP Biology High School student knows this. One wonders who crafted this document.Perhaps that is what is wrong with our Government.
Labels: Government, Law

LIONS, TIGERS AND BEARS

I live less than 20 miles from the southern tip of Manhattan as the crow flies. It is in the most densely populated state in the US. We have red fox and coyote in the neighborhood, not to mention deer, rabbits, chipmunks, turkey, and the squirrel. But we now have a bear, yes, a 200 pound bear walks across my driveway at night eating up whatever we have left behind.

Now it is not that I have anything against bears, we have one in New Hampshire, but this guy likes my daylilies, my precious hybrids. Do I call Christie? What will EPA say? And yes he did check out my car...hopefully he does not decide to take a ride.
Labels: Commentary

THURSDAY, JUNE 13, 2013

THEORY VS DATA: OR JUST A NEW GENE?

What comes first, the chicken or the egg? In science we often think the data is the dominant sine qua non. We see that ever so more today as we examine all of the researchers who “find” another gene “causing” cancer. The problem is that finding a new gene is just too easy and the Press is all too ignorant to ask what it really means.

There are two quotes worth noting, one from the work on DNA itself and the second from the folks who brought us Quantum Mechanics.

First, there is a quote from the book by Jusdon on DNA. In Judson there is a quote (p 93):

"It is also a good rule not to put too much confidence in the observational results that are put forward until they are confirmed by theory." Sir Arthur Eddington wrote in 1934: his paradoxical inversion of the inductive system as preached from Bacon to Russell has become an epigraph for the latter day recension of the scientific method as practices.

The second is a quote from a discussion on Quantum Mechanics by Gribbin. From Gribbin (pp 139-140) we have:

At one point Einstein had commented: "It is quite wrong to try founding a theory on observable magnitudes alone. It is the theory which decides what we can observe."

In both cases there is the imperative to ultimately put all data in the context of a world view, a model of reality that links inputs and outputs, and which can become both the language of the very concepts and the sounding board upon which measurements are made.

All too often we see researchers just dumping a ton of new genes and arguing that they are causative. On the other hand we have detailed pathway models demonstrating cause and effect. Yet the discoverers of the new gene seem never to place them in a context. They are at best correlative, and most likely nor causative.

References:

Judson, H., The Eighth Day of Creation, Touchstone (New York) 1979.

Gribbin, J., Erwin Schrodinger and the Quantum Revolution, Wiley (New York) 2013.

Labels: Commentary

CARROT OR STICK

The carrot or the stick is often the way we see motivating people to respond. The ACA appears to allow carrots but not sticks, except perhaps in some insurance pricing schemes when the carrot has failed. In a JAMA article the authors examine the ACA and the concept of incentives. They state:

But HIPAA did not render health factors completely irrelevant, and neither does the ACA. In fact, the ACA could be considered to strengthen the link between health status and insurance coverage terms in one respect. Under the HIPAA exception for "programs of health promotion and disease prevention," employers are permitted to tie premiums or co-payments to tobacco use, body mass index (BMI), or other health factors as long as certain requirements are met. The ACA continues and expands on this policy, supporting the use of outcome-based health incentives within both public and private insurance.

The HIPPA issue related to privacy. On the other hand ACA relates to "incentives", positive motivations to have the person do the right thing. The counter would be punishment for doing the wrong thing, say being taxed at ever increasing rates if your BMI exceeds 25.0.

However the do relate the ACA double edged sword approach where they state:

Programs' health-contingent incentives could not in aggregate exceed 20% of insurance coverage costs. For example, if the cost of coverage were $5000, which is close to the average cost of employer-sponsored individual coverage, a plan could give a reward equal to $1000 to nonsmokers or, alternatively, impose a $1000 surcharge on smokers. Programs were also required to offer a "reasonable alternative standard" or waiver for those for whom it was "unreasonably difficult due to a medical condition" to meet a program standard

They continue to discuss the two sides of motivation. They conclude:

If incentive programs are poorly designed, however, they may do little to change health outcomes. A reward based on achieving a BMI of 25 might lead to weight loss among individuals with BMIs of 26 or 27 but not among those with BMIs of 36 or 37.

Research on recurring errors in individual decision making suggests that premium adjustments may be less effective motivators than incentive programs that incorporate immediate and frequent feedback as well as highly visible and salient rewards and that harness behavioral motivators such as anticipated regret.

If incentives fail to change behavior, higher-risk individuals may be left in a worse financial position, undermining the ACA's efforts to weaken the link between health status and insurance costs and potentially threatening distributional equity.

This is a bit confusing. What is meant by a "worse financial position". Clearly if one has a BMI of 37 then one subjects oneself to very high risk for various diseases and that we then all must bear the ongoing burden of the costs of handling these. If however we actually considered the cost per incremental 0.1 in BMI and then applied it to each person then that would be an efficient cost recovery mechanism. After all we have the IRS into every other corner of our lives why not doing our annual physicals as well. Just imagine some morbidly obese GS9 with an attitude telling you to get up on a scale and then yelling out to her associate what you weigh and your BMI while hundreds of others wait in line. Not too far fetched from where we seem to be going.

Labels: Health Care

GENES AND PATENTS

The US Supreme Court has just ruled in the Myriad case. The Court holds:

A naturally occurring DNA segment is a product of nature andnot patent eligible merely because it has been isolated, but cDNA ispatent eligible because it is not naturally occurring.

(a) The Patent Act permits patents to be issued to "[w]hoever invents or discovers any new and useful . . . composition of matter," §101, but "laws of nature, natural phenomena, and abstract ideas"" 'are basic tools of scientific and technological work' " that lie beyond the domain of patent protection,The rule against patents on naturally occurring things has limits, however. Patent protection strikes a delicate balance between creating "incentives that lead to creation, invention, and discovery" and "impeding]the flow of information that might permit, indeed spur, invention." This standard is used to determine whether Myriad's patents claim a "new and useful . . . composition of matter," §101, or claim naturally occurring phenomena.

(b) Myriad's DNA claim falls within the law of nature exception.Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes. cDNA is not a "product of nature," so it is patent eligible under§101.

(c) cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. Its creation results in an exons-only molecule, which is not naturally occurring. Its order of the exons may be dictated by nature, but the lab technician unquestionably creates something new when introns are removed from a DNA sequence to make cDNA.

(d) This case, it is important to note, does not involve method claims, patents on new applications of knowledge about the BRCA1 and BRCA2 genes, or the patentability of DNA in which the order of the naturally occurring nucleotides has been altered.

This is a game changing decision and is worth the reading.
Labels: Law

WEDNESDAY, JUNE 12, 2013

PROSTATE CANCER TESTING

I noticed a piece which gives prices for various prostate cancer gene tests. The article in Spectrum Online states:

The newest test was developed by Genomic Health Inc., which has sold a similar one for breast cancer since 2004. Doctors at first were leery of it until studies in more groups of women proved its value, and the same may happen with the prostate test, said Dr. Len Lichtenfeld, the American Cancer Society's deputy chief medical officer.

The company will charge $3,820 for the prostate test and says it can save money by avoiding costlier, unnecessary treatment. Another test for assessing prostate cancer risk that came out last summer — Prolaris by Myriad Genetics Inc. — sells for $3,400.

We discussed the CCP test in a detailed White Paper and expressed our concerns, based not upon any deficiency but due to in our opinion a lack of reproducibility. We do not have any data on the second test. But if our understanding of the CCP test is correct it is used after a biopsy and tests 31 genes in the cancer ridden prostate. The test then provides some statistical measure of death in some period of time given some scalar metric based upon what appears to be an

undisclosed process of gene expression.

The the test allegedly tells a patient who has undergone a biopsy with some level of Gleason score that the have a good or bad chance of survival.

Thus the patient is charged for the biopsy, the path study, the test, and then gets to decide what? That is where I would have the problem.

The article continues:

About 240,000 men in the U.S. are diagnosed with prostate cancer each year, and about half are classified as low risk using current methods. Doctors now base risk estimates on factors such as a man's age and how aggressive cells look from biopsies that give 12 to 14 tissue samples. But tumors often are spread out and vary from one spot to the other.

The NY Times says:

The test looks at the activity level of 17 genes in the biopsy sample and computes a score from 0 to 100 showing the risk that cancer is aggressive.To see how well the test worked, testing was performed on archived biopsy samples from 412 patients who had what was considered low or intermediate-risk cancer but then underwent surgery.In many such cases, the tumor, which can be closely studied after it is surgically removed, turns out to be more aggressive than thought based on the biopsy, which looks at only a tiny sample of the tumor.

We have shown that if one uses 24 or more cores, depending on prostate volume, that one can reduce the risk of missing the diseased segments. We have moved from six cores, to 12, to 24, and some are as high as 36. With a highly competent urologist and 24 cores one should managed to have a high detection probability. Furthermore we know that if upon detection we have a Gleason of 7 or more than most likely we have a serious problem. Yes, many of Gleason 7 progress slowly, and yes it would be good to know which do not, yet the above tests in my opinion have a way to go. Just my opinion.

Yet one of my major concerns is the possibility that a prostate cancer stem cell may have migrated to a distant site, say the bone, and that the test would miss that event and provide a false sens of security. Furthermore, even in the biopsy samples the stem cell may have been missed and the cells detected may be considered indolent but the ore aggressive cells have remained in place.

Just grossly testing for the presence of certain genes is interesting but in my opinion far from conclusive.One need just look at the paper by Navin and Hicks and examine the various problems with the approaches mentioned above. As Navin and Hicks state:

Defining the pathways through which tumors progress is critical to our understanding and treatment of cancer. We do not routinely sample patients at multiple time points during the progression of their disease, and thus our research is limited to inferring progression a posteriori from the examination of a single tumor sample. Despite this limitation, inferring progression is possible because the tumor genome contains a natural history of the mutations

that occur during the formation of the tumor mass.

There are two approaches to reconstructing a lineage of progression: (1) inter-tumor comparisons, and (2) intra-tumor comparisons. The inter-tumor approach consists of taking single samples from large collections of tumors and comparing the complexity of the genomes to identify early and late mutations. The intra-tumor approach involves taking multiple samples from individual heterogeneous tumors to compare divergent clones and reconstruct a phylogenetic lineage. Here we discuss how these approaches can be used to interpret the current models for tumor progression.

We also compare data from primary and metastatic copy number profiles to shed light on the final steps of breast cancer progression. Finally, we discuss how recent technical advances in single cell genomics will herald a new era in understanding the fundamental basis of tumor heterogeneity and progression.

Thus the multiplicity of ways tumors progress means that taking samples at one time and place most likely will not reflect upon the true status of the systemic disease.
Labels: Cancer, Health Care

TUESDAY, JUNE 11, 2013

DATA, DATA, DATA

This flap about the monitoring of personal data reminds me of the general problem of data. Back some decades ago I did some work tracking Soviet nuclear subs, a summer job type thing. My task was to try various schemes on the massive data files to discriminate between whales and subs. Specifically my job was to determine the sensitivity of a single parameter on discrimination on a stored data base of alleged whales and submarines. It was not clear whether this was ever used or even if it was important.

Now I worked this data to death. There were tons of data. It was the worst job I ever did in my life. Working for the New York Sanitation Department in January 1960 shoveling snow was better. At least there was an achievement, no snow at the cross walks. I ran every possible variation, with little understanding of what needle in this haystack I was looking for.

But then what I did was to step back and re-frame the question and ask whether it was ever possible to do what the process I was thinking about would achieve what I set out to do. I did a detailed analysis of the situation and when complete, the data notwithstanding, it was clear you could not do what I was set out to do, at least the way I was set out to do it. Then again this may have been a real challenge or it may have just been one of those management games that large companies played, and after all it was just for the summer. What it did teach me was that one just does not wander aimlessly around data, one needs a theory, a model, a physical realization and embodiment. Once I created the model and did the analysis the data could become meaningful or meaningless. Sometimes data helps, often it can confuse. In fact one may have captured the wrong data.

Now what does this have to do with this current issue? Before answering that let me give two

other examples. First is Excel. I would argue that the market collapse of the dot com bubble was as much the fault of Excel as it was the hype, indeed the hype was Excel. For by then any moron could gin up data by the truckload, put it in an Excel spread sheet and come up with a trillion dollar business worth billions. And since it was based upon data and done with Excel it must be true. Nonsense!

The next example is the microarray and cancer genes. We have enabled the folks to run arrays on hundreds of genes and from that using again their Excel spread sheets we have almost daily announcements of new genes causing some form of cancer. Namely some loose correlation is causation.

Now to massive data. One needs discriminant functions, namely one must have some idea as to what to look for. Frankly given no initial data one can find anything and anything can be big, real big. Data supports theories, it is not the theory. Data can often be wrong; wrong by interpretation or by collection.

Now how does good Intel really work? The same old way it always has, feet on the ground, snippets at a bar in Athens, a coffee shop in Tangiers, a small bistro in Marseille. It is listening and gathering and having a team of dedicated smart loyal people, not Government employees.It used to work that way for a while. Today it has become all politics.

Besides the current problem is what has been going on for a long time now, sloppy control of data. Solve that problem and you solve everything. We did that once, it worked somewhat better than this mess. Perhaps we just kill the computers and reintroduce the typewriter.
Labels: Government

SUNDAY, JUNE 9, 2013

TYPING, A SKILL OR WHAT?

In her classic style Frances Woolley has written a somewhat interesting piece regarding the fine art of typing. She poses the issue as follows:

Learning how to touch-type is a classic example of a human capital investment. It requires hours of practice, but there is a big productivity pay-off. When typing becomes a purely automatic process, when there is no need to ever even glance at the keyboard or think about which key to use, the writer is free to concentrate on writing - something called cognitive automaticity.
A person who can type quickly can get things done rapidly and efficiently. I can answer emails, write memos or accomplish other routine tasks faster than most economists, because I can type quickly. Moreover, learning good posture at the keyboard has health benefits, because it reduces the risk of repetitive strain injury. So why isn't typing taught in school? Why doesn't every student graduate from high school knowing the the best way to use a keyboard? Why do schools no longer offer the kind of intensive training in typing that is needed to become a highly proficient typist, working consistently at 80 word per minute or more? I don't know, but I have theories.

Now I never learned to type. I use two fingers and somehow still manage to get out well over

500,000 words per year. In fact my hand writing is so poor that I could finally practice Medicine. But to comment on Frances; to what Frances was getting at, let me add an additional dimension.

Back in the 60s when I was doing my theses and drafts of my first books, I wrote everything in longhand on yellow pads and in pencil. I still have the first draft of the first book. The sweat stains from un-air-conditioned offices are still on the paper. When I wrote then I wrote with the typist in mind, for the typist was a true barrier to thought. I could not type, yes a little, but not as I do today. So I wrote in a rigid and final form. I had to be certain that what I wrote was the way it would be in final form because I dreaded the typists, they really hated doing draft after draft. It was the end of the 60s and liberation of all types was exploding, except for those of use who hated typewriters.

With computers and word processors I can now type everything, and retype, cut and paste, insert images, graphs, and best of all equations, I really love equations, I have not had a secretary since 1990. My folks tried to get me one once but for various reasons the secretary lasted three days and I was not even on this continent.

But I really think differently when I type, I have no fear of a typist, I can make changes, I can edit, add, cut and paste and integrate with images. In fact I now actually must type to think! That is a change. I cannot even create unless I put it to "paper", in a computer sense.

Frances continues:

When it comes right down to it, typing is manual labour. There is a fast way of doing it - the classic "home row" method. Self-taught typists can achieve good speeds - 50, 60 wpm - but not the ultra-fast speeds of a typist using the classic method . Creative and original approaches are generally sub-optimal. Yet telling students "your method is wrong" goes against the grain for teachers who want to encourage students to discover, explore, and work things out on their own.

Not really. To refer to Heidegger typing is at hand, it is the taking of the idea and explaining it in a linear manner. Back in 1990 I wrote a paper on Multimedia Communications where I said:

In the development of a theory for design of computer systems involving the human user, Winograd and Flores invoke the theories of the German Philosopher, Heidegger. Specifically they refer to four key propositions of the philosopher that impact the overall end user interface issue in the multimedia environment. These are:

1. Our implicit beliefs and Assumptions cannot be made explicit. We all too often may make the statement, "You know what I mean." In so doing we are creating to mistakes. First, the other may never know what we mean just by the nature in which we individually perceive experiences and objects. Second, we may, ourselves, not have the insight to our own true beliefs, because we all too often find ourselves questioning them. Hermeneutics, the study of meaning in documents, has been expanded by Gadamer to investigate human reasoning. Thus, indicates Gadamer, our understandings can change with the time and place. This changing makes the explicit articulation specious at best.

2. Practical understanding is more fundamental than detached theoretical understanding. Heidegger has a concept called "throwness", 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. We cannot expect the user to detail their beliefs and in fact those understandings are time varying.

3. We do not relate to things primarily through having representations of them.We relate to things themselves. We do not relate to a representation. The representation to the "thing itself" is done in the context of the task to be accomplished. For example, teleconferencing is useful is we are not to relate to the person but to a subject whose essences can be presented directly through the medium, rather than just a representation. We find that teleconferencing is inadequate for personal contact since the contact is through a representation.

4. Meaning is fundamentally social and cannot be reduced to the meaning giving activities of individual subjects.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. Specifically, social or conversational activity is the ultimate foundation of intelligibility. This means that both in the design process as well as in the operations process, the need is critical to have the communications channel be conversational if the intent is to convey intelligibility. If the intent is only to transfer predefined package from one point to the other them the conversationality is not essential. In a multimedia environment, intelligibility in the context of the various media and thus intelligibility demands conversationality.

Thus when we type, we become one with what we are typing, whether we have typing lessons or not. Typing is not manual labor, no more than writing notes, moving the paint brush, or slinging the hammer on marble. It is Hedeggerian thrownness wherein we become one with the work,
Labels: Commentary

SUNDAY, JUNE 9, 2013

DOWN THE RABBIT HOLE

This case regarding the release of secret info gets more Alice like by the hour. Now we have some 29 year old high school drop out in Hawaii having access to TS/SID/NF data from his local

terminal! And we are worried about the Chinese! Why not just post it on Facebook directly by the Intel Agencies.

But! Wait, is this too unbelievable, if so, perhaps it is not believable. Perhaps it is not what it appears to be. Why "escape" to Hong Kong. He apparently left his job because of seizures. So we have people with access to such secrets who also have seizures, the ADA at work!

What is this guy, who does he work for, why did he go to Hong Kong, and the list of questions go on. This is starting to sound like a plot from so poorly done Hollywood movie. The truth, if there be any, is no where near the surface.

As the Guardian states:

He has had "a very comfortable life" that included a salary of roughly $200,000, a girlfriend with whom he shared a home in Hawaii, a stable career, and a family he loves. "I'm willing to sacrifice all of that because I can't in good conscience allow the US government to destroy privacy, internet freedom and basic liberties for people around the world with this massive surveillance machine they're secretly building."

Well, he is paid well above a GS 15. Strange when we pay High School drop outs such a salary when we send back to China our PhDs.

The tale here is much more complex than what we are told, I would believe. This is too simple, too neat, too direct. Let us see what happens in the next twenty for hours.

THE RIGHT TO BE LEFT ALONE

Some one hundred and twenty three years ago Warren and Brandeis published a paper entitled, The Right to Privacy. It opens as follows:

That the individual shall have full protection in person and in property is a principle as old as the common law; but it has been found necessary from time to time to define anew the exact nature and extent of such protection. Political, social, and economic changes entail the recognition of new rights, and the common law, in its eternal youth, grows to meet the demands of society. Thus, in very early times, the law gave a remedy only for physical interference with life and property, for trespasses vi et armis.

Then the "right to life" served only to protect the subject from battery in its various forms; liberty meant freedom from actual restraint; and the right to property secured to the individual his lands and his cattle. Later, there came a recognition of man's spiritual nature, of his feelings and his intellect. Gradually the scope of these legal rights broadened; and now the right to life has come to mean the right to enjoy life--the right to be let alone, the right to liberty secures the exercise of extensive civil privileges; and the term "property" has grown to comprise every form of possession-- intangible, as well as tangible.

Thus in the beginning mankind felt they had a right to not have physical harm inflicted upon them. In today's world we kind of take that to be the case except perhaps with the exception of the TSA and their deadly X ray machines, but I lay that aside in this piece. They continue:

Thus, with the recognition of the legal value of sensations, the protection against actual bodily injury was extended to prohibit mere attempts to do such injury; that is, the putting another in fear of such injury. From the action of battery grew that of assault Much later there came a qualified protection of the individual against offensive noises and odors, against dust and smoke, and excessive vibration. The law of nuisance was developed. So regard for human emotions soon extended the scope of personal immunity beyond the body of the individual.

His reputation, the standing among his fellow men, was considered and the law of slander and libel arose Man's family relations became a part of the legal conception of his life, and the alienation of a wife's affections was held remediable. Occasionally the law halted--as in its refusal to recognize the intrusion by seduction upon the honor of the family. But even here the demands of society were met. A mean fiction, the action per quod servitium amisit, was resorted to, and by allowing damages for injury to the parents' feelings, an adequate remedy was ordinarily afforded.

Similar to the expansion of the right to life was the growth of the legal conception of property. From corporeal property arose the incorporeal rights issuing out of it; and then there opened the wide realm of intangible property, in the products and processes of the mind, as works of literature and art, good-will, trade secrets, and trade secrets.

Thus we see a natural progression protecting the person, a natural progression of civil law which Brandeis believe was building on the Constitution, not conflicting with it. Now or on of the most powerful parts of the paper:

Recent inventions and business methods call attention to the next step which must be taken for the protection of the person, and for securing to the individual what Judge Cooley calls ***the right "to be let alone."***

Instantaneous photographs and newspaper enterprise have invaded the sacred precincts of private and domestic life; and numerous mechanical devices threaten to make good the prediction that "what is whispered in the closet shall be proclaimed from the house-tops." For years there has been a feeling that the law must afford some remedy for the unauthorized circulation of portraits of private persons; and the evil of the invasion of privacy by the newspapers, long keenly felt, has been but recently discussed by an able writer.

The alleged facts of a somewhat notorious case brought before an inferior tribunal in New York a few months ago, directly involved the consideration of the right of circulating portraits; and the question whether our law will recognize and protect the right to privacy in this and in other respects must soon come before our courts for consideration.

The right to be let alone is a fundamental right, but the current administration in the act of "protecting" us has taken away that right. From mandatory health care, to mandated tracking of

all communications, to full body searches at any and all spots, to tracking of reading materials, to gathering information from employers and banks. Our right to be let alone has been dismembered beyond all repair. What would Brandeis think?
Labels: Commentary, Government

FRIDAY, JUNE 7, 2013

"CURIOUSER AND CURIOUSER" CRIED ALICE.

The Guardian now reports on more high level intel. One is interesting but a flow of such releases by the same person at the same time the current president meets with the head of China is, as Alice said, "Curiouser and curiouser".

The Guardian states:

It says the government will "identify potential targets of national importance where OCEO can offer a favorable balance of effectiveness and risk as compared with other instruments of national power".

It appears that these were planted and timed for maximum benefit. This is not subtle intel practices that I saw in the 60s and 70s, this is hatchet like. It appears that perhaps internal security has been breached, and badly so. Then one must wonder who is the adversary. This is a game, the Guardian seems to just be an intermediary, facilitating one side against the other.

From whence did these docs originate, if the classification was correct then they should be traceable, the holders of them limited. Yet of they were obtained via electronic means we have a fundamental problem. Namely such documents and facts should never leave the world of paper, never appear on a computer. Bring back typewriters, and place them in a safe. When you place them even on a word processor you invite a compromise.

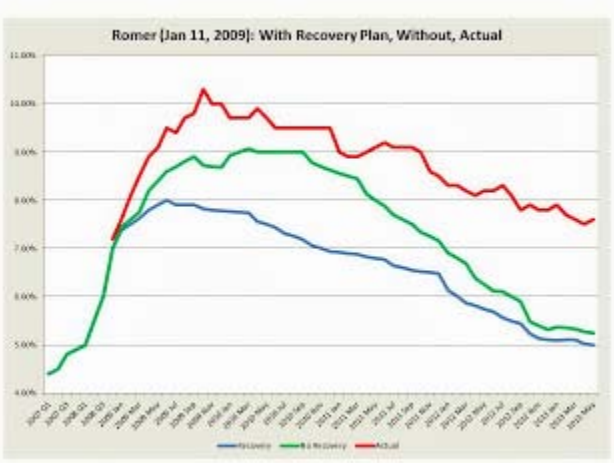
One should recall the classic release of highly classified data during the Falcon and the Snowman tale, when a tech in the vault of TRW in San Jose released highly classified data to the Soviets via a childhood friend who interfaced via the Mexico City Embassy of the USSR. The people were able to copy the documents, take them from TRW and then deliver them to the Soviets.

Then there was the Hansen episode, in the park behind the house I lived in in Virginia. The neighborhood was filled with intel types but the park apparently become a meeting location for all sorts. All of this a few blocks from Langley.

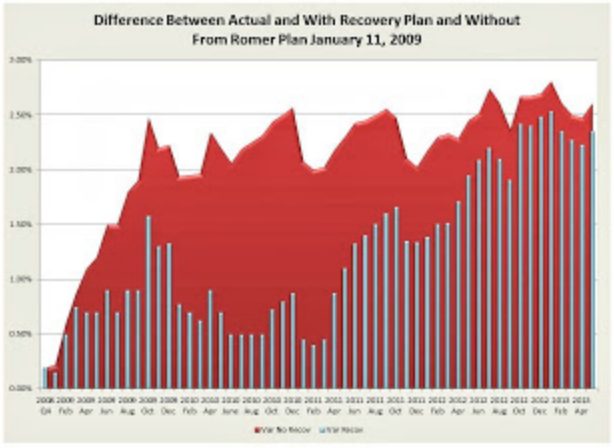
One just need understand that even with classic controls, things leak, in most cases because of sloppy oversight.
Labels: Government

EMPLOYMENT JUNE 2013

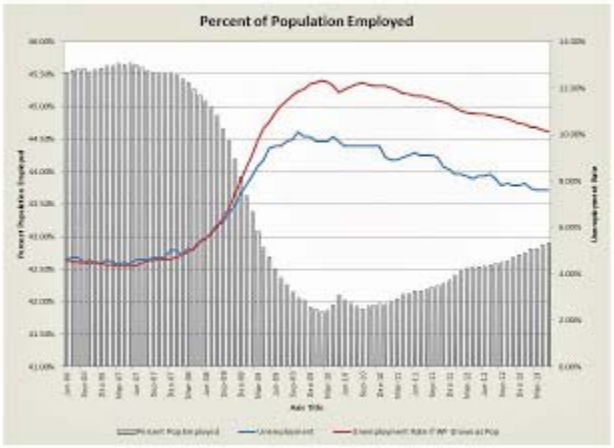
The current employment data brings little good news. Let us examine it as we always do by looking at the Romer Curve, that now infamous prediction of how well the current administration was to do based upon the wisdom of the economists.



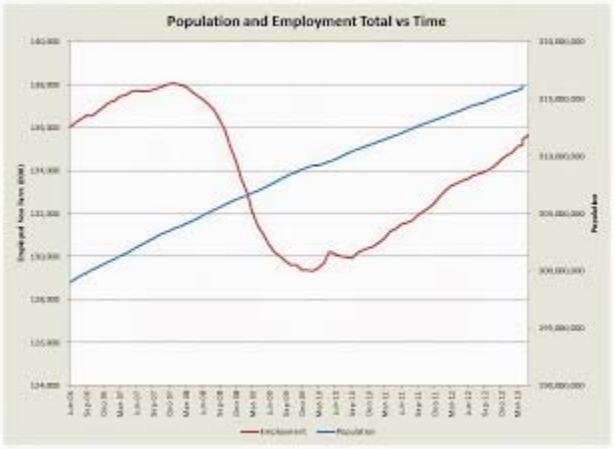
Now according to Romer we would well into a full recovery. Yet the real world has at best stalled.



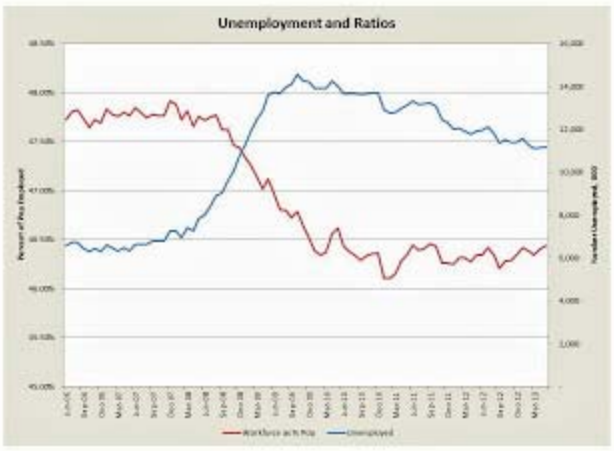
The above is her error curves demonstrating the digging of an ever deeper hole.



Here we can see some light. There is a continuing growth in those participating in the work force. True unemployment is now about 10.25% down from the 12+% at the peak but not really where we need it to be.



The above shows the narrowing of the gap between population and Employment. In a sense we are making some slow progress.



However when we look at the percent of workforce employed we still see that deadly and system drop. That is the problem to be addressed.
Labels: Economy

CCP AND PROSTATE CANCER

There is always an interest in determining the prognostic value of tumors and hopefully staging treatment. There has been a recent flurry of interest in using "cell cycle progression" CCP, gene testing, a method of taking gene products from biopsy samples and then using them to ascertain the most likely progression of the tumor.

We summarize here our opinions as stated in a recent White Paper.

CCP is a methodology proposed to do this. We take no position in this opinion paper regarding the efficacy of CCP as applied to PCa but we examine the original assertions in some detail. Conceptually it makes sense. It is as follows:

1. A handful of genes if over expressed, when combined with other metrics, can provide fairly accurate prognostic measures of PCa.

2. Selecting the genes can be accomplished in a variety of ways ranging from logical and clear pathway control genes such as PTEN to just a broad base sampling wherein the results have a statistically powerful predictive result.

3. Measuring the level of expression in some manner and from the measurements combine those in a reasonable fashion to determine a broad based metric.

4. Combining the gene expression metric with other variable to ascertain a stronger overall metric.

The CCP work to date has been focused somewhat on these objectives.

Let us now briefly update the work as detailed in the industry press. As indicated in a recent posting:[45[1]]

.....initially measured the levels of expression of a total of 31 genes involved in CCP. They used these data to develop a predefined CCP "score" and then they set out to evaluate the value of the CCP score in predicting risk for progressive disease in the men who had undergone an RP or risk of prostate cancer-specific mortality in the men who had been diagnosed by a TURP and managed by watchful waiting.

Thus there seems to be a strong belief in the use of CCP, especially when combined with other measures such as PSA.

The CCP test has been commercialized as Prolaris by Myriad. In a Medscape posting they state[46[2]]:

"PSA retained a fair amount of its predictive value, but the predictive value of the Gleason score "diminished" against the CCP score." he said. "Once you add the CCP score, there is little addition from the Gleason score, although there is some."

"Overall, the CCP score was a highly significant predictor of outcome in all of the studies,...it was the dominant predictor in all but 1 of the studies in the multivariate analyses, and typically a unit change in the score was associated with a remarkably similar 2- to 3-fold increase in either death from prostate cancer or biochemical recurrence, indicating that this is a very robust predictor, and seems to work in a whole range of circumstances."

Thus there is some belief that CCP when combined with other metrics has strong prognostic value.

In this analysis we use CCP as both an end and a means to an end. CCP is one of many possible metrics to ascertain prognostic values. There is a wealth of them. We thus start with the selection of genes. We first consider general issues and then apply them to the CCP approach. This is the area where we have the majority of our problems.
Let us first examine how they obtained the data. We shall follow the text of the 2011 paper and then comment accordingly.

1. Extract RNA

2. Treat the RNA with enzyme to generate cDNA

3. Collect the cDNA and confirm the generation of key entities.

[45[1]] http://prostatecancerinfolink.net/2011/02/09/is-ccp-testing-really-the-prognostic-tool-we-need/

[46[2]] http://www.medscape.com/viewarticle/805351

4. Amplify the cDNA

5. Pre amplify the cDNA prior to measuring in an array.

7. In arrays record levels of expression

Clearly there may be many sources of noise or error in this approach, especially in recording the level of fluorescent intensity. The problem is however that at each step we have the possibility of measurement bias or error. These become additive and can substantially alter the data results.

In this section we consider the calculations needed to develop a reliable classifier. This is a long standing and classic problem. Simply stated:

"Assume you have N gene expression levels, G(i), and you desire to find some function g(G(1),…,G(N)) such that this function g divides the space created by the Gs into two regions, one with no disease progression and one with disease progression."

Alternatively we could ask for a function f(G(1),…,G(N)) such that the probability of disease progression, or an end point of death in a defined period, is f or some function derived therefrom.

Let us begin with general classifiers. First let us review the process of collecting data. The general steps are above. We start with a specimen and we end up with N measurements of gene expression. In the CCP case we have some 31 genes we are examining and ascertaining their relative excess expression. Now as we had posed the problem above we are seeking a classifier to determine a function f or g as above which would either bifurcate the space of N genes or a function f from which we could ascertain survival based upon the N gene expression measurements.

Now from classic classifier analysis we can develop the two metrics; a simple bifurcating classifier and a probability estimator. The simple classifier generates a separation point, a line or plane as shown below, for which being below is benign and being above is problematic. This is akin to the simple PSA test of being above or below 4.0. However we all know that this has its problems. Thus there may be some validity in the approach for prognostic purposes. Clearly a high value indicates a significant chance for mortality, one assumes directly related to this disease.

Let us now examine the CCP index calculation in some detail. We use the 2011 paper as the source. The subsequent papers refer back to this and thus we rely upon what little is presented here. The approach we take herein is to use what the original paper stated and then line by line establish a mathematical model and where concerns or ambiguities we point them out for subsequent resolution. In our opinion the presentation of the quantitative model is seriously flawed in terms of its explanation and we shall show the basis of our opinion below.

We have provided a detailed examination in our recent White Paper. In our opinion there is a lack of transparency and reproducibility in the 2011 paper and thus one cannot utilize what is presented.

This area of investigation is of interest but it in my opinion raises more questions than posing answers. First is the issue of the calculation itself and its reproducibility. Second is the issue of the substantial noise inherent in the capture of the data.

1. Pathway Implications: Is this just another list of Genes?

The first concern is the fact that we know a great deal about ligands, receptors, pathway elements, and transcription factors. Why, one wonders, do we seem to totally neglect that source of information.

2. Noise Factors: The number of genes and the uncertainties in measurements raise serious concerns as to stability of outcomes.

Noise can be a severe detractor from the usefulness of the measurement. There are many sources of such noise especially in measuring the fluorescent intensity. One wonders how they factor into the analysis. Many others sources are also present from the PCR process and copy numbers to the very sampling and tissue integrity factors.

3. Severity of Prognosis and Basis: For a measurement which is predicting patient death one would expect total transparency.

The CCP discriminant argues for the most severe prognostication. Namely it dictates death based upon specific discriminant values. However as we have just noted, measurement noise can and most likely will provide significant uncertainty in the “true” value of the metric.
4. Flaws in the Calculation Process: Independent of the lack of apparent transparency, there appear in my opinion to be multiple points of confusion in the exposition of the methodology.

In our opinion, there are multiple deficiencies in the presentation of the desired calculation of the metric proposed which make it impossible to reproduce it. We detail them in our White Paper.

5. Discriminants, Classifiers, Probability Estimators: What are they really trying to do?

The classic question when one has N independent genes and when one can measure relative expression is how does one take that data and determine a discriminant function. All too often the intent is to determine a linear one dimensional discriminant. At the other extreme is a multidimensional non-linear discriminant. This is always the critical issue that has been a part of classifiers since the early 1950s. In the case considered herein there is little if any description of or justification of the method employed. One could assume that the authors are trying to obtain an estimate of the following:

P[Death in M months]=g(G1,...GN))

where Gk is the level of expression of one of the 31 genes. One would immediately ask; why and how? In fact we would be asked to estimate a Bayesian measure:

P[Death in M months|G1,...GN]

which states that we want the conditional probability. We know how to do this for systems but this appears at best to be some observational measure. This in my opinion is one of the weak points.

6. Causal Genes, where are they?

One of the major concerns is that one genes expression is caused by another gene. In this case of 31 genes there may be some causality and thus this may often skew results.

7. Which Cell?

One of the classic problems is measuring the right cell. Do we want the stem cell, if so how are they found. Do we want metastatic cells, then from where do we get them. Do we want just local biopsy cells, if so perhaps they under-express the facts.

8. Why this when we have so many others?

We have PSA, albeit with issues, we have SNPs, we have ligands, receptors, pathway elements, transcription factors, miRNAs and the list goes on. What is truly causal?

Basically this approach has possible merit. The problem, in my opinion, is the lack of transparency in the description of the test metric. Also the inherent noisy data is a concern in my opinion. Moreover one wonders why so much Press.

1. Cooperberg, M., et al, Validation of a Cell-Cycle Progression Gene Panel to Improve! Risk Stratification in a Contemporary Prostatectomy Cohort! https://s3.amazonaws.com/myriad-library/Prolaris/UCSF+ASCO+GU.pdf
2. Cooperberg, M., et al, Validation of a Cell-Cycle Progression Gene Panel to Improve Risk Stratification in a Contemporary Prostatectomy Cohort, JOURNAL OF CLINICAL ONCOLOGY, 2012.
3. Cuzick J., et al, Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort, British Journal of Cancer (2012) 106, 1095 – 1099.
4. Cuzick, J., et al, Prognostic value of an RNA expression signature derived from cell cycle proliferation genes for recurrence and death from prostate cancer: A retrospective study in two cohorts, Lancet Oncol. 2011 March; 12(3): 245–255.
5. Duda, R., et al, Pattern Classification, Wiley (New York) 2001.
6. McGarty, T., Prostate Cancer Genomics, Draft 2, 2013, http://www.telmarc.com/Documents/Books/Prostate%20Cancer%20Systems%20Approach%2003.pdf

7. Theodoridis, S., K., Koutroumbas, Pattern Recognition, AP (New York) 2009.

Labels: Cancer

THURSDAY, JUNE 6, 2013

TELEPHONE CALL TRACKING

The Guardian had published the Court Order demanding handing over of call records. On the one hand this is chilling and on the other hand it seems a bit dumb. Back in the 90s when I started one of the first IP networks globally I had discussions regarding the use of IP by those whose intentions were not necessarily pure. This was well before 9/11. IP is an ideal structure to hide in plain sight. Just send your packets one at a time over different paths and have them encrypted as well. This is a version of network coding.

Now what real "bad guy" will make a dial up call on the old MCI long distance or business network? Most likely not even an evil investment banker, although many have but then the Federal Attorney gets a wire tap. There most likely are hundreds of wire taps in New York City alone every day.

Thus on the one hand this is a bit of an over-reach but on the other hand it is collecting data on stupid terrorists and the like. Even back in the 40s there were ways to have a secure call. In the 70s there were also ways. So why collect this data, the real bad guys are off the radar. So really, again, why collect this data, national security? Remember real bad guys all too often hide!

Perhaps the old adage is true, nothing is what it necessarily looks like. Perhaps this is just a diversion for something else. If so what else?

But seriously, any "spy" worth their salt would assume that public networks are compromised. Thus using secure networks is the way to go, and one can secure the IP networks if one is smart enough. Like any such approach, never use the same transmit multiple times. Trust no one etc. Why look at the public nets this way, unless you just have a lot of dumb "spys".

But back to "nothing necessarily appears to be what it really is". Follow the motivation. Fact, current president is meeting with the head of China. China is being accused of snooping on the US. So what is a great diversion? Get the US to see that its Government is snooping on them, put the current president on the offensive. So where did the Guardian reporter report from, Hong Kong. Who gave him the document, if the Chinese can access the US Government secure servers then they easily could have gotten a copy of the warrant and then given it through some chain to the Guardian reporter. Follow the motivation. Just another thought.

Just wondering. This is a clear case where keen insight into the obvious is not helping.
Labels: Government, Telecom

THURSDAY, JUNE 6, 2013

THE EHR: A GOOD IDEA GONE BAD

The EHR was a good idea. Many physicians really need this once it works properly. In addition it was intended for sharing data between physicians for the purpose of lowering costs and increasing quality.

But, and this is a critical but, in my recent walks about the halls of local docs, I see the following. First, many have hired an additional staff person to type in the record. Why? Two reasons, first, they cannot figure it out, and second, the patients revolted when the doc spent all the time typing and clicking on the computer. I indicated as such early on. I had been working this issue for three decades, and still do not have a good idea what to do. Then there was that pediatrician from Boston who sat in DC and mandated an even poorer solution, in my opinion.

There is an interesting piece in Oncology Practice discussing this in an update. It states:

About 40% of physicians in the United States have adopted a basic electronic health record system, but few are able to use those systems to exchange clinical information with other offices or generate quality metrics, according to a survey of more than 1,800 physicians.

The Harris Interactive survey found that 45% of primary care physicians and 41% of specialists met the criteria for having a "basic" EHR system, defined as a system that allows physicians to maintain problem and medication lists, view laboratory and radiology results, record clinical notes, and order prescriptions electronically.

A much smaller portion of physicians – 10% of those surveyed – met the study's criteria for achieving "meaningful use" of their electronic systems. More primary care physicians (11%) were able to perform all 11 meaningful use elements identified by researchers, compared to 8% of specialists who were surveyed.

The greatest problem is transferring data in a meaningful manner. Consider the case of a colonoscopy. At one center, an academic center, the system is almost totally computerized. The report is detailed and complete with key photos of melanosis and polyps if present. All actions

taken by the physician are noted including any and all drugs and physical findings. This then gets linked to the path report. Not at a suburban clinic at best one has as a record is that the exam was performed and it was unremarkable. To add to the problem the report must be mailed to the attending! One does not even know what anesthetic was used! Were there diverticula or hemorrhoids.

Billions were spent by the current administration, or wasted if facts be known, and care decreased, costs increased, and data is jut useless.

Labels: Economics, Electronic Medical Records, Health Care

WEDNESDAY, JUNE 5, 2013

MISUNDERSTANDING SPECTRUM

The NY Times has an article discussing the upcoming spectrum auctions of the broadcast bands. It states:

Now, Washington is back in the business of putting vast chunks of wireless spectrum on the market. It has learned an important lesson: since 1993, the F.C.C. has leased spectrum to the highest bidder using Dutch auctions. From 2001 to 2010, it reaped a hefty $33 billion on behalf of taxpayers.But there is another lesson that the political system has not learned as well: how to foster competition. Cheap, competitive wireless broadband will be absolutely crucial for advancing the frontier of the digital economy. Yet as the government prepares to sell perhaps the last big chunk of valuable low-frequency spectrum that will be made available for wireless communications and mobile computing, pressure from Congress to raise as much money as possible threatens to get in the way of this objective....A critical concern is that AT&T and Verizon Wireless have deep enough pockets and a clear interest in keeping competitors out at any price. The two companies control roughly two-thirds of the cellular communications market and hold the licenses to 80 percent of the far-reaching, low-frequency spectrum most valued by mobile providers.

Now with the 5G developments and the ability to go as high as 100 bps/Hz in bandwidth utilization the incumbents have tons of capacity yet their game is and always was, and always will be to keep any potential competitor out. That is the conflict an FCC has. The conflict is that the price any new entrant would pay is always less than what the incumbent is willing to offer.

New incumbents will innovate whereas the old guys will just do more of the same, not that it is that bad but it is quite expensive. The incumbents are at best a duopoly and at worst a de facto monopoly, same genes, just different bodies.

The FCC is faced with a problem, actually many problems. First they are generally dumb, technically speaking. The FCC management just does not understand the potential of wireless, and in fact as I have examined in the recent books by Administration hangers on, neither does anyone in DC. Bandwidth is NOT the issue, capacity is, and capacity has exploded. Prices are

kept high by limiting the players. Thus to the incumbents the cost of keeping out a competitor or even fronting a shill is the cost of doing business.

The 1996 Telecom Act had some potential but it was destroyed by the then Administration and most importantly by the FCC, the FCC under that Administration and the one following.

This ultimately leads to the question; what good is the FCC? Technology runs circles around it and the folks running through it all too often just use it as a stepping stone to feed at a higher level of the trough.
Labels: FCC, Telecom

TUESDAY, JUNE 4, 2013

PROGRESS ON CANCER THERAPEUTICS

The NY Times has an article on Cancer Therapeutics, following the annual ASCO Conference in Chicago. Regrettably the focus is on immune system therapeutics almost exclusively. In fact there is a quote:

The new drugs work by disabling a brake on the immune system called the programmed death 1 receptor, or PD-1. And although the data presented at the meeting was from the earliest stage of testing only, the drugs were the center of attention here, with some doctors predicting that cancer treatment was about to shift. "If you look five years out, most of this meeting will be about immunotherapy," said Dr. Mario Sznol, a professor of medical oncology at Yale.

This is akin to Rosenberg some twenty five years ago, a dream that the immune system alone will be the means to the end. Somehow this article fails to account for the pathway blockers such as those blocking BRAF and MEK.

The article continues:

Harnessing the immune system is appealing for several reasons. It might be applicable to many different types of cancer. It might produce longer lasting remissions than can be achieved by chemotherapy or the newer targeted drugs. And it seems somehow more natural and holistic.

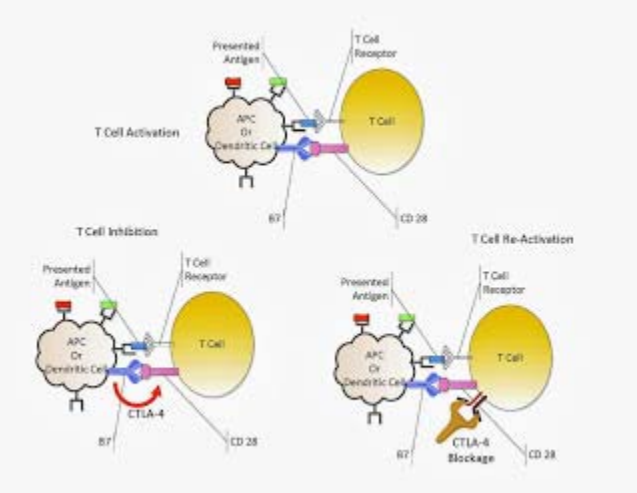
This is a classic statement of those seeking the Holy Grail. In reality one suspects that we will be identifying and targeting mutation after mutation and not just allowing the immune system to respond. After all the PD-1 inhibitor just enable another path to work on T cell attack. This is the second of many possible but T cells are most likely not the sine qua non.

I am still intrigued by TVEC and the viral attack. Perhaps what we will see is a typical combine approach. However there are many approaches and the Press all too often send out hope to patients well ahead of reality. The PD-1 Trials were Phase 1 Trials after all!

We have summarized the results in a recent White Paper for reference.
Labels: Cancer

MONDAY, JUNE 3, 2013

MORE PROGRESS ON MELANOMA THERAPEUTICS



There seems to be an increasing competition between pathway inhibitors and immune system enhancers in the treatment of melanoma. Two papers, one by Wolchok et al and the other by Hamid et al have shown significant progress in the immune portion.

CTLA-4 and PD-1 can be inhibited and such inhibition allows T cells to function by attacking the malignant cells. In effect we have re-activated the immune system to go after the cancer cells.

As NEJM states:

Wolchok et al. and Hamid et al. report in the Journal the results of phase 1 clinical trials showing that the combination of PD-1 and CTLA-4 antibody blockers leads to improved treatment outcomes in patients with melanoma, without an escalation of toxic effects.

The results of these trials are striking and complementary. In the trial by Hamid et al., a PD-1 monoclonal antibody was administered in patients who had had a relapse after CTLA-4 antibody monotherapy (ipilimumab); the authors found that durable and clinically significant responses were as common and robust as were those observed in patients who had not received ipilimumab therapy previously. Thus, progression of melanoma after anti-CTLA-4 therapy does not preclude a response to anti-PD-1 therapy.

Wolchok et al., who in part report similar data for sequential CTLA-4 and PD-1 antibody therapy, also tested concomitant administration and found that at the maximum tolerated dose, 53% of patients with advanced, treatment-resistant melanoma had objective tumor responses, with tumor regression of at least 80% in every patient who had a response.

Surprisingly and importantly, the use of ipilimumab and either one of two PD-1 monoclonal antibodies — whether the PD-1 and CTLA-4 antibodies were given sequentially or together — resulted in a rate and severity of adverse events that were no higher than those observed with the individual drugs alone.

It is expected that from these trials we can eventually see a combination therapy and then a selected genetic individual therapy.

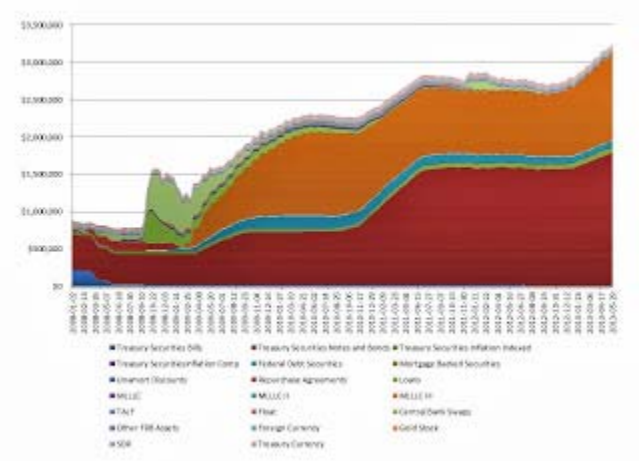
Finally as NEJM so properly puts it:

The clinical successes of CTLA-4 and PD-1 antibody immunotherapy in cancer are the outcomes of the correct recognition of the therapeutic potential of the molecules at the time of discovery, preclinical studies that showed high therapeutic potential, and well-designed and well-executed clinical trials. This partnership of basic science, translational science, and clinical medicine should be celebrated.

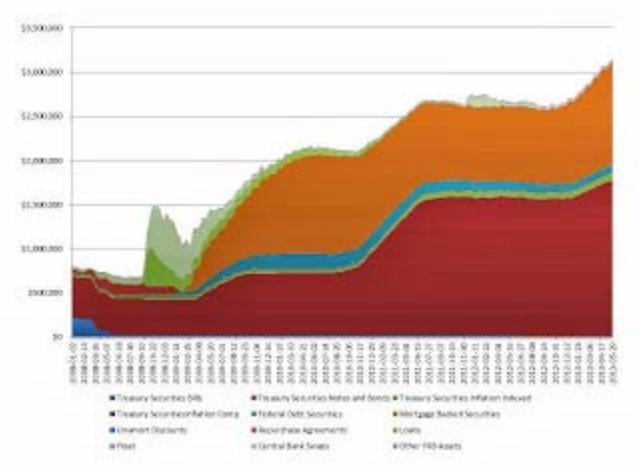
These two papers focus on the immune system approach. We have seen that if we can combine this approach with the pathway blocking approach that perhaps there may be some added efficacy, yet the results are not yet in.
Labels: Cancer

SUNDAY, JUNE 2, 2013

FED BALANCE SHEET JUNE 2013



The FED's Balance Sheet is exploding again. The total form is shown above, with week average numbers.



By eliminating some minor items the chart above clearly shows the explosion in Treasury holdings as well as Mortgage Backed Securities. There was a concern when it was at $2.5 Trillion but it is heading to $3.5 Trillion.

The problem is that the ratio of FRB debt, they call it assets, to Federal Government debt is exploding. This will make the turn around ever so more painful when the FED unloads this junk.
Labels: Economy

SATURDAY, JUNE 1, 2013

GENOMICS: STATISTICS VERSUS SYSTEMS

As NEJM recently noted[47][1]:

This is the age of massive genome surveys — at least for a little while longer. Sixty years after Watson and Crick's discovery, and a decade after the completion of the Human Genome Project, large-scale sequencing efforts directed at human disease abound, especially for cancer and rare congenital syndromes. International research teams supported by public funding agencies such as the National Institutes of Health and by private foundations such as the Wellcome Trust are rapidly enlarging the catalogue of genetic changes associated with neoplasia and other ailments, using ever faster, ever cheaper sequencing methods and heavy-duty bioinformatics.

Critics of big genomics projects have argued that such work is resource-intensive, is not hypothesis-driven, and amounts to little more than molecular philately. But as discoveries from these projects stack up, and as terabytes of observational data yield new insights into disease biology and prompt the development of pathway-driven targeted therapies, the usefulness of such approaches is becoming undeniable. When the Cancer Genome Atlas (TCGA) wraps up its 8-year effort next year, it will have provided detailed information on 10,000 cancer genomes for less than the cost of a trio of F-22 Raptor stealth fighters.

Let us examine where and where "not" models function. The issue we are interested in is that to

[47][1] http://www.nejm.org/doi/full/10.1056/NEJMe1303816

develop models and substantiated inferences we need a well understood reality for cause and effect. Namely gravity causes a force between two masses, it is a measured effect. Charge causes a force between two particles, it is a measured effect. In gene structures PTEN modulates PI3K, BRAF activates MEK and the pathways are well known. We know ligands, we know receptors, we know gene activators.

We also understand how these function, the forces, charges, conformations. We know how to inhibit and activate. We know these by facts not by correlations. Thus when we know these facts we have a basis for, indeed a demand for, using these dynamic models as an integral part of our understanding. We cannot and must not resort to random correlations. At times everything can be correlated.

Let me first explain by examining what human intellect has developed using models like this and then examine those thing where our knowledge is severely lacking. The driver for this is that genomics is more akin to physical systems which we can do a great deal with and NOT akin to Economics and its correlations which frankly led us nearly to an economic collapse.

Inherent in each of the areas where the use of the knowledge of relationships is integral to the descriptions, and not correlations, is also simple yet high level descriptives; Schroedinger's Equation, Navier Stokes Equation, Fokker Plank Equation, Kushner Stratonovich Equation. We have argued elsewhere that for genomic systems we are almost already there, just a few more steps.

Where They Work:

Thermodynamics

Early 19th century thermodynamics did not understand the true nature of heat, namely the movement of molecules and the statistical behavior. From the gross concepts we arrived at such things as internal energy, heat, enthalpy and other gross measures of a system's thermodynamic properties. With the development of statistical mechanics there was the move from gross measurement to understanding the statistical distribution of the molecules and this was presented via the Fokker Planck equation, a means to examine the detailed statistical fine structure of complex mixtures with thermodynamic issues.

Fluid Flow

Understanding fluid dynamics was initially a study with many tables and data taken from past experiments. Slowly as the theory evolved the Navier Stokes theory came forth and constructs such as flow fields evolved and then random changes in turbulence theory also was developed.

Stochastic Dynamic Systems

Complex systems, namely entities which are based on physical realities, aircraft control systems, chemical process controls, and the like can be modeled by a complex multidimensional spatio temporal model. Applying statistical methods developed by Wiener and Kolmogoroff one saw the development of the Kushner Stratonovich equations and then saw them extended to

distributed system as well. This analysis allows one to analyze highly complex multidimensional stochastic systems in time and space.

Wiener considered these in his studies of Cybernetics, and furthermore it was Wiener who also started the development of understanding complex organic systems.

The most important elements in using system models is our ability to ascertain Observability and Controllability; the ability to reproduce the model and the ability to send the states in the model to a desired end point. We also need to have the ability to identify the coefficients in the model. We often have good initial guesses but having measurement means that we can continually refine them

Electronics

When the transistor was invented the manager of the people who did it promptly published a book on solid state theory. Very few had a clue as to what Shockley was saying and frankly for those who used the device no one really cared. The electronics designer knew the linkages, and how to modify the, A good electronics designer knew that if this voltage went up the other went down, or whatever.

One knew the equations of the voltages and currents, one understood the complexities of the time varying circuits. There was a substantial amount of well proved physics behind all of this. However a good engineer also understood the ebb and flow, as for example a good neurologist can be examining the patient understand where the lesion is and then find out what the lesion is.

We are starting to get to that point with genomics. We know if we activate a kinase receptor then we activate a certain set of pathways which activate a certain set of transcription factors. A good Genomics Engineer does not need to "know" the protein structures, just what they do, at a very high level, yet detailed enough to catch the unique events which may occur.

Quantum Mechanics and Electrodynamics

Erwin Schroedinger came up with a simple manifestation of electrons in a quantum world. Feynman came up with simple diagrams to show what sub atomic particles are doing when they interact. Now solving the Schroedinger equation for a complex organic molecule is not readily achieved it can be attacked using sophisticated computers.

Where The Models do NOT Work:

Economics

Economics pretends to be mathematical. In reality, other than the tautologies of balancing financial sheets, the demand and supply theories are pure abject speculation. Econometrics is merely a fallacious use of correlation theory. There is no fundamental cause and effect, no demonstrable demonstration between input and output. This should be a warning for those

working in Genomics. Just having a correlation is not causality and furthermore there is an underlying reality that is being ignored.

Social Sciences

The social sciences have tried to ascertain human responses. Approaches such as those used in election prediction may function in the short term but humans are all too often less than a herd and change opinions all too frequently.

Psychology

Psychology is strewn with the dead bodies of mathematical approaches to understanding human behavior. The problem is that we do not understand the brain, yet, and thus models of thinking, such as those in artificial intelligence are at best primitive guesses.

Fundamental Requirements

To have a Genomic Model or something useful we must have the following:

1. A Verifiable Realization of How the System Works. This entails the understanding of pathways and their effects on cell proliferation and movement.

2. Some Understanding of What Causes Changes in Pathways. Here we have a difficulty. We not only have somatic changes, but we have epigenetic changes such as micro RNAs and even methylation and the like. We also must understand germ line predispositions. These are gene predispositions inherited as well as SNP predispositions which can result in subsequent translation of proteins.

3. Environmental Understandings: This would include the extracellular matrix issues and its environment as well as the ability of the invading malignant cells to activate surrounding benign cells to assist in proliferation.

4. An Acceptable Measure of the Malignant Cell in Space and Time. As with the Fokker Planck equation or the Kushner Stratonovich model this may mean a measure such as the average number of a specific type of malignant cell per volume at each spatio-temporal location.

5. A Realization for the Progression of Somatic Changes: This means an understanding of the statistical nature of the somatic genetic changes as cells progress in time. For example what happens when we go from MDS to AML. This is not AML de novo. We do not need the details but the transition rates and the possible states. This issue is akin to the electronics world where we need higher level understanding and not the details.

6. We Need Ability to Integrate Parameter Identification with Stochastic Models: Clearly if we know the models and if we know that certain factors are the drivers of these models, we may use this to identify the parameters at the same time we are estimating the states.

7. We need a Methodology to Quantify Our Representations and to validate them: This is akin to having a Kushner Stratonovich equation. It is what we have developed by using average number of cells by type at specific spatio-temporal sites. I believe we have the techniques, they are built on the many other approaches.

The Genomic Model

The Genomic Model is a systematizeable model. It is s system wherein we have well known causes and effects. We know that if a ligan attaches to a receptor then one has an activated pathway that induces a transcription factor which results in cellular proliferation. We know cause and effect. We know the rates of these factors. We can also develop models wherein we can estimate the average number of cells of a particular genetic structure at a specific time and at a specific place in the body.

The NEJM article concludes:

In 1803, a few years before the inaugural issue of the Journal, Thomas Jefferson commissioned Meriwether Lewis and William Clark to survey the vast unknown American frontier. Lewis and Clark departed from St. Louis, where Ley et al. initiated the AML genome survey. Less than a century later, the western frontier was declared "closed," but land surveyors did not disappear; today, they focus on construction projects and property boundaries. Likewise, although the initial epic AML genomic survey that began in St. Louis is now largely complete and surveys of other neoplasms will soon conclude, the use of genomics in quotidian practice is just beginning.

Now if I were to interpret this correctly it sends just the wrong message. The developments in Genomics are not Lewis and Clark like, they require Newtonian and Maxwellian insight. Fundamental laws and relationships, causality, albeit stochastic, and determine ng the right measures.

Thus in a sense one could imagine the Genomics Engineer being akin to the electronics engineer, or even to the neurologist. As many a medical student would recall from anatomy, the tracing of the cranial nerves is a critical skill, but one enhanced by seeing how they migrate from back to front. Diagnosis of cranial nerve issues are resolved by understanding the network. In a similar manner we would hope the same is double with Genomics pathways,

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Labels: Cancer

FRIDAY, MAY 31, 2013

WIRELESS BROADBAND

There is a piece in Technology Review about 5G wireless.

The writer states:

Samsung says its new transceiver can send and receive data at speeds of more than a gigabit per second over up to two kilometers—and it could deliver tens of gigabits per second at shorter distances. This compares to about 75 megabits per second for the latest standard, known as 4G LTE. The Samsung technology relies on 28-gigahertz frequencies, which can carry commensurately more data but can be blocked by buildings, people, foliage, and even rainfall.

Samsung says it has greatly mitigated these problems by sending data over any of 64 antennas, dynamically shaping how the signal is divided up, and even controlling the direction in which it is sent, making changes in tens of nanoseconds in response to changing conditions (among other features, it can catch stray reflections of signals that had bounced off an obstruction).

In my review of the Crawford book I indicated as such. This is just the first of many embodiments of Gbps to the user wireless. This is also why Verizon abandoned FIOS and why one should wonder about CATV.

It continually amazes me how regulators and lawyers are often clueless about technology and develop policies based upon bad technology and ignorance of what is doable. Well that is Washington after all.
Labels: Broadband, CATV

PSA ISSUES KEEP RETURNING

The Trustees of SSI and Medicare have just issued their annual report on the health of that system[48][1]. Needless to say the system faces challenges, substantial challenges. The ACA proposes various ways to manage them and for better or worse it is rationing. Not a direct and blatant form of rationing but a more subtle and possibly sinister form which is the result of "new" or "updated" clinical testing regulations. At the heart of this is the PSA issue.

The AUA has issued a new set of guidelines which put additional pressure on PSA testing[49][2]. The recommendations are as follows:

1. The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C) In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.

[48][1] http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/Downloads/TR2013.pdf

[49][2] http://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-Detection.pdf

2. The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C) For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized.

3. For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B) The greatest benefit of screening appears to be in men ages 55 to 69 years.

5. The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C) Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

Simply stated the guideline limits testing to men 55 to 69 years of age. It does not recommend testing for men over 69 years of age, the age at which most prostate cancer occurs.

Now the evidence used which I have reviewed in my work on Prostate Cancer Genomics[50][3] demonstrates the clear problems with the major studies, problems that many in the field have recognized and thus in a similar fashion discount the study out of hand. Thus the basis for these recommendations is highly tainted and suspect.

Now in a paper written for the magazine Columbia Medicine, the alumni magazine for P&S grads and affiliates, the author states[51][4]:

The PSA controversy exploded in May 2012, when the U.S. Preventive Services Task Force gave the test a resounding "D" grade, recommending against its use as a screening tool. The independent panel of experts in prevention and primary care (no urology or oncology experts were on the panel) found that the test led to "overdiagnosis" of prostate cancer and, consequently, overtreatment. For Dr. Benson, as for many urologists across the United States, that line of thinking is unworkable on multiple levels. "There's no such thing as overdiagnosis; there's only overtreatment," he says. "And you can't decide whom to treat and whom not to treat, you can't establish risk, without diagnosis. So the concept of overdiagnosis is dangerous, and it will preclude patients from getting life-saving therapy when it's indicated."

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[50][3]

http://www.telmarc.com/Documents/Books/Prostate%20Cancer%20Systems%20Approach%2003.pdf

[51][4] Baruchin, A., To Test or Not to Test? To Treat or Wait and See? Columbia Medicine, Spring 2013, pp 20-25.

Dr Benson is head of Urology at Columbia University Medical Center and a world expert in treating this disease. I know the group there quite well and Benson and his team are truly world class. Benson is at the forefront of the battle. The article continues:

Dr. Benson stresses that the overall boundaries are clear. "The goal for prostate cancer treatment is death from something else," he says. "Prostate cancer is, in general, a slow growing cancer, so to take an 85-year-old man with a PSA of less than 4 and say he needs ongoing PSA screening is insane. But to take an 85-year-old man who has never had a PSA ever in his life and say he shouldn't get one, just to see where he's at, is also crazy. I think every man, regardless of age, deserves one PSA. If that one PSA places you in a category where the chance of your dying of prostate cancer is low, then you don't need to have biopsies and additional PSA testing. This is a $15 blood test. The rub here is not in the PSA; the rub is in what people do with the data."

Benson is also quoted as follows:

One of the department's most interesting areas of current research is in confirmatory biopsies to decide eligibility for active surveillance among men who come to Columbia after being diagnosed elsewhere. "I have greater confidence in our ability to thoroughly biopsy the prostate," says Dr. Benson, who performs biopsies with 24 to 30 cores rather than the more typical 12. To test the accuracy of initial biopsies at other facilities and consequent eligibility of patients for active surveillance, Dr. Benson selected 60 incoming patients and, before enrolling them in active surveillance, repeated their biopsies to be sure that the original tests hadn't missed prostate cancer that might be of greater risk.

This is a critical difference, namely the increased core density. We have demonstrated the probability of detection versus number of cores, and also total prostate volume. Going from the old six cores to 24 dramatically increases the detection probability, especially is using trans-rectal ultrasound guiding by ax experienced urologist. The difference between a procedure at Columbia versus at some local clinic can be orders of magnitude in terms of detection probability. Also the sequelae problems are generally much lower, even with more cores.

Finally Benson states:

For Dr. Benson, his current touchstones show the way forward. "There are two telling statistics," he says. "One is that before PSA screening, the most common presentation was a patient with metastatic disease. And the second thing is that metastatic disease is normally rare and the death rate has been reduced by 40 percent. What we have to do is find ways of continuing to have a death rate reduced by 40 percent while not treating people who don't need treatment. That has to be the goal."

Eliminating a test which has a false alarm rate is clearly NOT the way to go, it is especially not the way if we want an informed patient as part of the decision process.

The problem here is that PSA measurements and other types of non-invasive measurements are critical and especially if we have temporal data for the patient, namely annual or even semi-

annual PSA tests along with %Free PSA, and we can calculate velocity and other measures, normalize them for Prostate volume, then we have a substantially better test. Combine that with competent and experienced urologists and biopsies then we can ascertain what the true state of reality is.

Having some panel decide based on faulty data is NOT the way to proceed.

Labels: Cancer, Health Care, Politics

WEDNESDAY, MAY 29, 2013

TWO MORE MELANOMA THERAPEUTICS

The FDA just approved two more melanoma therapeutics.

They state:

The U.S. Food and Drug Administration today approved two new drugs, Tafinlar (dabrafenib) and Mekinist (trametinib), for patients with advanced (metastatic) or unresectable (cannot be removed by surgery) melanoma, the most dangerous type of skin cancer.

Tafinlar, a BRAF inhibitor, is approved to treat patients with melanoma whose tumors express the BRAF V600E gene mutation. Mekinist, a MEK inhibitor, is approved to treat patients whose tumors express the BRAF V600E or V600K gene mutations. Approximately half of melanomas arising in the skin have a BRAF gene mutation. Tafinlar and Mekinist are being approved as single agents, not as a combination treatment.

The FDA approved Tafinlar and Mekinist with a genetic test called the THxID BRAF test, a companion diagnostic that will help determine if a patient's melanoma cells have the V600E or V600K mutation in the BRAF gene.

The FDA is rapidly issuing approvals on many of these therapeutics.

Cost and long term efficacy are still issues.
Labels: Cancer

CHAOTIC DATA OR YOU JUST DO NOT KNOW ENOUGH

In a recent Scientific American piece the author bemoans the wealth of unorganized data available regarding cancers.

The author bemoans:

The field of genetics has flourished with the publishing of the complete human genome in 2001, aided by the advent of fast, affordable sequencing technology. A completed genetic code of a

healthy person allows us to compare against the genetics of cancer. With advanced analytical techniques, and decades of research into the characteristics of different forms of this disease, it seemed that it was finally time to pull out the answers from the code itself by looking for the mutations that cause or support the cancer's growth – the differences between the cancer cell and a normal cell. But when the answers didn't bubble up from our statistics and reams of data, it became clear that the questions left for us were far more complicated.

Yes indeed the questions are complex. But we do have examples of previous work to guide us. Cancer is an amalgam of ligands, receptors, pathway elements, transcription factors, SNPs, miRNAs, and the ECM environment. Cancer cells move, mutate, and affect and are affected by their local environment. It is a stochastic distributed dynamic system. Fortunately we have been studying these for decades, if not for most of the past century. The issue is to understand what drives what and how to control it.

Cancer is a stochastic distributed temporally varying field, cells changing and flowing with ever changing genetic characteristics. We can understand these characteristics and even predict to some degree where they will go in the future. That is the challenge and the opportunity. The author seems to totally miss this point.

She continues:

One method for addressing chaos of this sort is to develop a statistical plan. We want to be able to take the information we know, look at the probabilities that certain changes will occur, and use statistics to determine what the cancer will likely do next. This challenge seems insurmountable when you look at the variables we must contend with: rapid evolution, unchecked growth, subtle migration, and so on. Changes that occur in the genome during cancer initiation and progression involve massive genetic rearrangements, damage, and mutation.

This makes it difficult to distinguish between causes and consequences of the cancer. It would be far easier if each gene, or even each chromosome, carried out its business without interaction with the rest of the cell. But not only can changes in one area of the genome have profound direct and indirect effects on the expression of genes elsewhere, we now have evidence that cancer cells can send these activity-altering signals to other cells, both tumor-derived and normal.

Frankly a "statistical plan" is the worst path to go. You most likely can correlate anything with anything. Economists do it all the time and look where they have taken us. We know of can know what affects what and how that occurs. We can and must stipulate the system relationships. We must have a system model NOT some set of correlations.

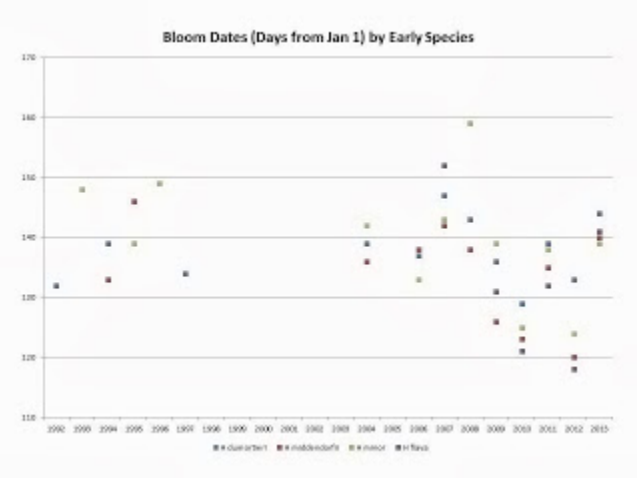
This I fear is the difference between the bench worker, the physician, and the engineer. Is cancer genetics ready for the engineer? I believe that the door for such an entry is now opening. Not everything is in place but we may have the key pieces to begin the journey.

We know causes, we understand the consequences. If BRAF V600 is present we even know how

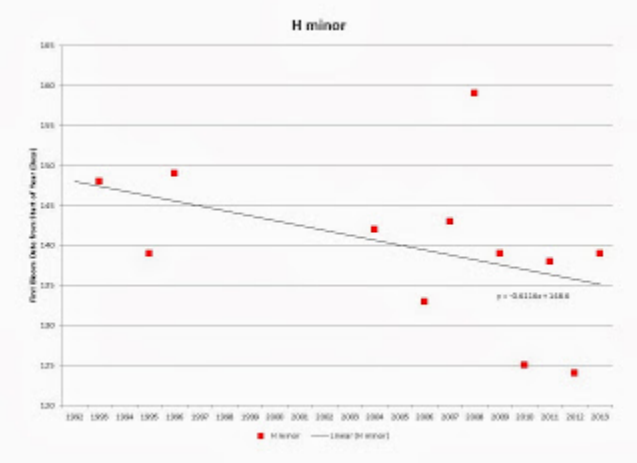
to inhibit it, for a while. We must then understand how to take the next step. Cell by cell we must understand the genetic progression as a system, not as a set of correlations.
Labels: Cancer

TUESDAY, MAY 28, 2013

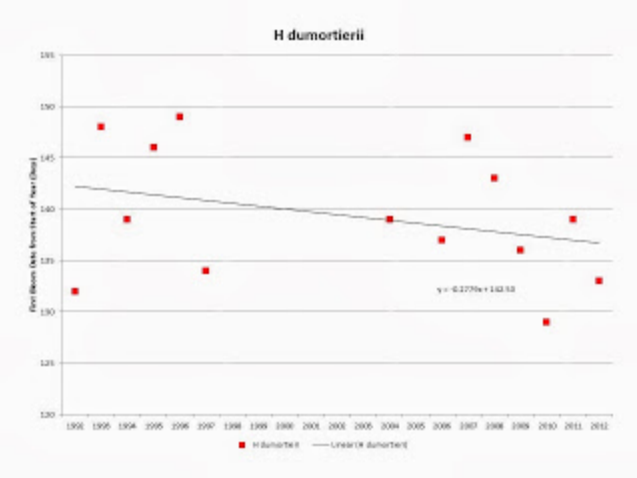
WEATHER OR CLIMATE



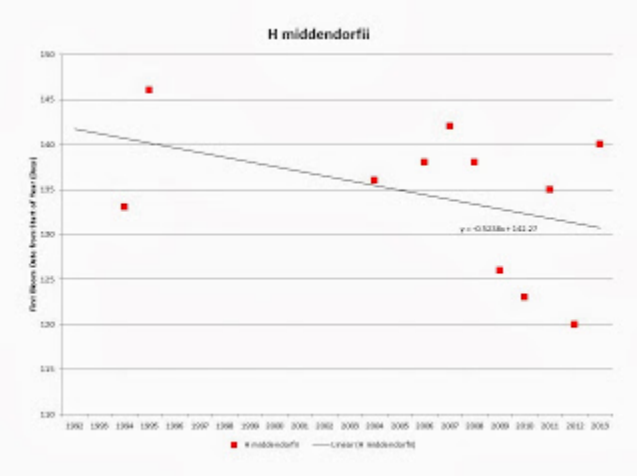
I have been trained in science and engineering and thus the facts are the facts. Do we have global warming? Global, I cannot say, but locally we have some short term trends. The above is the bloom dates from the beginning of the year for early blooming Hemerocallis. I have 22 years worth of date and well, there may be a trend. But when you look at the data one is always asking what is going on. This graph is a composite of four species. Let us examine each.



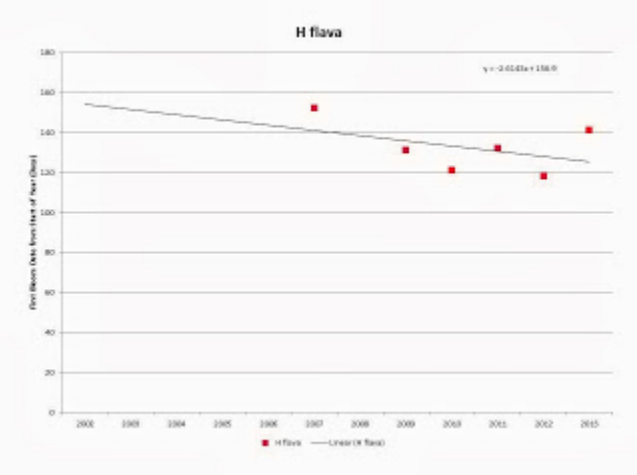
H minor shows a downward sloping trend. Namely we are seeing earlier bloom times. Over 21 years we see from the regression a change from 147 days down to 135 days. That is a significant change. But what if we eliminate outliers? It would get worse. 2010 and 2012 were warm spring seasons and thus early blooms. They would drag everything down. So we just let the data speak for itself.



H dumortieri is a late bloomer, relatively. We see it going from 142 down to 137, only a five day decrease.



H middendorfii goes from 142 down to 131. That is a 9 day drop. It is generally one of the earliest. But look at the data, it is quite spread out.



H flava is of too little data. Not clear that we can say much.

But the question is; can we say that this is a trend or just normal variation? Trends would result in February blooms at some time which is doubtful. But it is interesting to always look at facts and species plants do tell us a great deal. The problem is the "noise" from any micro climate changes. For example the Hurricane got rid of many tall trees. Yet the flowers come out before any significant tree foliage. Thus perhaps we have a stable micro climate. Just a thought.
Labels: Commentary

MONDAY, MAY 27, 2013

THE LEFT AND TAXES

We have laws, including Tax Laws. And we have Tax Lawyers. They are very expensive. My Tax Lawyer costs 4 times my Accountant. My Tax Lawyer is really important, my accountant makes sure I do everything right, but my Tax Lawyers makes sure the IRS understands that I did it right. I fear the IRS more than the Devil! As very well we all should.

But then again there are laws. If we follow them, then we have no problems. One of the Left Wing Economists located at Columbia, that school which denied Catholics admission because of their religion, not that I hold a grudge, states:

The world looked on agog as Tim Cook, the head of Apple, said his company had paid all the taxes owed – seeming to say that it paid all the taxes it should have paid. There is, of course, a big difference between the two. It's no surprise that a company with the resources and ingenuity of Apple would do what it could to avoid paying as much tax as it could within the law. While the supreme court, in its Citizens United case seems to have said that corporations are people, with all the rights attendant thereto, this legal fiction didn't endow corporations with a sense of moral responsibility; and they have the Plastic Man capacity to be everywhere and nowhere at the same time – to be everywhere when it comes to selling their products, and nowhere when it comes to reporting the profits derived from those sales.

With all due respect, there is no difference between the two. The laws says such and such and you then follow the law. What does this character mean by "should"? According to him? Who is he? The arrogance of the Left is amazing. If we do not like it then change the tax law.

Frankly we should eliminate all corporate taxes. Imagine what that would do! It would make all these companies move here, hire people here, rent and build facilities here. Then we can tax the result via personal taxes. After all we really do not get that much from companies. The big ones pay less as a percent of profits than the smaller ones. So "level the playing field", is that not the Socialist dictum, make the tax zero!

Besides why should we ever listen to a Socialist!
Labels: Economy

MONDAY, MAY 27, 2013

SLOW NEWS DAY - X RAY SCANNERS

Yes, X Ray scanners use X Rays. X- Rays cause cancer. Yes X Ray scanners penetrate only the top layers of the skin. Yes melanocytes reside there. Yes, X Rays mutate genes. Yes X Rays can mutate melanocyte genes. Yes mutated melanocytes can become melanomas. Yes melanoma kills, really kills.

Now to the NY Times, it has a complaint about TSA X Ray machines. But a few years ago I wrote a long analysis of the X Ray scanners and melanoma. Yes it exists and X Rays are causitive. In fact look at my draft book on melanoma genomics.

The author states:

I have never walked through an airport body scanner — or, as I think of it, "the cancer machine." In the years since these radiation chambers began appearing in airports across the United States, I have developed a variety of tricks to avoid submitting myself to them.

Good for the author. He continues:

The T.S.A. assures us that neither the X-ray scanners nor the millimeter wave machines pose a heath risk. But frankly I'd prefer to avoid being irradiated, even a little bit.

T.S.A. officers seem to take it personally when I opt out. They sigh, they roll their eyes, they snort derisively. I always have the impression that, at some point in their training, they have been told that passengers who opt out are foolish and selfish, because that is how I tend to be treated — with disgust.

Yes I have opted out. You see I have a predisposition. Then again it is the Government. Even more so it is TSA, one of the most troglodyte like elements of the current administrations task force of enforcers. Their science is not only defective but is harming Americans by the millions. Remember that it the Beltway Bandit firms who write the reports. These are the companies who hire the less than qualified and then produce expensive reports justifying Government attacks on it own citizens.

Now let me tell you how I really feel.....

The TSA X Ray program is a major cause of latent cancers. It irradiates American citizens by the millions and does so with no understanding of the results. Perhaps that is why I drive everywhere. Or get the Fascist strip search. I really like Putin, at least he knows how to run a country!
Labels: Commentary

TREATING THE PATIENT VS FOLLOWING THE BOOK

There is an interesting article in JAMA comparing Evidenced (Guideline) Based Medicine versus Personalized Medicine. This is critical since the ACA fosters on physicians the EBM approach and may ultimately penalize them for deviating therefrom. After all it is the Government.

For EBM the authors clearly state:

Evidence-based guidelines are generated based on the body of clinical data available for a particular question. The highest level of evidence assigned in a guideline is based on multiple randomized controlled clinical trials. In general, randomized clinical trials have specific inclusion and exclusion criteria designed to represent a population broad enough and sufficiently enriched to attain a requisite number of end points and demonstrate a statistically and clinically significant difference in outcome. Subgroup analyses (both those that are prespecified and other post hoc analyses) are often performed to identify characteristics within the study population that are associated with greater benefit from the intervention, with no benefit, or even with harm. Yet these analyses are accompanied by warnings that findings should be cautiously interpreted.

The classic example is the prostate cancer tests and the breast cancer monitoring. The problem is always the issue of the subgroups and the users understanding of these limitations. The authors specifically state:

Indeed, there is well-deserved skepticism regarding the utility and accuracy of subgroup analysis from clinical trials, and these analyses are therefore generally not used in the formulation of guidelines. Patients (including those enrolled in trials) have multiple characteristics, each of which may influence the behavior and significance of other characteristics. Analysis of a subgroup showing that a single characteristic influences outcome is of limited clinical significance unless multiple variables that may modify the importance of the single variable are considered. However, if well-conducted analyses from multiple sources demonstrate concordant findings, perhaps these subgroup analyses should be considered when guidelines are constructed and revised, given the impracticality of performing randomized clinical trials to answer the question of appropriateness for every possible subgroup.

For example it is well known that prostate cancer is not the same in all men. Most is indolent and some highly aggressive. But how does one tell the difference. The "Guidelines" fail in all manners of reasonableness in addressing this.

Now the authors characterize Personalize Medicine as follows:

The President's Council of Advisors on Science and Technology noted that personalized medicine "refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their

susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Let us avoid any insight from the current president and his minions, for personalized medicine does really mean tailoring treatment down to the therapeutic level. For example, if we have a metastatic melanoma, then by understanding the receptor, ligand, pathway, and other elements broken in the mets we can develop not only a patient specific but CELL specific therapeutic. That is the future, and it is a future than can be achieved with what we have at hand today.

The authors conclude:

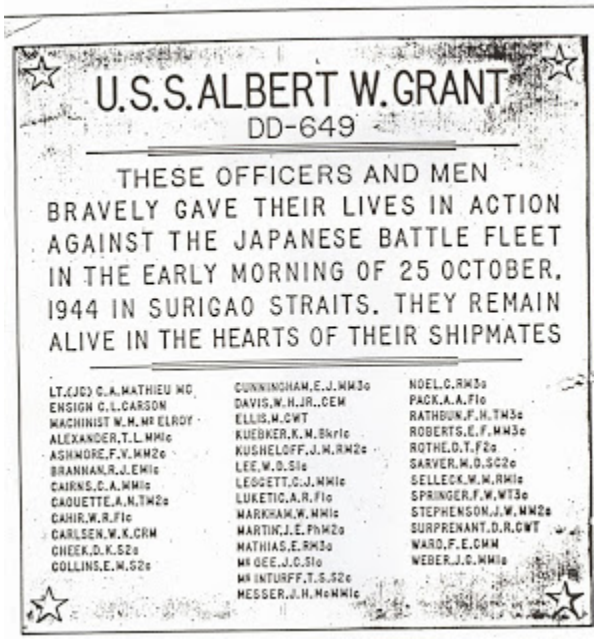
The conflict between guideline-based medicine and personalized medicine predominantly occurs when considering withholding a therapy that is recommended or supported by the guidelines but that may not be beneficial for an individual patient.

If a subpopulation may not benefit from the therapy, it is important to identify the subpopulation and verify this finding in an appropriate clinical trial. This presents a genuine opportunity to deliver better health care at lower costs by withholding the intervention. Cultivating a health care culture poised to explore these opportunities is critical.

*This will entail more active participation from a range of stakeholders, including physicians who will need to embrace equipoise when the data support this position; insurers (i**ncluding the Centers for Medicare & Medicaid Services**) who have traditionally not been involved in the design, funding, and conduct of clinical trials; regulators who will need to develop policies to enable and support this type of patient-centered research; and health care organizations and quality-measurement groups who will need to develop more nuanced approaches to assessing quality of care and processes that monitor guideline implementation.*

The key observation here is that as most physicians know all patients are different. Some benefit some do not. The reasons why are still often clouded in our ignorance. Will we allow our ignorance to dominate our treatments? Perhaps under ACA we not only will but must. Reimbursement may be the least of the problems. Failure to follow Guidelines, the "Rules", may very well place the physician at jeopardy. If the IRS has its say then perhaps failure to follow any Guideline may result in criminal charges, audits, and the like. This may be making physicians rule followers rather than diseases solvers.
Labels: Health Care

MEMORIAL DAY



The list of men lost on the AW Grant, DD 649, at the Battle of Leyte, and all others.

Labels: Commentary

SUNDAY, MAY 26, 2013

IS THERE A GENETICS OF HUMAN OBESITY?

There seems to be a persistent search for the genetic basis of human obesity. Again the basic fact of life is that 3500 kcal equal one pound of body weight. So if you burn 2000 kcal per day and consume 2350 per day you gain one pound in ten days. That is a simple law. Genes or no genes.

Now in a recent NYAS paper the authors search for the elusive cause, neglecting the apparent truth. They state:

Although a number of significant findings have been made, it appears that very little of the apparent heritability of body mass index has actually been explained to date. New approaches for data analyses and advances in technology will be required to uncover the elusive missing heritability, and to aid in the identification of the key causative genetic underpinnings of obesity.

In the past two decades, family studies and animal models have helped us to identify many genetic events associated with obesity. Subsequently, GWAS have driven the transition from primarily studying monogenic traits to ones of a more polygenic nature. GWAS have also revolutionized the genomics of obesity field, in that it offers an unbiased approach to uncover novel common genetic variants contributing to the pathogenesis of obesity.

Despite these great advances, the combined results of linkage, candidate gene, and GWAS approaches have explained very little of the variance in BMI, suggesting that there are still many genetic findings to be made, most likely being rarer variants exhibiting small effects. In order to fully characterize this missing heritability, larger and larger sample sizes are going to be required to improve statistical power. New technologies, such as next generation sequencing, will help us identify these elusive obesity-associated variants, particularly as the price of these techniques continues to drop.

In addition, most of variants that capture the association with obesity from current GWAS are not themselves causative. As such, how to move from association to causality remains a big challenge for common complex diseases like obesity. Therefore, we need to develop new approaches for analysis to characterize the true causative genes and perform functional studies to determine their roles in obesity. Once at least some of these challenges have been mastered, we will have a clearer picture of the genomics of obesity. This, in turn,will help us produce more efficacious therapies and will guide us on the path to personalized medicine.

Somehow the basic element of obesity is missed. How does a gene make you eat more? Perhaps you have a lower BMR but the equation holds for almost all humans. Why waste time on genes. One must tell fat people they are fat because they fail to control intake, it is their fault.
Labels: Health Care, Obesity

TRAVEL AND TOURISTS

The NY Times has a small piece on travel. As the author states:

But not long ago, on a journey through India, I began to see things a little differently. For two weeks, I had been fairly battered by the daily chaos of budget travel. Then, on my last night in Kolkata, I met up with some particularly affluent friends who had spent their vacation escorted by private staff from one security-gated refuge to the next, and who were staying in a palatial five-star hotel on the outskirts of the city. In their cocoon of opulence, they quizzed me about my comical but vivid excursions, which had left me both exhausted and exhilarated. I began to realize that they suffered their own form of travel envy. The sense of control money provided them had also served to deaden their experience.

The economic gulf between travelers is part of a great tradition. Since the birth of leisure travel, aristocrats have been devising creative ways to isolate themselves from hoi polloi.

Now I have traveled a great deal. I have started companies in some twenty countries and can manage about six languages. Perhaps that is the key.

I am reminded of my first trip to Russia as a tourist. It was 1995 if I recall and we went via a FinnAir tour, but unlike the rest of the Americans we went local. We stayed in the InTourist hotel, the old KGB managed facility, where Russian was required, took local cabs to meet our rich American fellow travelers at the Europa.

When we went to the Ballet we had a ticket for $0.75 each since I dressed in a local style and spoke in Russian, the other Americans paid $75 from the Concierge. My tickets were from the local box office. We hired a local Russian driver, a fried of our InTourist guide, but since we spoke Russian, and dressed not as Americans, we were shown St Petersburg the way only a Russian would be. Later my Russian partners were always amazed that I would rather take the metro in Moscow than a limo.

In Thailand I managed to disappear into the countryside, with a few words of Thai, and in Italy my limited Sicilian allowed me to get places no American would be allowed.

After 9/11 I was stranded in France, and off to Normandy, where my French was accepted and the people were wonderful. We lived in Bayeux for the duration. We did not wear shirts festooned with logos, no sneakers, always had jackets, shirts, real shoes. A few words of the language and we saw the soul of the people.

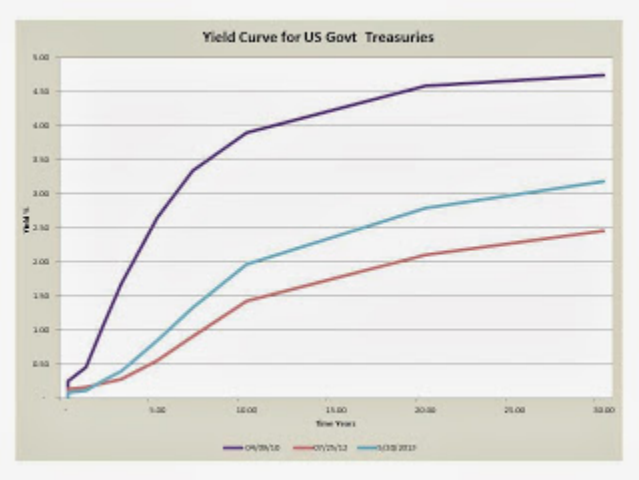
I remember my days as a US corporate executive, the limos and managed tours, one saw nothing, one walked away from the opportunity with nothing.

I remember sitting at bars, speaking a little Russian and Greek, learning more of the world than any CIA analyst in Langley. Even more so, more than any Secretary of State.

Why does one travel, to escape, to learn, to mingle? Or perhaps if one has excess of funds just to show off. Yet than one can do that with less exercise.
Labels: Commentary

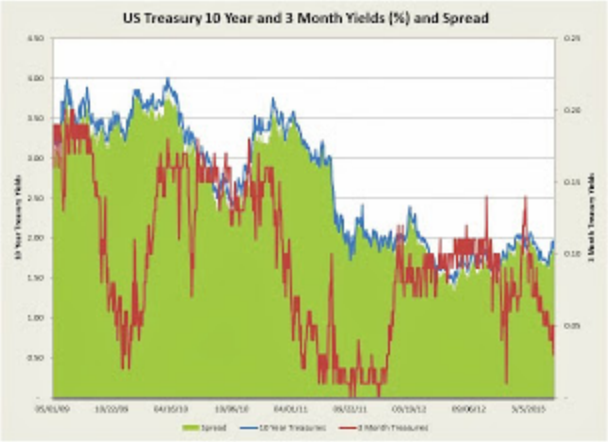
TUESDAY, MAY 21, 2013

TREASURY SPREADS AND YIELD CURVES



The Treasury spreads and yield curves are still depressed. The FED is keeping the demand down and the rates low as we have been watching for the past 4+ years.

There still is a low spread between the 30 years and 30 day numbers as a percent of the maximum numbers. There is some creep back up recently and it is going to late 2011 numbers. If the FED no longer controls the buy side one can expect significant increases.

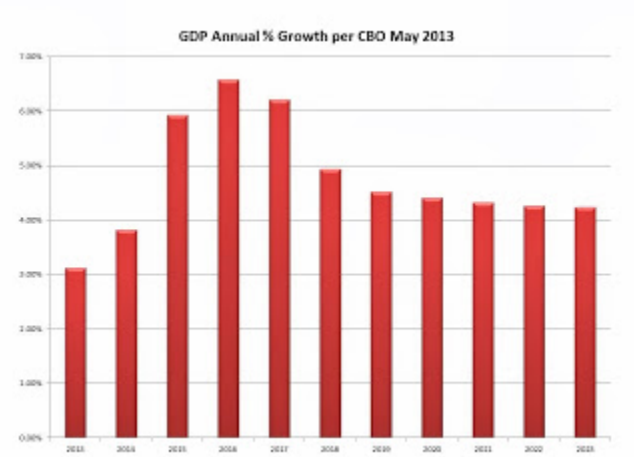


The more typical 10 year and 90 day spreads and yields are shown above. Here we see the 90 drop in yield closing in on some of the prior lows and the 10 year yield remaining somewhat fixed.

Sooner than later the FED will let go and these will increase substantially. When is always the question.
Labels: Economy

SUNDAY, MAY 19, 2013

HOW DUMB DO THEY THINK WE ARE?



The CBO delivered a report on projections for 2013 through 2023. The graph above is a simple calculation of the annual growth rates of the GDP over this period, and NOT presented in the report.

We are now at about 2.5% annual growth rate The CBO has it going to almost 6.5% in just a few years, by 2016. Who in their right mind believes that! Then it flat lines at 4.25%. What is the basis for that number? Try and read the report. If we cannot get true and reliable numbers with

some basis, then why waste the time and money.

Things are really getting worse by the minute.
Labels: Economy

THURSDAY, MAY 16, 2013

MER, MELANOMA AND INHIBITORS

The focus on pathways, receptors, ligands and promoters as control elements for cancer has seen a great deal of development in the past decade. One key approach is the development and identification of inhibitors, molecules which can block an over excited pathway. We examine here a specific recent such example as relates to melanoma. It is already well known that BRAF suppression is an effective approach albeit often of limited duration. The development of inhibitors for a selection of evolving pathway aberrations will most likely be the way to turn a deadly disease into a chronic but manageable problem, assuming that one can get permission to use such molecules, a process which not is costly and lengthy.

We use a recent paper by Schlegel et al and use MER as a prototypical example of pathway control via inhibitor blockage.

MER is a tyrosine kinase ("TK") receptor ("TKR")[52][1]. As Marks et al state there are 85 members in the TK family and 58 of these are receptors. The receptors are divided into various families based upon their structures and one family contains Axl, Sky and MER, also known as the TAM family[53][2]. This family, as we shall see, has immunoglobulin like regions on the outside of the cell surface and kinase domains on the inner surface. The family also has a dual fibronectin III-like domain on the outside just below the immunoglobulin domains, of which there are two.

Generally the receptors are activated by ligands which in turn result in the phosphorlyation of the kinase region and associated area and then commence the activation of the related pathways. Now these pathways are the ones that result in proliferation and loss of localization and thus result ultimately in metastasis.

We use this example for two reasons: (i) it is a good example to demonstrate the activation of pathways and metastatic growth; (ii) it also is a good example of how inhibitors can function on receptors and thus can inhibit metastatic growth.

As Schlegel et al state:

[52][1] From NCBI we have (2q14.1): *This gene is a member of the MER/AXL/TYRO3 receptor kinase family and encodes a transmembrane protein with two fibronectin type-III domains, two Ig-like C2-type (immunoglobulin-like) domains, and one tyrosine kinase domain*.

[53][2] TAM, (**T**YRO, **A**XL, **M**ERTK)

Receptor tyrosine kinases (RTKs) are frequently ectopically expressed, overexpressed, or hyperactivated in tumor cells and are therefore attractive targets for cancer therapy. C-MER proto-oncogene tyrosine kinase (MERTK), a member of the TAM (TYRO, AXL, MERTK) family of RTKs, has been characterized as a therapeutic target in hematopoietic malignancies and several solid tumors including lung, prostate, and brain

There is a subtle question posed but not answered here. Is it over-expression, and if so by what ligand, or is it an excess production of MER and thus an over-expression. What is the status of the benign cell, and is this the dominant pathway. Clearly by having too active or too many MER receptors, actually any TAM like receptor will do, leads to proliferation. This goal of blocking the receptor so that it does not start the process is a valid approach.

The authors clearly state:

Stimulation of melanoma cells with the MERTK ligand GAS6 resulted in the activation of several downstream signaling pathways including MAPK/ERK, PI3K/AKT, and JAK/STAT. MERTK inhibition via shRNA reduced MERTK-mediated downstream signaling, reduced colony formation by up to 59%, and diminished tumor volume by 60% in a human melanoma murine xenograft model.

Namely we have a ligand, GAS6, which activates the MER pathway. Is that ligand over expressed. On the other hand the molecule shRNA reduced the activation.

They specifically state:

In addition, Sensi et al. found that melanoma cells often secrete GAS6, a ligand of TAM receptors, indicating a mechanism of TAM autocrine signaling in melanoma…. The mechanism of MERTK activation in melanoma cells is not clear, but Sensi et al. have previously described melanoma cell expression and secretion of GAS6, the common ligand for all members of the TAM family of proteins, suggesting a method of autocrine and/or paracrine activation of MERTK. Since expression of MERTK by melanoma cells increases during progression from primary to metastatic melanoma, it would be interesting to determine whether corresponding increases in GAS6 levels occur in serum from patients with metastatic melanoma, implicating serum GAS6 levels as a potential early marker of melanoma progression, as in other cancers.

Thus possibly inhibiting GAS6 may be profitable as well[54][3]. However the focus here is receptor inhibition.

1.1 MER AND MELANOMA

[54][3] As NCBI states: *This gene product is a gamma-carboxyglutamic acid (Gla)-containing protein thought to be involved in the stimulation of cell proliferation, and may play a role in thrombosis. Alternatively spliced transcript variants encoding different isoforms have been found for this gene*. Located at 13q34. http://www.ncbi.nlm.nih.gov/gene/2621

Let us consider a recent development in understanding MER and melanoma. We return to the recent paper by Schlegel et al where the author's state:

C-MER proto-oncogene tyrosine kinase (MERTK) is a receptor tyrosine kinase with oncogenic properties that is often overexpressed or activated in various malignancies. Using both protein immunohistochemistry and microarray analyses, we demonstrate that MERTK expression correlates with disease progression.

MERTK expression was highest in metastatic melanomas, followed by primary melanomas, while the lowest expression was observed in nevi. Additionally, over half of melanoma cell lines overexpressed MERTK compared with normal human melanocytes; however, overexpression did not correlate with mutations in BRAF or RAS.

Stimulation of melanoma cells with the MERTK ligand GAS6 resulted in the activation of several downstream signaling pathways including MAPK/ERK, PI3K/AKT, and JAK/STAT. MERTK inhibition via shRNA reduced MERTK-mediated downstream signaling, reduced colony formation by up to 59%, and diminished tumor volume by 60% in a human melanoma murine xenograft model.

Treatment of melanoma cells with UNC1062, a novel MERTK-selective small-molecule tyrosine kinase inhibitor, reduced activation of MERTK-mediated downstream signaling, induced apoptosis in culture, reduced colony formation in soft agar, and inhibited invasion of melanoma cells. This work establishes MERTK as a therapeutic target in melanoma and provides a rationale for the continued development of MERTK-targeted therapies.

Thus, like to work that led to BRAF V600 inhibitors, we see MER TK is another interesting target. The authors also provide an inhibitor molecule as well.

1.2 TYROSINE KINASES AND MER

Tyrosine Kinases receptors have received a great deal of attention especially in the area of cancer metastasis and in cancer control. They are as Verma et al state:

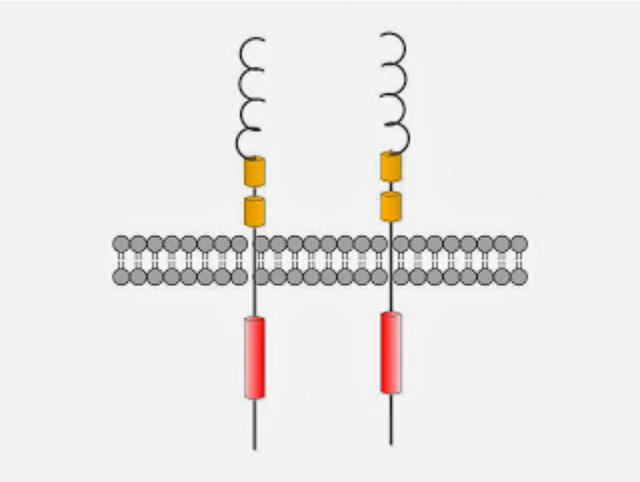
Receptor tyrosine kinases (RTK) are a large family of transmembrane proteins exhibiting great diversity in their extracellular regions, although sharing in common a highly conserved intracellular tyrosine kinase domain. They function as sensors for extracellular ligands, the binding of which triggers receptor dimerization and activation of the receptor's kinase activity. This activation leads to the recruitment, phosphorylation, and activation of multiple downstream signaling proteins, which ultimately change the physiology of the cell. RTKs regulate cellular processes, including survival, growth, differentiation, adhesion, proliferation, and motility. Fifty-eight known RTKs in the human genome are classified into 20 families by amino acid sequence identity within the kinase domain and structural similarities within their extracellular regions.

There are many such tyrosine kinase receptors. One class is the TAM family and as Verma et al state:

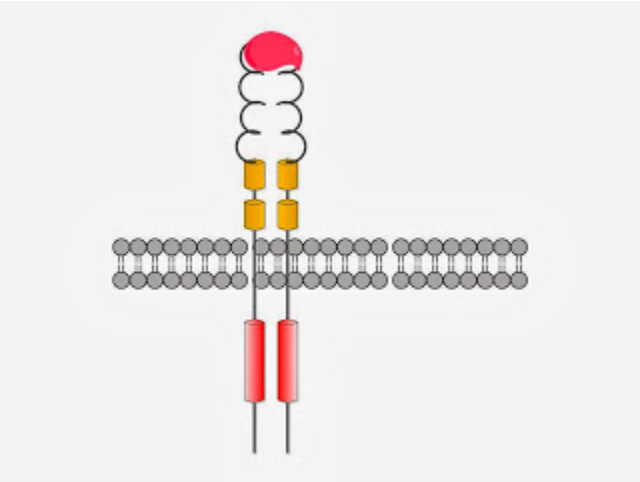
One subfamily is referred to as the TAM family, identified in 1991, comprising Tyro-3 (also called Sky), Axl, and Mer. The TAM receptors are characterized by a combination of 2 immunoglobin-like domains and dual fibronectin type III repeats in the extracellular region and a cytoplasmic kinase domain. The primary ligand for TAM receptors is growth arrest-specific 6 (Gas 6), a fairly large (75 kDa) vitamin K–dependent protein known to activate downstream signaling

We depict a simple structure below containing the elements specified above.

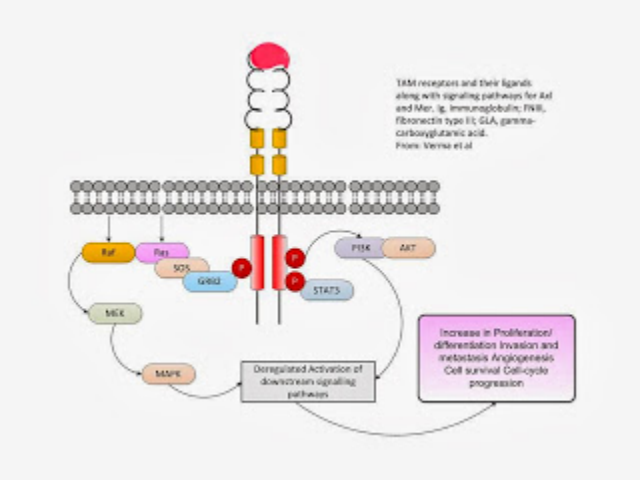
Let us consider a simple development of MER controlled pathways. The Figure below shows two separate and un-activated MERTK molecules with the immunoglobulin terminals on the outside and the kinase areas on the inside.



Now along comes a GAS6 ligand, and it attaches to and connects the MERTK molecules at the immunoglobulin ends and this activates the kinase tails inside the cell.



Once activated the kinase ends commence pathway activation via the phosphorylation process. The pathways are depicted below.



It is the activation of these pathways by the excess GAS6 production or the excess MERTK production or both that results in excess proliferation and metastasis.

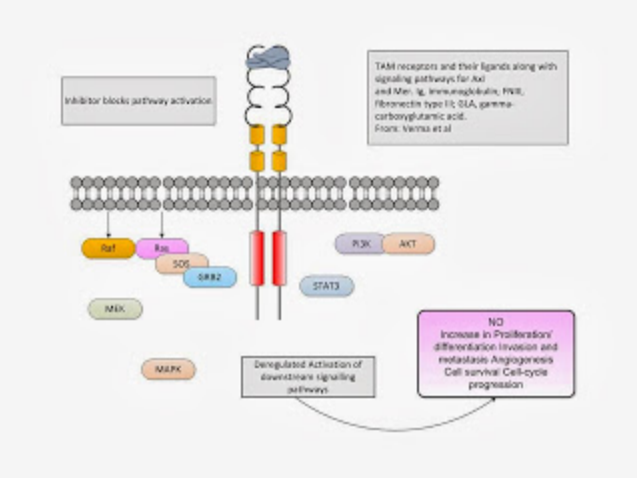
As Verma et al relate about the pathway:

Studies using chimeric Mer receptors expressed in NIH3T3 fibroblasts linked downstream signaling pathways, such as PI3K, phospholipase C-g (PLCg), and ERK, to Mer activation. Gas 6–dependent activation of Mer stimulates phosphorylation of ERK1/2, leading to cellular transformation and increased proliferation and DNA synthesis.

The ultimate downstream targets of the pathway differ according to cell type and tissue microenvironment. In leukemia cells, ligand-dependent activation of EGF receptor (EGFR)–Mer chimeric receptor stimulates phosphorylation of Akt, ERK 1/2, and p38 mitogenactivated protein kinases (MAPK), which results in decreased apoptosis but no change in proliferation (30). Expression of CD8-Mer chimera in pro-B cells results in transcriptional activation of NF-kB via PI3K/Akt.

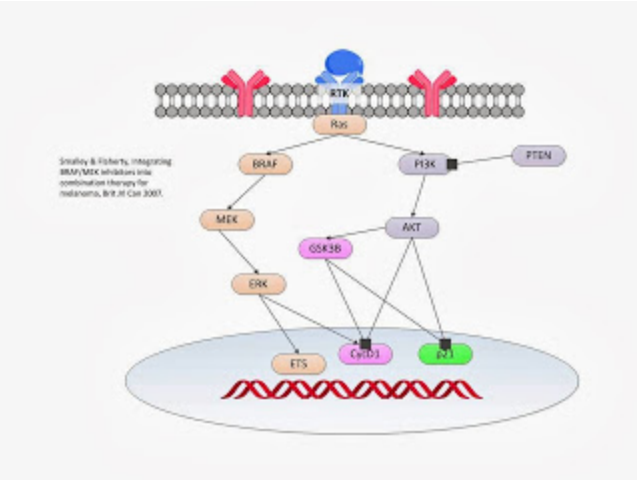
Additional activation of p38/MAPK and meiosis-specific serine/threonine protein kinase 1 (MEK1) occurs via CD8-Mer, leading to protection from apoptosis. Some atypical signaling pathways involved in cell survival have been studied as a link between Mer and the actin cytoskeleton via growth factor receptor-bound protein 2 (Grb2), Shc, and Vav1. Downregulation of the proapoptotic tumor suppressor WW domain-containing

We depict below how one can inhibit this process. We depict an inhibitor molecule which binds to the sites as before but now does not activate the TK pathways. The inhibitor must be stronger in affinity than the GAS6 which most likely is still in ECM abundance.



Note above the RAs to RAF (especially BRAF) to MEK to MAPK pathways flow. We have examined this in details elsewhere[55][4]. The implication is that by targeting the TK Receptor, one targets all elements of the pathway. It should be noted however that the separate pathway elements may be activated and over expressed via other factors such as epigenetic ones. Thus the suggestions of Schlegel et al are of great merit but should be balanced by understanding the epigenetic issues as well.

An example of a pathway and its control with BRAF functionality is depicted below:



This simple explanation is also a paradigm for many other such pathway activations and especially for those of the tyrosine kinase verity.

1.3 MER AND MIRNA

[55][4] See McGarty, Melanoma Genomics, DRAFT, 2013.

There are other dimensions of interest here as well. In cancers there unfortunately is not just a single point of failure. There often are multiple. We show here just another example where MER and miRNA play an interesting role. This is an essential point to make because all too often the initial observers may all too often jump at a simple solution leaving behind a complexity of other factors which take control.

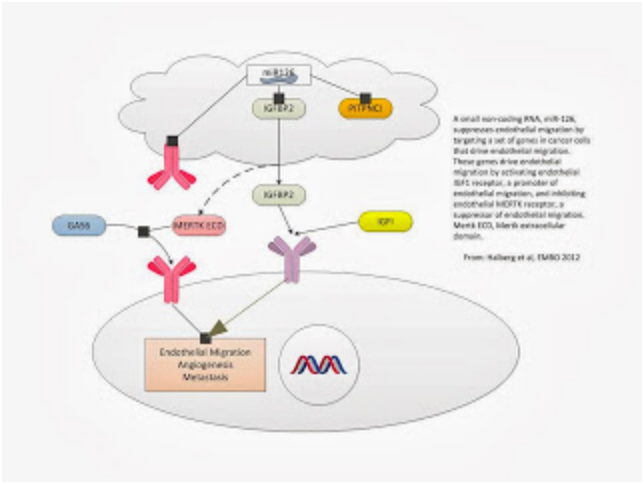
Let us consider a miRNA control using MER. As Halberg et al state:

Tumours require the establishment of vasculature for their increasing nutrient, energy, and oxygen requirements as well as for removal of metabolic waste. Cancer cells within a tumour generate such pathologic vasculature by recruiting endothelial cells to the tumour site. This is accomplished by secreting molecular factors, such as the well-known vascular endothelial growth factor (VEGF, into the extracellular space.

VEGF binding to VEGF receptors on endothelial cells results in the migration and recruitment of endothelial cells. In this way, proteins expressed by cancer cells can regulate the cellular and structural content of tumours—giving rise to continued tumour growth. Recent work has revealed a major role for another class of genes— known as small non-coding RNAs (microRNAs)—in the regulation of endothelial recruitment and tumour angiogenesis.

One member of this family (miR-126) was recently found to inhibit endothelial recruitment by suppressing a set of cancer genes that activate endothelial migration. In this way, a non-coding RNA expressed by cancer cells could shape the tumour and metastatic microenvironment.

This is thus depicted below from the Halberg paper. Here we have two cells, the top cell is a cancer cell where miR126 is blocking IGBP2 and blocking the MERTK receptor which in turn would have blocked the entrance of GAS6. But since miR126 has blocked the blocker, we have excess GAS6. Thus we have a problem, namely the GAS6 "overproduction" is really a failure to block resulting from the cancer cell miR126 production.



It is critical always therefore to look across all paths, direct as well as epigenetic.

As Zhuang et al state:

Angiogenesis plays a crucial role during tumorigenesis and much progress has been recently made in elucidating the role of VEGF and other growth factors in the regulation of angiogenesis. Recently, microRNAs (miRNAs) have been shown to modulate a variety of physiological and pathological processes.

We identified a set of differentially expressed miRNAs in microvascular endothelial cells co-cultured with tumour cells. Unexpectedly, most miRNAs were derived from tumour cells, packaged into microvesicles (MVs), and then directly delivered to endothelial cells.

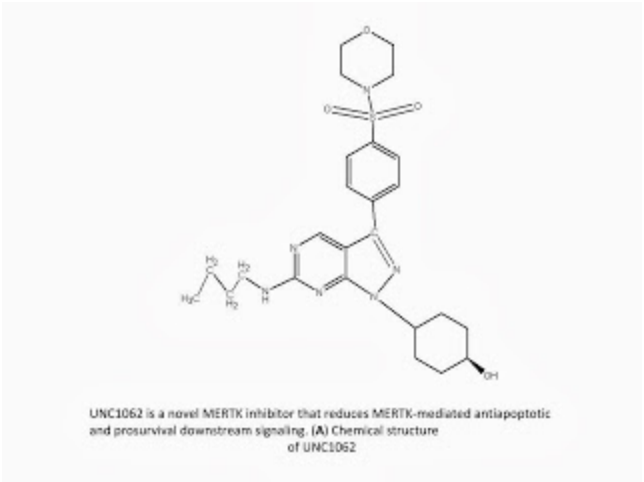
Among these miRNAs, we focused on miR-9 due to the strong morphological changes induced in cultured endothelial cells. We found that exogenous miR-9 effectively reduced SOCS5 levels, leading to activated JAK-STAT pathway. This signalling cascade promoted endothelial cell migration and tumour angiogenesis.

Remarkably, administration of anti-miR-9 or JAK inhibitors suppressed MV-induced cell migration in vitro and decreased tumour burden in vivo. Collectively, these observations suggest that tumour-secreted miRNAs participate in intercellular communication and function as a novel pro-angiogenic mechanism.

1.4 INHIBITORS

Inhibitors of pathways are being developed at a rapid rate. Knowing the pathway and molecular structure of the receptors it is somewhat readily possible to develop a strong inhibitor, a molecule that interferes with the normal ligand.

Schlegel et al have developed and tested an inhibitor of the MERTK receptor and it is shown below.



UNC1062 is a novel MERTK inhibitor that reduces MERTK-mediated antiapoptotic and prosurvival downstream signaling. (A) Chemical structure of UNC1062

Schlegel et al characterize this molecule as follows:

A novel MERTK tyrosine kinase inhibitor, UNC1062, inhibits MERTK mediated signaling, promotes apoptosis, and inhibits colony formation in melanoma cells. While activating mutations in BRAF and NRAS occur in melanoma at rates of 41% and 18%, respectively, lower mutation frequency or gene amplifications in other signaling molecules, such as RTKs, can also contribute to melanoma pathogenesis.

UNC1062 was developed as a MERTK-selective tyrosine kinase inhibitor. Its structure is based on a previously published pyrazolopyrimidine scaffold, and it has an improved affinity and specificity profile compared with its parent compound, UNC569 .

UNC1062 potently inhibits MERTK kinase activity in vitro and exhibits specificity within the TAM family. Treatment of HMCB and G361 cells with increasing concentrations of UNC1062 resulted in a potent dose-dependent reduction in MERTK phosphorylation

In the work of Verma et al they present an interesting collection of molecules which exhibit inhibitor characteristics (see their Figure 2). This is an expansion of what Schlegel et al have presented.

Again from Schlegel et al we have:

MAPK/ERK and PI3K/AKT are 2 of the most frequently dysregulated pathways in melanoma. These 2 pathways not only play a role in melanoma development and progression, but are also involved in primary and secondary resistance to BRAF inhibitors.

The observation that MERTK signals via both pathways, as well as through others whose roles in melanoma biology are currently unclear (e.g., STAT6), not only highlights the complex regulation of these pathways by membrane receptors, such as MERTK, but may also provide a therapeutic advantage, since targeting MERTK may disrupt signaling in multiple pathways.

These observations and the data presented here suggest that MERTK-targeted therapies could potentially be considered for patients, irrespective of BRAF and NRAS status and/or prior treatment with BRAF inhibitors.

The latter observation is of possible significant merit. Namely the MERTK targeting allows for alternative pathway blocking, namely doing so at the source of pathway activation.

1.5 OBSERVATIONS

We conclude with some general and specific observations. This work by Schlegel et al is of significant importance for reasons already indicated.

1. **MERTK presents an attractive target for metastatic diseases.**

To best summarize, we use the words directly from the paper. Schlegel et al conclude:

We believe this work has led to several novel insights.

First, MERTK expression is significantly elevated in distant metastatic tumors compared with primary melanomas.

Second, MERTK is overexpressed in approximately half of melanoma cell lines, irrespective of BRAF and NRAS status, and is an active receptor.

Third, targeting MERTK suppresses prosurvival pathways such as STAT6, AKT, and ERK1/2.

Fourth, targeting MERTK suppresses colony-forming potential and migration.

And fifth, targeting MERTK in vivo retards tumor growth in a human melanoma xenograft model.

The finding that MERTK expression is highest in distant metastatic melanomas compared with primary melanomas and the roles of MERTK in colony formation, migration, and invasion suggest that MERTK plays a role in the progression of primary melanomas and the development of distant metastases.

Similar to the observations in this report, the migratory nature of glioblastoma cells could be reduced by MERTK inhibition with either shRNA knockdown or a MERTK monoclonal antibody, suggesting that increased MERTK expression may contribute to outgrowth of the metastatic tumor.

2. **MER and other TAM receptors show significant impact across broad areas of cancer activity.**

Now Verma et al present an interesting summary table as show below which recounts what cancer types are also upregulated TAM pathways. The breath of such upregulation is significant. It also may present significant opportunities for blockage molecules, namely inhibitors of the total pathway.

Cancer type	Upregulation of Axl/Mer/Gas
Acute leukemia (ALL, AML)	Axl, Mer
Astrocytoma	Axl, Mer, Gas 6
Breast cancer	Axl, Mer, Gas 6
Colorectal carcinoma	Axl
Esophageal adenocarcinoma	Axl
Gastrointestinal stromal tumors	Axl
Gastric cancer	Axl, Mer, Gas 6
Hepatocellular carcinoma	Axl
Kaposi sarcoma	Axl
Lung cancer	Axl
Mantle cell lymphoma	Mer
Melanoma	Axl, Mer
Ovarian cancer	Axl, Gas 6
Osteosarcoma	Axl
Pancreatic ductal adenocarcinoma	Axl, Gas 6
Renal cell carcinoma	Axl, Gas 6
Prostate cancer	Axl, Mer
Thyroid cancer	Axl, Gas 6
Uterine endometrial cancer	Axl, Gas 6

3. **GAS6 Inhibition on MERTK by inhibitors is an attractive approach to metastatic melanoma**

Developing receptor inhibitors is a powerful approach to controlling metastatic growth and proliferation.

As Verma et al state:

A potential ability of sAxl to serve as a natural antagonist of Gas 6 could have clinical relevance. Similarly, the membrane-bound Mer protein is cleaved in the extracellular domain via a metalloproteinase (38). Further studies are needed to establish sAxl and sMer as important biomarkers for correlation with disease stage and predicting prognosis.

As Segal et al state:

A subset of genes, including the small monomeric GTPase RABB33, the proto-oncogene MERTK, the glycopeptide hormone STC1, and the neuropeptide GAL were shown to discriminate CCS/MSP from both STS and melanoma.

We further surveyed specific genes of interest and found melanoma differentiation antigens TYRP1, TYRP2/DCT, and MART-1 to be expressed at varying levels in the CCS/MSP specimens. PMEL17 was most consistently expressed in all four tumors in a similar distribution to that of MITF. Interestingly, SOX10, which induces MITF expression, was expressed in all CCS/MSP and most melanoma specimens

Thus it appears that this approach and ones like it are useful for thorough examination as attractive and effective means of metastatic control and management.

However there is still a long way from this point to approved therapeutics.

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Labels: Cancer

WEDNESDAY, MAY 15, 2013

POWER LINES AND LEUKEMIA

There has been an ongoing debate as to high power lines and cancer, especially leukemia amongst children. A recent study from France alleges a correlation, apparently without causation.

The study in BJC states:

The present study, free from any participation bias, supports the previous international findings of an increase in AL incidence close to VHV-HVOL. In order to investigate for a potential role of ELF-MF in the results, ELF-MF at the residences close to HVOL are to be estimated, using models based on the annual current loads and local characteristics of the lines.

Increased odds ratios (ORs) were observed for AL occurrence and living within 50m of a VHV-HVOL (OR¼1.7 (0.9–3.6)). In contrast, there was no association with living beyond that distance from a VHV-HVOL or within 50m of a HV-HVOL....

In conclusion, the present study has generated additional findings, based on a recent nationwide unselected population-based study, that support the hypothesis that living o50m from a 225 or 400 kV HVOL may be associated with an increased incidence of childhood AL. No increase in risk was observed further from those lines and no increase in childhood AL risk was detected within 50m of the 63–150 kV HVOL. Model-based estimates of ELF-MF exposures will be used to investigate for potential involvement of ELF-MF in the observed association.

It does leave one wondering what the cause is. One is always concerned about correlation and causation. Especially here.
Labels: Cancer

MONDAY, MAY 13, 2013

BOWMAN V MONSANTO

The US Supreme Court today decided Bowman v Monsanto in the benefit to Monsanto. It stated:

Held: Patent exhaustion does not permit a farmer to reproduce patented seeds through planting and harvesting without the patent holder's permission.

(a) Under the patent exhaustion doctrine, "the initial authorized sale of a patented article terminates all patent rights to that item," Quanta Computer, Inc. v. LG Electronics, Inc., 553 U. S. 617, 625, and confers on the purchaser, or any subsequent owner, "the right to use [or] sell" the thing as he sees fit, United States v. Univis Lens Co., 316 U. S. 241, 249–250. However, the doctrine restricts the patentee's rights only as to the "particular article" sold, id., at 251; it leaves untouched the patentee's ability to prevent a buyer from making new copies of the patented item. By planting and harvesting Monsanto'spatented seeds, Bowman made additional copies of Monsanto's patented invention, and his conduct thus falls outside the protections of patent exhaustion. Were this otherwise, Monsanto's patent would provide scant benefit. After Monsanto sold its first seed, other seed companies could produce the patented seed to compete with Monsanto, and farmers would need to buy seed only once.

(b) Bowman argues that exhaustion should apply here because he is using seeds in the normal way farmers do, and thus allowing Monsanto to interfere with that use would create an impermissible exception to the exhaustion doctrine for patented seeds. But it is really Bowman who is asking for an exception to the well-settled rule that exhaustion does not extend to the right to make new copies of the patented item. If Bowman was granted that exception, patents on seeds would retain little value. Further, applying the normal rule will allow farmers to make effective use of patented seeds. Bowman, who purchased seeds intended for consumption, stands in a peculiarly poor position to argue that he cannot make effective use of his soybeans. Bowman conceded that he knew of no other farmer who planted soybeans bought from a grain elevator. In the more ordinary case, when a farmer purchases Roundup Ready seed from Monsanto or an affiliate, he will be able to plant it in accordance with Monsanto's license to make one crop.

The issue is simply that Monsanto developed a seed protecting itself against Roundup. However when corn is made from the seed, it is made by cross fertilizing naturally with plants like itself

and others. Nature does the mixing. Bowman took the F1 seed, namely the first cross, and planted it. He then treated it with Roundup killing off the plants without the gene protection and selecting the good genes. The Court then says by this ruling that you may genetically engineer something, and under the old interpretation you protected the something you engineered, via vegetative propagation. But now it protects against cross propagation by fertilizing. This is a dramatic extension of plant patents. The old law allowed you to patent a purple flower. You then propagated it by cuttings and it was still yours. However if you used it to cross with another flower the resulting plants were yours. Perhaps no longer!

Does that mean I need the Patent basis for every plant I use, and for how many generations. This decision creates a real mess. It is a shame out Judges have no knowledge of Biology.
Labels: Law

ANOTHER USE OF PSA TESTS

In a just released paper the authors note that the PSA levels of a man in his 40s are a strong determinant of whether he will come down with PCa.

The paper states:

Measurement of PSA concentration in early midlife can identify a small group of men at increased risk of prostate cancer metastasis several decades later. Careful surveillance is warranted in these men. Given existing data on the risk of death by PSA concentration at age 60, these results suggest that three lifetime PSA tests (mid to late 40s, early 50s, and 60) are probably sufficient for at least half of men.

Specifically they note:

In an earlier paper, we showed that PSA concentration at age 60 had a strong association with the risk of death from prostate cancer by age 85 (AUC 0.90), with extremely low risk (≤0.2%) in men with PSA concentration below the median (≤1.0 µg/L). Taken together with our current data, this suggests a simple algorithm for prostate screening. All men with a reasonable life expectancy could be invited for PSA screening in their mid to late 40s. Men with a PSA concentration <1 .0="">µg/L would be advised to return for screening in their early 50s and then again at age 60, whereas men with PSA ≥1.0 µg/L would return for more frequent screening, with literature suggesting repeat tests every two or four years.

The choice of 1.0 µg/L as a tentative threshold might vary according to preference. At age 60, men with PSA at median or lower—that is, ≤1.0 µg/L (or possibly below the highest quarter, ≤2.0 µg/L, depending on preference)—would then be exempted from further screening; men with a higher concentration would continue to undergo screening until around 70.1

The ROC for this type of test was lacking but survival data was present. The lowering of the age to 40 and the PSA level less than 1 till 60 is interesting and worth following.

Labels: Cancer

ACADEMIC COSTS

As by now we all know the costs of College education has exploded beyond any reasonable level. In the NY Times today a left wing academic presents a self justifying demand that the Government should spend more on College support, not less.

This economist states:

Some wonder how the American ideal of equality of opportunity has eroded so much. The way we finance higher education provides part of the answer. Student debt has become an integral part of the story of American inequality. Robust higher education, with healthy public support, was once the linchpin in a system that promised opportunity for dedicated students of any means. We now have a pay-to-play, winner-take-all game where the wealthiest are assured a spot, and the rest are compelled to take a gamble on huge debts, with no guarantee of a payoff.

Even if compassion isn't a factor — even if we focus just on recovery now and growth and innovation tomorrow — we must do something about student debt. Those concerned about the damage America's growing divide is doing to our ideals and our moral character should put student debt at the top of any reform agenda.

Now one must remember that he is at Columbia, and that Columbia has always been a bastion of socialist and communist sympathizers who also have in my experience harbored abject hatred for Catholics and the like, as demonstrated in my rejection for being a Catholic in 1960. Not that I still remember it, just like yesterday! Still have the letter and all. Again MIT had no problem.

The real problem is two fold:

1. Costs: Consider what it costs to educate a class. Let us do a simple example. Sort of back of the envelope. Assume a class has say 30 students. Let us assume the average Prof teaches two of these a semester, I know some big whigs like the author of the piece may be exempt, but let us look at the typical schlub. Now assume the typical student take 5 of these courses and thus a faculty member supports 2 of them and this means 2.5 faculty members are the cost of the classes. Let us assume we pay them $150,000. so the costs per 30 students is $375,000 per year! Now divide by 30, and that is a cost for the teacher of $12,000 per year. Use 100% overhead, not unrealistic in a service business, especially economics, and you get the total cost per student in say economics of $24,000 per year. However the charge is $48,000! Whoops, where did it double? Administration and excess building overhead. Why, the Government supports and in some cases demands it. So here we have another economist who seems to be ignorant of the old adage, profit equals revenue less costs.

Now there are other economists who also fail to examine the numbers. For example Becker states:

The growth in tuition is not explained by any conspiracy theory, but mainly by increases in the cost of producing college education. Professors and other teachers are the principal input in colleges, so that the cost of these teachers is an important determinant of the cost of producing

education. College teachers are well educated since they almost always have Masters degrees, and at the better colleges and universities they are very likely to have PhDs or similar advanced degrees.

Colleges have to compete for highly educated persons against employers in both the private and public sectors. Since after 1980 earnings of highly educated persons has risen rapidly in these other sectors, colleges have had to pay a lot more for their faculties and administrative staffs. The greatly increased pay of faculty has substantially raised college costs, which in part have been passed on to students through higher tuition and other fees.

This analysis also explains why tuition has grown most rapidly at 4-year private colleges and other elite schools. These schools tend to have faculties that are considered the most skilled and productive, and they invariably have PhDs or other advanced degrees. Since the rise in earnings in recent decades has been greatest for the most educated individuals, the costs of more elite colleges and universities have risen faster than that of other schools. They too have passed through to students some of these much greater costs via much higher tuition.

In my opinion what he says is total nonsense. It was necessary to get great engineering Profs even in the 50s. It is not the salaries. It is the overhead. If one were to make a statement like this then one must be able to have a basis. I have seen the numbers and the costs. It is the cost of all these new Deans, the new buildings with their staff and maintenance. The massive growth in infrastructure, human and inert, is what is the driver. College Presidents are recruited for their ability to raise money while not really bothering the faculty. The problem with raising new funds for buildings is that these monsters need care and upkeep. They need "management" and they consume resources that are just added to the tuition burden. For the most part no College President has a clue about this until one of the "cost centers" economically explodes.

It is a shame that the economists who are justifying these increases have not a clue from whence they come. Perhaps that is why I have never seen an economist run a real company. Just our Government.

2. Majors: Let us face it, one really goes to college to get a job. Employed, the fact that you now have a skill that someone can use to make money. If you are a philosophy major, a fine arts major, a French Literature major, perhaps you cannot find a job. That is your problem. Should you be educated in that fact? Not really, it becomes one of those things you learn as part of life. Should you be allowed to gamble with other people's money when the odds are stacked against you? I would not think so. Then why give aid to those majors which are unemployable. Give tuition support to Engineering students, not art students. Give it to Computer Science and Bio students, not French Literature. Want to major in philosophy, get a wealth set of parents and live off of them. Not us.

Thus this economist has missed all of the key issues. The problem is that we allow these things to happen.
Labels: Academy

THURSDAY, MAY 9, 2013

CAVEAT POLITICS

Science details the intent of Congress to institute a Science Laureate for the United States. Beware what one asks for. It would undeniably be a "politically correct" person whose contributions may all too often be questioned.

The magazine states:

"The U.S. Science Laureate will be a national role model who can encourage students to learn more about the sciences," Hirono said in the statement. "By elevating great American scientific communicators, we can empower students - especially girls and minorities - to get excited about science."

What gets people excited by science is all too often a visceral reaction to things not readily reproduced. It is that stumble across a set of books in a library, some presentation they get hauled into, or emptying out trash cans.

The last places to award anything is the Government. Just look at the Peace Prizes, non-peer related awards. Even Nobel Prizes have political content, yet generally driven by some explainable notion. But a Science Laureate awarded by the Government? People would wonder what favor was called in for that award. In a sense we are becoming more like pre-revolution France by awarding titles and pensions to anyone by the Government.

For example they want the person to:

introduced legislation that would empower the president to select a "nationally renowned expert" who would "travel around the country to inspire future scientists,"

Now any scientist worth their salt will not be taking two years off at the peak of their career to talk to High School students in the backwaters of the country. It makes no sense. With all the problems we have one wonders why this is even considered.
Labels: Politics

SUNDAY, MAY 5, 2013

THE PATIENT AND THE FACTS

There is an interesting piece today in the NY Times by a Resident at one of the Harvard Teaching Hospitals. I guess it has become fashionable for residents to now discuss the insight they have obtained halfway through their training process. The responses are more telling than the piece, and they are worth a read. Namely the consensus is the person is quite naive. Why, because they felt that as an Intern they managed to convince Resident s and Attending to change a protocol for some terminal patient. Was that good or bad? Well it all depends.

Statistics are often used, by physicians and patients, to justify actions. Take some of the recent

melanoma therapeutics. Fifty percent of the patients last an additional six months. Yet some 20% keep going on. Thus if you are one who has the choice for the drug, what do you bet on? Frankly the bet only applies to a large cohort, and never to a single patient. You just do not know, what will happen will happen. There is always a bit of fatalism.

However people like Kaplan managed to change the survival for Hodgkin's disease, It went from 0% to almost 90% with radiation and multi drug cocktails. Yet along the way there were many failures and distressed families. Yet as a species we learned and made progress.

All too often it is the family who demands all life extending actions, often at massive costs and incurring great distress for the patient. This is a difficult issue, it involves the ultimate demise of all of us and all too often our own demise is denied, for good reason.

As the author states:

And yet studies have shown that patients almost universally prefer to be told the truth. If physicians cannot deliver the hard facts, not only do they deprive their patients of crucial information, but they also delay the conversation about introducing palliative care.

Many times the physician just does not know. Certain malignancies, such as prostate cancer, may be indolent or aggressive. The physician really does not know, at least at this time. The "truth" is that one just does not know. On the other hand a Stage IV melanoma with brain mets may in almost all cases be terminal. Should the patient be told, yes, and should the family, yes. Is there much to do about it, possibly, but frankly what may be done will be to add to a data base of understanding ant note necessarily be curative.

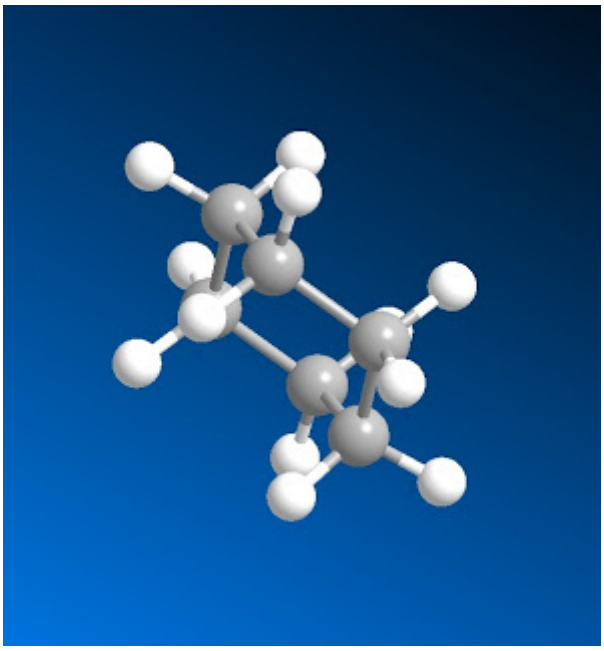
The author concludes:

The patient's condition got worse. The tumor grew to the point that we had to put in a tube to deflate her intestines. She developed clots in her lungs, but we couldn't treat them with blood thinners because she was already bleeding internally. She had to get all of her medications and nutrition through an I.V. It was clear to the team that the more humane thing to do would be to focus on her symptoms and keep her comfortable rather than trying to extend her life. But there was nothing we could do to uproot the horror of irrational optimism that had spread through her body like a cancer uncontrollable.

In the case of colon cancer mets to the liver one sees the ascites expanding the abdomen, the severe discomfort, and the care is at best palliative. This was know for centuries, and the author seems to be grasping this for the very first time. There is the perception that the physician must treat each new symptom of the terminal illness rather than just making the patient as comfortable as possible. That is why the most insight to this issue resides in the commentaries when discussing the lack of experience of the author.
Labels: Cancer

THURSDAY, MAY 2, 2013

ORGANIC CHEMISTRY AND THE 21ST CENTURY



On PLOS Blogs there is an interesting piece on Organic Chemistry and Medicine. The author remarks:

I looked up Friedel-Crafts alkylation, a phrase hovering in my distant memory, and soon discovered that this is the addition of a carbon-containing group to a benzene ring. According to the textbook, "In Friedel-Crafts alkylation, the electrophile is typically a carbonium ion. It, too, is formed in an acid-base equilibrium, this time in the Lewis sense," followed by several reactions.

"What has this to do with setting a bone, removing a spleen, delivering a baby, or treating cancer?" I bellowed to my husband.

"The human body is a giant chemistry set that's making and breaking covalent bonds," he answered, obviously brainwashed. So I asked the same of the good Dr. Fowler.

"If anything, a molecular knowledge is more important for physicians and people going into health care now than it ever was. My dermatologist said, 'I never use organic!' But skin cancer is a perfect example of photochemistry of the skin," Fowler said.

Having taken this back in 1962, a decade or so before the author, and retaking it a year ago, fifty years later, I saw the difference up to the point where the mass of memorized reactions started again, halfway through the second semester. Molecular knowledge is important, just look at the hydrogen bond and DNA. But it is not organic that one needs for melanoma but pathways and reaction rates, stuff we never had fifty years ago.

The problem with Organic is that it the revenge by all those 19th century German Chemists, memorizing reactions which any good physician or cancer researcher may look up but not have memorized.
Labels: Education

THE SALES TAX ISSUE

The current issue about placing sales tax requirements on Internet sales will have significant unintended consequences. The loss of such a tax is a true loss to the state involved but the costs are much more than just the tax.

Back a couple of decades ago I saw the complexity up close when we started operating cellular systems here in the States. I had to have complex tax schedules for each state and city and then apply them in a complex manner. The costs associated with that process are quite significant.

Namely":

1. You must maintain adequate detailed and current tax tables for thousands of various municipalities, not just 50 states.

2. You have to collect and distribute the taxes.

3. You have to account for and audit the process.

4. You have to file local and state forms ad infinitum.

5. You have to deal with complex annual state and local audits in locations which are often near impossible to get to.

By the time you add the staff, the software, the system integration, the accountants, the lawyers, and so forth it may easily increase costs by 5-8% on top of taxes from 4-14%. That is a possible 22% increase to the consumer.

Now I heard some lobbyist from the Retail Industry say that you just get the software and there are no costs. Frankly the woman was clueless, truly clueless. Now that Internet sales are a significant part of our economy just watch what this does!
Labels: Government

WEDNESDAY, MAY 1, 2013

HAPPY MAY DAY

Spring is finally here, despite the early morning frost.

So enjoy what appears to be one of the best Springs in a few years.

And Happy May Day.

Labels: Commentary

TUESDAY, APRIL 30, 2013

PROSTATE CANCER AND SNPS

SNPs are single nucleotide polymorphisms, simple the single base has been replaces by another somewhere in the DNA and this results in a higher predilection to PCa. In a recent Nature Genetics paper the authors state:

More than 70 prostate cancer susceptibility loci, explaining ~30% of the familial risk for this disease, have now been identified. On the basis of combined risks conferred by the new and previously known risk loci, the top 1% of the risk distribution has a 4.7-fold higher risk than the average of the population being profiled. These results will facilitate population risk stratification for clinical studies.

These are germ line mutations and given the germ-line predisposition ones risk is increased substantially. They continue:

Epidemiological studies provide strong evidence for genetic predisposition to prostate cancer. Most susceptibility loci identified thus far are common, low-penetrance variants found through genome-wide association studies. Fifty-four loci have been identified so far.

Finally they state:

With the identification of these new loci, 77 susceptibility loci for prostate cancer have now been identified. On the basis of an overall twofold familial relative risk for the first-degree relatives of prostate cancer cases and on the assumption that SNPs combine multiplicatively, the new loci reported here, together with those already known, explain approximately 30% of the familial risk of prostate cancer. Taking into consideration these SNPs and this risk model, the top 1% of men in the highest risk stratum have a 4.7-fold greater risk relative to the population average, and the top 10% of men have a 2.7-fold greater risk.

What does this mean for health care. Is is prognostic and if so why? One of the problems with SNPs is that the pathways they control are not clear. SNPs just sit there and we know that if they are there then the risk is greater. The lingering question is still what do they really do?
Labels: Cancer

TUESDAY, APRIL 30, 2013

THE ENLIGHTENMENT

The Enlightenment by Pagden is a compelling book. It is not a history, it is not a work of comparative philosophy, and it is not a work of political theory. It is a view of the enlightenment by topics and through the focus of these topics it draws in the principal players in the Enlightenment again and again, intertwining their views in an ever more complex web. Each time Pagden does so he addresses another set of issues and often brings current affairs to the fore as well.

The core of the Enlightenment was the focus on reason and its tremendous powers and the total abhorrence of institutional revealed religion. Faith conflicted with reason. The Enlightenment totally rejected the Scholastics and their use of reason and logic. In a strange way reason dominated even the experimental efforts that surrounded the Enlightenment figures. The author states in his Preface that reason was not overthrowing the passions, but that the claims of reason were to be rejected as well as accepted. The author does also address the concern of Eurocentrism and the placing of the Enlightenment on a secondary state, a place where he believes it is not to be.

The author begins with an attempt to define the Enlightenment, or "Enlightenment" as process. To be enlightened meant being critical and for this capability it meant the use of reason (p 21). He provides a remark from Kant that it is but a few men, since most men and all women are but sheep, which use reason. For others if they can pay others for such things as what to eat, what is moral, then there is no need to think, reason. Yet amidst the mass of historical references the definition of either Enlightenment or the Enlightenment still is elusive. It is built upon reason, but it also appears to be a period based upon a revolt, a revolt from the way things were done, and especially the way one held religious belief.

Chapter 1 presents a somewhat historical context for the beginning of the Enlightenment. On p 33 there is a discussion of the end of the Thirty Years War, with the Peace of Westphalia. This event, the War, still hangs over much of central Europe. Many of the political divisions were religious divisions, and these divisions set the stage for conflicts for centuries to come.

Chapter 2 describes the change which the Enlightenment brought. It also presents one of the most convolved sentences I have ever read. On p 66 the author states:

"The Enlightenment, and in particular that portion which I am concerned, was in part, as we shall now see, and attempt to recover something of this vision of a unified and essentially benign humanity, of a potentially cosmopolitan world, without also being obliged to accept the theologians' claim that this could only make sense as part of the larger plan of a well-meaning, if deeply inscrutable, deity."

There are eight commas. But the sentence does accurately describe exactly what the author intends it to be. Yet it is also exemplary of style, which at time may be a bit daunting for the reader.

On p 69 the author provides insight to the debate that lurks below the surface between Hobbes and Rousseau. For Hobbes mankind was fundamentally and aggressive animal and needed the Leviathan to control them. For Rousseau mankind was originally pristine pure and was thereafter corrupted. Both men reached their conclusions by reason devoid of any scientific evidence or facts. That in a sense was the fatal flaw of the Enlightenment. It assumed the overwhelming power of reason as a sine qua non.

On p 77 there is a discussion of natural law and its deficiencies. The author states:

"The entire scholastic theory of moral and political life rested, as we have seen, on the idea that our basic understanding of the law of nature was made up of certain "innate ideas" or "innate senses".

Then on p 79 he addresses the assault by Locke on this principle by stating:

"Few historians of philosophy have paid much attention to this length onslaught on the notion that there might exist no "innate Principles" or Innate Characters of the Mind which are to be Principles of Knowledge" beyond "a desire of Happiness and aversion of Pain".

There was thus on the one hand a rejection of innate laws of nature, one that could be reasoned, and the application of reason to all existence.

Chapter 3 is a Chapter regarding a world without God. To some sense it is the Enlightenments fracturing of the past centuries and an attempt to break loose. He contends that man and the result of the Enlightenment can adapt to a civil society san religion. As he says on p 109:

"If it appears to do so now, that is only because of the fear that the Church has, over the centuries, inculcated in it."

The author seems to align himself very much with those iconoclasts of the Enlightenment as one progress through this chapter.

He continues in Chapter 7 with a discussion of laws. On the one hand we have Montesquieu, and on the other hand we have Robespierre. As he states on p 309:

"Furthermore, political virtue was conceived of as a sentiment and not, as Montesquieu put it, "the consequence of knowledge". True, the virtuous citizens had to be able to distinguish good laws from bad, but they did not require any special knowledge to do that; they did not need to understand precisely what a republic actually was, or how its institutions operated, or did they – as the ancients would, in fact, have assumed that they did – have to be actively involved in it, in order to love it; for the "last man in the state can have this sentiment as can the first"."

There are times when I had difficulty discerning the author from his subjects. This sentence gave me pause. If citizens were to distinguish good laws from bad, how much did they truly have to know? Does this not apply especially to any republic, where representation in a legislative body reflects to some degree the public? I believe the author has some point to be made here but they are somewhat poorly extracted from the sources.

On p 321-322 the authors delves into the Great Society of Mankind by an interesting allusion to foreign aid. To him it would have been an unacceptable concept in the Enlightenment but as an act consistent with Enlightenment thinking it would be congruent.

In his Conclusions he discusses the enemies of the Enlightenment. The discussion is generally in line with modern thinking but there appear to be several divergences. On p 395 there is a discussion of Communitarianism. The author states that Communitarians have much in common

with 19th Century nationalists. He discusses the source as Hegelian in part. But he sees the Communitarians as enemies of Enlightenment thinking. This discussion is very interesting and worth a read several times.

He again returns to the Thirty Years War as that seminal event which in a manner kicked off the Enlightenment. For most Americans this is an event at best hidden in the dark past of the World History book. However for a European, this is a dividing line between the past and the present. It was a war of the people, a war of faith, not a war of territory. Even today one feels it when dealing with Poland, Sweden, Austria, Germany, France and so forth.

But the Enlightenment is also a collection of characters. The author brings them to life in his style of topical discussion. Voltaire becomes almost a current day Cable TV commentator, irascible, while at the same time amassing a personal fortune. He went after the Catholic Church, in the guise of attacking religion, but praised the British for their religious tolerance while at the same time the British were massacring the Irish for their faith. At the other extreme he discusses de Tocqueville and his view of the Americas while not discussing the de Tocqueville writing on Ireland the French Revolution.

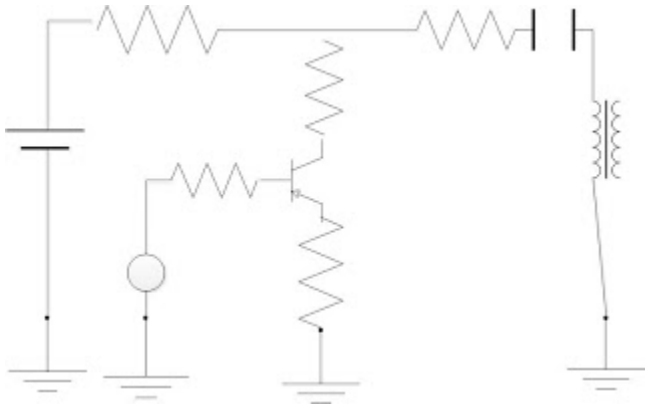
There is a wealth of books on the Enlightenment and those of Gay, Cassirer and Israel are but three that come to mind. This book is not in that class. The former are historical works that flow in some linear manner; either temporally of thematically. This book is kaleidoscopic in style, with flashes of insight coming and going and then within those flashes incorporating vignettes of the main characters who are players on the stage of the Enlightenment. This is not a text of the type of Skinner who may include all players so that the ones that we see so often are placed within an historical context.

This book, in summary, is a delight to read, albeit not in a linear fashion. It has brilliant flashes of insight and explanation, yet there are times when one yells back at the words in total disagreement. This book draws out thinking in some depth about the Enlightenment more than a linear historical work. It was a delight to read.

However it does pose the question: who is the Voltaire of today? Is it some "Talk Radio personality, some Cable "New" commentator? They are irreverent, attacking the "system". Then again one may ask who is Robespierre?
Labels: Books

MONDAY, APRIL 29, 2013

ECONOMICS AND CIRCUIT DESIGN



One of the things an engineer does when designing a circuit is to think through what goes up, and what goes down.

Now there are several ways of doing this. The young engineer writes out all the equations and then begins to solve them. The engineer was educated in the laws of electromagnetic theory and its applications to circuits and then understanding these laws, which are demonstrable in the real world since it is from this world that they came, the engineer determines the performance of the circuit. The experienced engineer who has done this for many years can intuit the performance by saying this goes up and this then goes down.

Now economists like to think that they too have theories based upon fact. Don't ever let them trick you on this one, they are based upon belief. A great example is in the NY Times today from the Gnome from the South, who states:

Why did spending plunge? Mainly because of a burst housing bubble and an overhang of private-sector debt — but if you ask me, people talk too much about what went wrong during the boom years and not enough about what we should be doing now. For no matter how lurid the excesses of the past, there's no good reason that we should pay for them with year after year of mass unemployment.

So what could we do to reduce unemployment? The answer is, this is a time for above-normal government spending, to sustain the economy until the private sector is willing to spend again. The crucial point is that under current conditions, the government is not, repeat not, in competition with the private sector. Government spending doesn't divert resources away from private uses; it puts unemployed resources to work. Government borrowing doesn't crowd out private investment; it mobilizes funds that would otherwise go unused.

Just read through this and you can see the belief set. For example, does Government spending take money from private use or not? Well not rally but somewhat, yet again ....

The answer is it all depends, it is not black and white. People respond to beliefs, not to facts. I call this the Extended Rowe Conjecture. Namely there is a battle between belief and fact. Belief

often wins. If the Government increases corporate taxes to pay for its excess, or even alludes to the potential, companies move and respond so as to counter this.

Also there is a systemic loss from the labor pool. Tens of millions of jobs have just downright disappeared. Why? Outsourcing? Not really, we have become dramatically more productive, a fact that has been building for decades. This drives out human labor. It is inevitable. So should Government continue to pay these people in anticipation of a return. It is akin to Waiting for Godot. He will not come.

Government spending terrifies people. Why, because of the added regulatory burden, the costs to comply, and the list goes on. Furthermore it poses a greater risk of uncertainty.
Labels: Economics

FRIDAY, APRIL 26, 2013

WHY ARE ECONOMISTS SO NASTY?

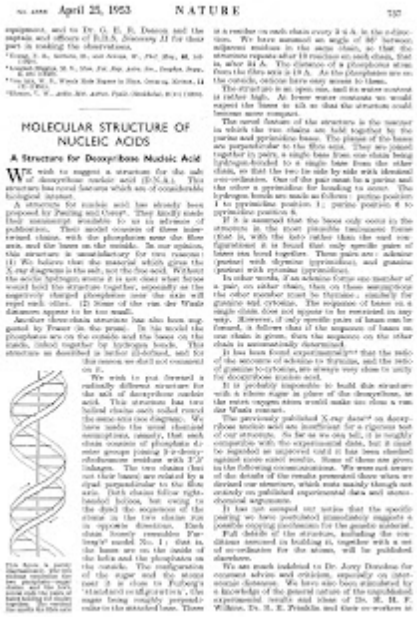
I have been following the Reinhart and Rogoff debate. Now I have done thousands of spread sheets over the years, more likely tens of thousands. Once I was interviewing a person as head of my M&A group in a start up and I was explaining something to him. He found an error in my Excel spread sheet and then told me. I hired him on the spot. For two reasons, first, he found the error and corrected it, and second, he told me, especially during an interview. Now he did go to IIT in India and he did have an MBA from Chicago. Neither did I hold against him. After all, I am told in India if you cannot get into IIT then you try MIT. It was sort of the Avis of high tech.

But still as I read some of the comments they are so vitriolic that one wonders if economics is no more than some religious cult. I have never seen such a battle over say the force balances on a three element truss! Maybe there is a "discussion" over the true function of PTEN on a cancer pathway but the way out is through experiment. It is not a belief set but a fact set.

Now this battle highlight several things about economists. First the left leaning ones are real nasty. Second, there are no facts behind the theory. Third, the Canadians are real nice.
Labels: Economics

THURSDAY, APRIL 25, 2013

HAPPY 60TH BIRTHDAY TO DNA



MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

Sixty years ago today Watson and Crick published their seminal paper on the structure and reproduction of DNA.

Molecular Structure of Deoxypentose Nucleic Acids

In such a short communications they managed to start a movement that has led to the understanding of so many things about the biology of life itself.

So Happy 60th!

Labels: Commentary

WEDNESDAY, APRIL 24, 2013

MORE THOUGHTS ON BELL LABS

The ***Idea Factory*** is a well written presentation of what happened in Bell Laboratories in its early and middle lifetime. The author has captured the view from within the Lab and has presented a history that is in many ways presented in a manner in which the Lab people would have wanted it presented. His conclusions however are subject to significant debate, if not being downright wrong.

I write this review having heard the author present his work in Madison, NJ to an audience almost totally filled with hundreds of former Labs staff and also as one who spent a great deal of time at the Labs from 1964 through 1972, while going back and forth to MIT, plus over fifty years in the industry.

The author presents the often told tales of Shockley and the transistor, Shannon and information theory, as well as all the management types who formed, directed, and molded the Lab like Kelley and others. Many of these people I knew firsthand and as any observer the view is all too often colored by one's position at the time.

The driving presumption of the author is best stated in his introduction where he says:

"Some contemporary thinkers would lead us to believe that twenty-first century innovation can only be accomplished by small groups of nimble profit seeking entrepreneurs working amid the frenzy of market competition. Those idea factories of the past, and perhaps their most gifted employees, have no lessons for those of us enmeshed in today's complex world. This is too simplistic. To consider what occurred at Bell Labs, to glimpse the inner workings of its invisible and now vanished "production lines" is to consider the possibilities of what large human organizations might accomplish."

This conclusion is frankly a significant over-reach, if not just out right wrong, since it is posited without any basis in fact contained within the book. The author never really looks at the many other parts of the Lab, the tens of thousands who worked on miniscule parts of large systems. The R&D group at Murray Hill was but a tiny part of an enterprise whose overall goal was to ensure the monopoly that AT&T had been granted by the Federal Government and to maximize the profit made in that monopoly.

To understand one must recognize that in the old Bell System profit was defined as a return on investment, meaning the invested plant. Revenue thus equaled expense, plus depreciation plus that profit construct; namely the company could charge whatever it wanted to subject to the regulators limited control. The game was thus to maximize profit, which in turn meant to maximize the invested plant, and not to be maximally efficient in a competitive sense, there was no competition. Understanding the ground rules of the old Bell System is essential to the understanding of Bell Labs. No other company, save perhaps the power utilities, functioned in such a manner. This was the basis of the world view of the Labs, a world of monopolistic control.

But the “creative destruction” of the free market did begin to surround the Labs. It surrounded the Labs in the areas in which the author appears paradoxically to make them most successful. Let me discuss just three examples.

Satellite Communications: The author speaks glowingly of Pierce and his vision of satellite communications. Yet Pierce wanted dozens of low orbit satellites, apparently driven by his desire to have low time delay for voice. He wrote a paper which appeared in Scientific American proselytizing the idea. Based upon that proposal, COMSAT was formed and capitalized based upon a need for this massive investment not only in space segment but also in the complex tracking earth stations. A few days after the COMSAT IPO Hal Rosen and his team at Hughes launched Syncom I, the first synchronous satellite. Within weeks they launched Syncom II. Synchronous satellites provided global coverage with only three satellites, not the dozens demanded by Pierce’s world view. COMSAT was then off with its own satellite, Intelsat 1 and its progeny using not Pierce, but Rosen. Somehow this minor fact is missing from the book.

Digital Switching: Fred Kappel was the Chairman of AT&T in the 60s during the time of the development of the first Electronic Switching System, the No 1 ESS. This system was developed by people such as Ray Ketchledge and others. They had deployed a computer based system, albeit still with analog mechanical switches called Fereeds. Fereeds were small mechanical switches that clicked and clacked. The Fereeds made the new computer elements be the dog still wagged by this old technological tail cross-connection technology. Kappel wanted an all-digital switch and the Labs kept putting him off. But at the time he had another card up his sleeve. AT&T also owned Bell Canada and their Bell Labs entity called Bell Northern Research. So off he went and got them to build the all-digital switch. The entity doing it became Northern Telecom, NORTEL. NORTEL subsequently became a major switch supplier of their new and better switches to the Operating Companies. Thus, in a true sense, Kappel used the entrepreneurial spirit of the Canadians to do what the mass of people at Bell Labs would not do.

The Internet: Now in the mid-1970s the ARPA net was in early development and some of the basic principles were evolving from Government, Academia, and a bunch of small start-up companies like Linkabit and BB&N. ARPA, the DOD advanced research arm had an office called IPTO and they wanted to expand the Internet more aggressively using the public telephone network. Yet since AT&T was a monopoly they somehow had to co-opt AT&T to agree. A first step was to go to a meeting at Murray Hill and seek their support. So off go a couple of folks from ARPA and in Murray Hill they met the standard Bell System meeting of a few dozen people. The senior person, a VP I was told, began to lecture them that if they wanted this accomplished just send them the money and they would deliver what they felt was the correct design. The ARPA folks walked away somewhat aghast and immediately reached the conclusion that they would develop what became the Internet, totally independent of AT&T. This was, in a sense, the final straw since it sowed, in my opinion, the seeds for AT&T's ultimate destruction, not the Judge Greene breakup.

The author, in my opinion, misses many other R&D entities which had a significant role in the evolution of technology, oftentimes well exceeding Bell Labs. Let me discuss just a few:

MIT Rad Lab: At the beginning of WW II Vannevar Bush set out to establish a center for R&D focusing on radar. Bell Labs had tried to capture this jewel but Bush wanted a more innovative and competitive center and as such he chose MIT and from that came the Rad Lab. The Rad Lab was composed of engineers, but they were drawn from many places and the best part was that when the war was over they went back to those many places. The Rad Lab designed radar but radar had the same elements as communications, and specifically digital communications. Thus from the Rad Lab came such innovations as the modem, designed by Jack Harrington, to interconnect signals from distributed sites. From the Rad Labs came rapidly effected engineering systems, and the terms system is critical, because the parts all worked together. From the Rad Labs came a set of book, the Rad Lab Series, which became the bible for engineers who entered the wireless world and the digital age. The Rad Lab was a petri dish that bred hundreds of engineers who went forth and created the core “startups” in the Cambridge 128 areas and also in Silicon Valley.

DoD Design Companies: It is well known that many of the transistor companies were driven by the demands of DOD. Also many of these same types of companies in Silicon Valley and in the 128 Corridor were driven by DOD money as well. Groups of engineers educated from the Rad Lab type entities of WW II came out and started small companies fed from the DOD demands in those days. It allowed for many bright engineers to experience the “startup” albeit at the Government trough.

This this book has strengths and weaknesses. Its strengths are:

1. A well written story of some of the key players in Bell Labs.

2. A well described evolution of the development of the management techniques.

3. An excellent discussion of some of the major personalities in the R&D world at the time.

Its weaknesses however should be considered when taking the author’s conclusions to heart. Namely:

1. This is truly a tale written from the perspective of Bell Labs. It totally fails to consider the competitors and thus when reaching his conclusion the author does so without any basis in fact. He totally ignores the weaknesses of such a system as Bell Labs and moreover he fails to consider the alternative entities such as the Rad Lab and its offshoots. In my opinion this is the major failing of this book. It would have been much more credible and useful if the author had looked at Bell Labs in the context of the total environment; the strengths and weaknesses and the competitors and alternative models of research.

2. The monopolistic structure of AT&T was a major driver for what people do and why. The issue of return on investment being the profit, and not revenue less expenses, is a true distortion of what is done and why. This idea of a world view is a formidable force. It molded what the Labs and AT&T did and why they did it. The author seems to be totally devoid of any notion of its import.

3. There were many failures at Bell Labs, and those failures were never truly perceived by those within the system, and it was this blind spot that in my opinion also led to its downfall. The author missed a great opportunity to follow up on this. Instead we see all these Herculean minds making great successes and yet the system collapses.

4. Bell Labs was enormous in size and scope at its high point. I had spent time at Holmdel, Whippany, Indian Hill, Andover and even a brief stint at the remains of West Street. Yet the focus is on Murray Hill and a small part of a small part. This is especially disturbing in light of the author's global conclusion which is reached without a single discussion of these areas. To do Bell Labs justice one must perforce covers these as well. The Pierce, Shockley and Shannon tales are told again and again, but the efforts of the hundreds of thousands of others over the decades are still silent. In the presentation by the author before a mostly former Ball Labs group it was clear that my observation on this point had substantial merit.

Overall there is a significant story to be told but this author does not accomplish it. In fact the author's statement denigrating the entrepreneur and the process of "creative destruction" is made without any attempt to understand the difference between a monopolistic structure and competitive markets. Perhaps if we had kept the old paradigm we would still have our black rotary dial phones.
Labels: Books, Telecom

HAVING A GRASP OF BASIC FACTS

In the book by Crawford, ***Captive Audience***, she develops the argument that the COMCAST and NBC merger was an example a writer who in my opinion had a good tale to tell but was ill equipped to do it.

This is a difficult book to review. Not because of some of its conclusions, which I am hearty agreement with based upon hands on experience, but because the author all too often steps well outside her area of expertise and opines on things which are just wrong.

Moreover this is one of those books on Amazon which has some sort of following. No sooner had I posted it then people started stating it was not a helpful review without comments, at least as yet. Now this review gores both oxes; the cable company and the clique who seem to follow what the author writes with religious zeal. It will interesting to see how these results evolve.

However her conclusions are of merit despite the confusion of her argument.

1. **"Cable Companies are bad"**. She has some very valid point here as she demonstrates through the vehicle of the Comcast and NBC merger. She argues that such a merger should never have happened. One could provide substantial grounds for preventing is, most on antitrust issues, but they were never truly approached by the current administrations. The reasons why is a tale unto itself.

2. **"Fiber is the only way."** Here I argue she is clearly wrong and is so since she does not understand the technology. Since this is a key point in her argument one wonders why she did not at least reach out to find better support and understanding.

3. **"Government is the best market regulator."** This is an extreme position which has mixed, at best, results. In fact it has been clear in the technology space that the Government is the worst regulator.

Let me address the above points and relate them to the text itself:

1. Wireless has substantially more capacity than the author understands.

2. The cost of fiber is dominated by local costs such as franchise acquisition, costs of pole attachments, and the delay costs of laying the fiber.

3. There exists a significant body of law the antitrust laws which can and should be used to manage the industry not just regulation.

4. Cable companies are monopolies for the most part and should be regulated as such.

Let me now provide some details contained within the book specifically supporting the above:

On p 78 the author speaks of the abandonment by Verizon of fiber deployment. Why did Verizon abandon its buildout? Frankly there are two. First there were the exploding legal costs and delays in getting local franchises. These were exasperated by the local cable companies but facilitated by the local towns who often did not understand the economics of competition, they just asked for more as they were advised by the incumbent cable operators. Second, and this is a critical element, was the success of wireless in expanding bandwidth efficiency. Namely with only a 1 bps/Hz a decade earlier they now were at almost 10 bps/Hz and they could see ultimately even another order of magnitude increase. This focus on wireless was most evident with the succession to the CEO position with the wireless head taking the helm. Thus it was to some degree a problem with the incumbent but it also was an understanding that the wireless alternative was more than viable.

On p 90 there is an interesting discussion regarding the "interstate access charges". In fact these were the interconnect fees. The author refers to the Prodigy effort, but such an effort was doomed from the start by the massive overhead put on it by IBM, yet at the same time they were facing the overhead of AT&T. The access charge issue is a simple one. There were local phone companies and long distance ones, at that time.

The local companies demanded and received a fee for interconnecting to the local company. Even though the local companies were separately paid by the customer, they were allowed by the FCC to impose this charge to third parties such as an AOL or Prodigy. Fortunately the FCC abandoned this stance. The author seems to have not fully understood this issue.

On p 95 the author tries to outline the history of on line capabilities using the AOL and Time Warner as an example. In fact it began in 1978 with Warner Cable and the QUBE system. This was the first two way cable system that allowed interaction and online purchasing. This Warner, and perforce Time Warner, had been developing this for almost two decades. In the early 1980s

Warner Cable developed the first “Electronic Shopping Mall” a two way video on demand d system in a joint venture between Warner, Bank of America and GTE, with Bell Atlantic and DEC participating. That effort collapsed when Warner ran into financial difficulties. Chase Bank and others did the same during the videotex period. The author appears to posit this sudden even with Time Warner and AOL when in reality there had been many trials, tests, and attempts.

On p 125 the author states that Edison invented the telegraph. What of Morse? Perhaps some fact checking of simple facts would help.

On p 129 and on the author refers to Sen Franken so many times one wonders why? The book was not written by Franken and based upon his public record he was both new and definitely not an expert in regulatory issues and technology. This continual referencing becomes a distraction.

On p 133 there is a discussion of the new channels being cash cows. However there is a very serious issue here. The cable companies bundle up packages of programs which they also own and demand that anyone providing one provide the full package and at premium prices. The consumer gets the full sports package and pays for it no matter if they have ever seen a single sports event. This is the major failing of the FCC and the FTC. Legally this is akin to bundling, a practice clearly prohibited by the antitrust laws. But to data the DoJ has never acted upon this, nor has the FTC.

On p 156 on the author delves into the cable versus wireless issue and here she is well out of her depth. It is a pity because this area is a significant one for possibilities. Let me first outline the wireless argument and then return to the text:

1. Wireless capacity can be measured by the number of bits per second, bps; it can deliver to a user.

2. The user demands bps depending on the application and the number of them the user may have. For example HDTV had been a bid user of bandwidth.

3. Now two things have occurred technically over the past ten years. First bandwidth efficiency, measured in bps/HZ, has increased from 1 bps/Hz to now 10 bps/Hz. Yet at the same time the data rate required for video has collapsed, going from 100 Mbps down to 4 Mbps. Thus supply, that is bps/Hz, has exceeded the demand, such as Mbps. Namely we can now easily use wireless for HDTV.

4. The acquisition of bandwidth by the wireless companies has continued and now provides almost universal service. Wireless does not require franchises or pole attachments, and can be delivered in a short order.

5. Wireless efficiency now at 10 bps/Hz is anticipated to increase to 100 bps/Hz. That means that a 20 MHz spectrum could provide a 2 Gbps channel to a single user, and with multibeam antennas it can to so to a plethora of users. This backs up directly to a competitor of fiber. And at a tenth the cost!

On p 160 the author again reinforces her lack of technical understanding and capabilities. She states:

“When people want to download a lot of data, say to make a video call, they overwhelmingly opt for high speed wired connections.”

Perhaps she has not been made aware of the iPad.

This distortion continues throughout this chapter. She does it again on p. 161,

On p 251 she states:

“Will wireless help America reach the president’s goal of one gigabit to every community? No.”

The answer is yes, and since the wireless companies have hundreds of MHz not the 20 above, they can well exceed that.

On p 258 she describes the franchises being exclusive. In fact almost all were no-exclusive. The problem was the cost of overbuild.

On p 263 she demands “For starters most Americans should have access to reasonable priced 1-Gb symmetric.” Now I assume she means 1 Gbps not 1 Gb. it is rate not totality, and she

On p 265 she begins her argument of moving to a utility model. She states “To do this though American needs to move to a utility model.” Frankly the issue should be one of bundling or tying in and the control is the existing antitrust laws. The problem with the utility model is all too well known. The FCC controlled and was controlled by AT&T before divestiture. The result was very slow development of technology and capability. The utility model sets prices based on a return on investment, namely the provider is guaranteed a profit based on invested capital, and their costs are covered no matter how inefficient. The result is a capital intensive and bloated system. Better would be a real competitive market where the barriers to entry are not enforced by the Government but the Government enforces the antitrust laws already on the books.

On p 267 she also makes statements regarding the costs of fiber. Based upon my experience doing this her numbers are categorically wrong. The most significant costs not included is the franchise acquisition costs, often in excess of $1,000 per sub, plus the costs of pole attachments and the delay costs associated with dealing with local regulators.

On p 267 she further states “The government standardizes, regulates, provides tax subsidies, and puts price supports in place every day.” One could just imagine the Government standardizing wireless or broadband structures. They have no technical depth and furthermore the politics that would ensnarl such would be unimaginable. The Government should just stand apart from any standards. Let the technical people deal with that, and live or die by their decisions.

On p 269 she gets into the Internet discussion. Again for some reason she uses Franken as a foil but they are a distraction. The fact is that indeed ARPA, specifically IPTO, developed the early

Internet deployment in the 1970s. In fact I ended up with the task of deploying the international circuits for IPTO. Then through the early 1980s it somewhat slowed but with the help of Kahn and Cerf the IETF was formed and began an open source development of what could be called standards, albeit very flexible one. Then the DOD abandoned it and spun off a separate network and the result almost went nowhere but at the end of the 80s we saw such academic networks such as NYSERNET evolve and the NREN come forth. Thus the Internet history is a mixed bag of public and private parentage and the bright line alluded to by the author is without merit.

The book is worth reading but only if one can work through the mire of the author's statements for which she has no basis or those which are just outright technically in error.

The classic book on telephone change is the **Coll** book, ***Deal of the Century***, outlining the breakup of ATT. Coll is a brilliant writer and deals with facts he both understands and can explain. The author of this book had such an opportunity but she clearly went well beyond her ken and the result is that between the facts and opinions are prognostications based on fact-less presumptions. The issue she is focusing on is truly an important issues and needs as much public understanding as possible. The cable companies have secured for themselves a protected niche and have further vertically integrated in a manner which later 19th century antitrust minds would find abhorrent. This is ever so true in view of the channels they control; information and communications.
Labels: CATV, FCC

MONDAY, APRIL 22, 2013

PUBLIC INTELLECTUALS AND RELIGION

I have written extensively on the "Public Intellectual", a term often self-applied as a term of adulation. But this becomes ever so more an issue when that person also assumes the mantle of religious spokesperson, at least for their point of view.

The University of Notre Dame, that football school out in the mid-west, is hosting a conference on this which is described as[56][1]:

This international conference, hosted by the Notre Dame Institute for Advanced Study, will focus on the roles played by public intellectuals—persons who exert a large influence in the contemporary society of their countries by virtue of their thought, writing, or speaking—in various countries around the world and in their different professional roles. Leading experts from multiple disciplines will come together to approach this elusive topic of public intellectualism from different perspectives.

The agenda includes such topics as[57][2]:

[56][1] http://conferences.nd.edu/events/public-intellectualism-in-comparative-context-different-countries-different-disciplines
[57][2] http://ndias.nd.edu/assets/97153/pi_schedule_25_march_2013_web.pdf

1. The Religious Leader as Public Intellectual
2. Islam and the Public Intellectual
3. The Blogger as Public Intellectual
4. The Economist as Public Intellectual
5. The Former Diplomat as Public Intellectual
6. The Philosopher as Public Intellectual

Now what do these who fill these roles have to say, is it if any value, and if not who are the putative true Public Intellectuals in their areas who have such statements to make. We examine these issues somewhat herein. Moreover there is the compelling question of communitarianism versus individualism. Namely as one looks at the Religious issue, examining the now current issue of Social Justice, are we individually responsible or responsible as a community?

If one examines the recent Treatise from the Vatican[58][3] one would gather that the Church has almost eliminated individual responsibility for communitarian approaches, in fact the very call of Social Justice is Justice emanating from Society as a whole and not from the individual to others. In fact Social Justice demands that the individual is sublimated to the community, society, and that there is some magic group of all perfect society managers who make the "right" decisions for all.The Treatise specifically states (p 145, from Vatican II):

"If economic activity is to have a moral character it must be directed to all men and to all peoples. Everyone has the right to participate in economic life and the duty to contribute, each according to his own capacity, to the progress of his own country and to that of the entire human family. If, to some degree, everyone is responsible for everyone else, then each person also has the duty to commit himself to the economic development of all."

Now economic activity is neither moral nor amoral in and of itself. It is akin to farming, to hunting, to breathing, to perhaps even reproducing. The act has a moral element when and only when it causes an immoral act; that is it causes a robbery or murder. Now to view in economic terms the statement "each according to his own capacity..." is as Marxian as "to each according to his means and to each according to their needs..." The statement is full of communitarian elements and devoid of individualistic responsibilities. This is a prototypical statement from Vatican II, and in ways it is as we shall discuss the basis of the conflict resulting therefrom as described by Wills.

The concept of their being a Social Doctrine of the Church is in many ways a total denial of individual responsibility. Yet the very essence of the teachings in the New Testament is directed towards the Individual. Thus in a way the progression of the Church's doctrine has been in response to the Liberalism and Enlightenment doctrines and rather than emphasizing the Individual duties the response was to create a parallel universe which "agrees" with these "pagans" but uses words more akin to what the Vatican would be comfortable with.

[58][3] See Compendium of the Social Doctrine of the Church, US Conference of Bishops, 2004.

From an interview with one of the speakers, the erstwhile Religious one defines Justice as follows[59][4]:

For me it is a commitment to justice, to making the good of others, the good of the world community the ground on which I make choices. Justice is more than niceness or random acts of kindness. Justice is a principle of life. For example, from a religious perspective in this day and age, I believe justice requires me to have as much respect for Islam, as I do for Catholicism. We do Islam a great disservice if we judge the entire tradition on the basis of a few radicals. My spirituality directs me to recognize the spiritual foundation, the truth and vision in every religion.

John Ryan, a Catholic priest in the late 19th through mid-20th century wrote a great deal on the concept of Justice, and Distributive Justice as her termed it. His view was that it was necessary to take from the rich to support the poor and he was a severe critic of capitalism. Moreover his views were that "society" owed the poor and he saw the individual qua individual as irrelevant.

As Ryan states[60][5]:

"The Christian conception of the intensive limitations of private ownership is well exemplified in the action of Pope Clement IV, who permitted strangers to occupy the third part of any estate which the proprietor refused to cultivate himself. Ownership understood as the right to do what one pleases with one's possessions is due partly to the Roman law, partly to the Code Napoleon, but chiefly to the modern theories of individualism."

What Ryan says is that no individual or person has the true and clear right to their property. In fact the Clement argument is one of using the fallow land. Farmers left one third of their land fallow so as to allow it to recover. Clement then believe that fallow land should be put to use, albeit destroying the value in the future. No one has ever claimed Pope's were infallible in science and agriculture.

Ryan then quoted Herbert Spencer:

"Violence, fraud, the prerogative of force, the claims of superior cunning, these are the sources to which these titles may be traced. The original deeds were written with the sword rather than the pen; not lawyers but soldiers were the conveyances; blows were the current coin given in payment; and foe seals blood was used in preference to wax."

Strange as this may be as a quote, it does allow him to draw in Spencer, the strong promoter of 19th Century individualism to justify his claims; a claim that simply states that no property has any "legal" and read that as "moral" basis. In fact Ryan's belief is that not only should the one third be shared but that there should be no private property at all.

[59][4] http://www.huffingtonpost.com/janet-haag/what-is-prayer-a-conversa_b_603667.html
[60][5] See Ryan, Distributive Justice, Macmillan, 1916, p. 23.

The problem here is a serious one. In the Gospels there was always an acceptance of several important issues:

(1) What was the State was the State's and what was God's was God's. For example you had to obey God's law but if that violated the State's law so be it and you thus suffered the consequences. Thus the martyrs. God's law was imposed on the individual, not the group, martyrs died individually.

(2) The duty to obey God's law was incumbent upon the individual. This was to a degree a break with the Old Testament Law as applied to the Israelites, who were viewed as a group. Jews as a group, and to a degree as individuals in the Group, had the duty. But since the Christians were polyglot and disparate, the group identity was abandoned in terms of their religious duty, and thus the burden was on the individual. What did "you" do, not what does the group do.
Now who are putatively true Public Intellectuals in the area of religion? I would argue that Gary Wills fits the profile quite well. He is a true intellectual, as evidenced by his wealth of experience and understanding, and he addresses key issues worth the discussion, and he does so with a level of expertise worth of an intellectual. Finally he communicates in a manner which is readily available to a wide audience, albeit educated, yet he does not write for the specialist.

I am reminded of my first Wills book, "Bare Ruined Choirs" published in 1972 and reflecting on Vatican II and the change in the Catholic Church. He was no an apologist, far from it, he demonstrated a breath of understanding the exceeded the classic religious writer. One may not agree with Wills on everything, and I am one who has many point of disagreement, but his writings are always worth reading. He is not a Hans Kung, namely he does not personalize and internalize his invective, and in fact one finds no vitriol in his words.

Thus who are the true Public Intellectuals? Posner[61][6] has taken a cut at that a few years ago, and I wrote a brief work examining that plus the issue of individualism[62][7]. The Posner discussions attempt to demonstrate the decline in the Public Intellectual. One can readily argue that the decline may in many ways have been a collapse after the interdiction of the Internet.

Let us examine two of the speakers at this conference; strangely bot are somewhat obese in my opinion, which may in itself reflect an attitude. The religious public intellectual purports to be both a contemplative and yet a rather outspoken public figure. Her writing is nowhere near that of Wills, and in fact can be somnolence creating. She appears to be confrontational with the Vatican and has developed a clan of believers who may be almost cultist in nature. She lacks the true intellectual base and her issues are ephemeral rather that of substance.

The economics representative is acerbic and critical to an extreme of those with whom he differs. If one examines his blog one see a flow of almost venom like comments against those who show even the slightest level of disagreement. Both however believe apparently in the anti-individualism of the left.

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[61][6] See Posner, Public Intellectuals: A Study of Decline, Harvard U Press, 2003.
[62][7] http://www.telmarc.com/Documents/Books/Public%20Intellectual%2001.pdf

Finally, I return to Wills and a possible cause of all this mess. I would argue that it was the strength of the arguments of Augustine, as demonstrated in the brief book by Wills[63][8] that set the path to this point of view. Strange as it may be, for on the one hand it was Augustine that introduced individual salvation via Grace but on the other hand institutionalized Original Sin, a communitarian artifact. Wills argues that there are hidden expressions of Augustin in such works as his Confessions, and I would argue that they are indeed.

Augustine became a believer of the evil of sex, and that in many ways was a result of his own lurid and self-centered life. He fathered a child and then abandoned the child, who eventually died at a young age. He abandoned his "wife" and took up the Faith, even though his "wife" was a Christian before him. As they say the worst prohibitors of habits are those who have forsaken them; thus former smokers are adamant anti-smokers, and converts are more true believers that those born into the faith. Much of what we trouble about in today's Catholic Faith may emanate from Augustine, the Reformation and Luther were a direct result therefrom. Perhaps Pelagius was right, as were the Donatists.

Labels: Individualism

SEQUENCING WHAT GENE?

Today in the NY Times is a story about the major hospitals sequencing genes on cancer patients. The article states:

Sequencing an entire genome currently costs in the neighborhood of $5,000 to $10,000, not including the interpretation of the information. It is usually not reimbursed by insurance, which is more likely to cover tests for genetic mutations that are known to be responsive to drugs. The treatments themselves, which are sometimes covered, typically cost several times that.

Even optimists warn that medicine is a long way from deriving useful information from routine sequencing, raising questions about the social worth of all this investment at a time of intense fiscal pressure on the health care system.

"What's the real health benefit?" said Dr. Robert C. Green, a Harvard professor and a medical geneticist at Brigham and Women's Hospital in Boston. "If you're a little bit cynical, you say, well, none, it's foolish."

The real question is "what gene?". Namely are we sequencing the genes of the person which made them what they are, or are we sequencing the genes of the cancer. And even worse, what cancer cells since they have the nasty habit of mutating at a rather rapid rate.

The germ line genes may or may not tell us a great deal, unless we understand what went wrong and when. Very few cancers are germ line related, most are somatic. Stuff happens, and then it happens again and again.

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[63][8] Wills, G., Augustine, Viking, 1999.

As we have argued in our recent work on cancer cell dynamics there is a highly complex but measurable and modelable process to examine this complex somatic process. Furthermore we have explicitly demonstrated that for prostate cancer and melanoma.

Specifically any such program should:

1. Catalog the germ-line genes. It is always good to know where you are starting from.

2. Monitor the somatic genes of a cancer as it progresses.

3. Understand the "expression" not just the genes since expression is modulated by epigenetic factors such as methylation and miRNAs as examples.

4. Perform the analysis using a fact based model which is spatially and temporally based along with recognizable mutation paths.

5. Validate the models and use them for prognostic purposes.

Labels: Cancer

WEDNESDAY, APRIL 17, 2013

MATHEMATICS AND LANGUAGE

As usual Frances Woolley has written a spot on piece about "language" and in this case mathematics and economics.

She states:

Bad notation makes a paper difficult to follow. Papers that are hard to read and understand get rejected, or receive lower grades. But what makes for good notation?

First, symbols should be easy to remember....

(Second) ... avoid multiple subscripts or subscript/superscript combinations whenever possible...

(Third) ... One other rule is ... Generally speaking, greek letters are used for parameters of the model ...

(Fourth) ... Once one has a model, one has to figure out what goes in between the equations (hint: economics). Every symbol used in a paper needs to be defined clearly the first time it mentioned. If the symbol has not been used in a while, it is a good idea to give the reader a hint as to what it means.

Now I have struggled with this for decades. Here is a variation of Woolley but written with my set of rules:

1. Write for your audience. If you are writing for pure mathematicians then you need all that stuff. If you are writing for the real world then just say what you mean and no more. You are NOT a pure mathematician and who cares if you have a Banach space. You never use that fact.

2. Follow Ockham:

a. Say as little as you have to to explain the concept. Do not add all sorts of stuff to show how "smart" you are.

b. Be a nominalist, namely there are no abstract Platonian constructs, only the reality of the moment.

3. Write equations so that they are obvious. If w is a variable that depends on x and t then write w(x,t). That's all, no more. If w is one of i=1,...,n elements then write a simple subscript. As Frances says choose a variable to be obvious. x is good for position, t for time, and then go from there.

4. Define it and repeat the definition as often as possible. Why? Because I may not have read the obscure definition hidden in the midst of paragraph 23.

5. Structure your presentation. Long paragraphs are tedious. Number or bullet your points. Highlight the fact that you are making. Unless your are a pure mathematician, assume it is not clear to the reader or that you can leave it as a simple exercise for the reader.

I have found that Economists try to pretend that they are pure mathematicians. I had taken a few pure mathematics courses at MIT and I can assure anyone that I am not nor will I ever be a pure mathematician. However I am a reasonably good engineer so writing equations are as an Ockhamist. I try to think of the reader, since I am using a language that should be clear and simple.
Labels: Economics

SUNDAY, APRIL 14, 2013

HIGH TECH START UPS AND NEW YORK CITY

Now I have done almost a dozen start ups and half a dozen turn arounds. In addition I was born in New York City and worked there as well. The new Cornell center as described in the NY Times is:

Though Cornell and the Technion are taking it further, the relationship between most engineering and computer science schools and the business world is already so fluid as to startle someone with a liberal arts background. Professors routinely take breaks from academia to go into business. Former students and professors create companies based on work done within university walls and reach back into them to collaborate and recruit talent. Universities often own pieces of new ventures.

This kind of cross-pollination helped create thriving tech sectors in the areas surrounding the Technion, Stanford, the University of Texas and the Massachusetts Institute of Technology — something Mayor Bloomberg wants for New York. And it is of growing importance to universities, not just for their ability to draw top faculty and students, but also for their finances. "Technology transfer," the private-sector use of university-born innovations, has become a multibillion-dollar source of revenue for schools.

When Mayor Bloomberg asked business leaders about the city's economic prospects, the complaint he said he heard most often was a shortage of top-notch talent in computer science and engineering. The hope was that a new graduate school could turn the tech sector into another pillar of the city's economy, like finance, medicine and media. In 2010, the mayor announced a contest, offering city-owned land on Roosevelt Island worth hundreds of millions of dollars, and up to $100 million worth of capital improvements.

Now New York is NOT Cambridge, it is not Silicon Valley and it is cer6tainly not Tel Aviv. It is New York. It costs a fortune to live there, the taxes now beat even California, getting around is impossible, and the ability to get start up spots is just zero!

Also start up folks are born, not made, and they are often with one leader and a few good followers. I have always seen teams but I have always seen the leader. I was with my first start up in 1969, funded by EG&G venture arm and it went belly up. I was just a technical consultant but I learned more from that failure than almost anywhere else. There were lots of reasons, but the primary one was not paying attention to details.

I also found on my third return to MIT, or it may have been my fourth, that my doctoral students by the mid 2000s thought that to do a start up you needed a Harvard MBA and/or lawyer to head it up, that engineers could not do so. My reply, "What do I look like, chopped liver!" I still do not know how that would be translated to Mandarin.

What is needed is a critical mass of the right technical people in an economically livable environment with access to good ideas and capital, as well as a technical support network. And New York City is in my opinion the last place in the world to find that!

One need just look at the MIT area. There is a wealth of talent, plenty of low cost facilities, plenty of capital, and plenty of places where one can live on a low budget. To some degree that is also the case in certain areas of Silicon Valley, at least for those renting. Yet New York City would at best require a substantial commute, and that back and forth eats up a great deal of the creative spirit. Brooklyn is becoming more costly and the Bronx is still a long commute on almost any train, and the office space is costly, and that does not include the union problems. One must remember that one cannot attach a nail to a wall, almost everywhere, without union labor at extreme costs.

Go across the river to New Jersey and the world does change on several fronts. Lower cost real estate and living conditions and easier travel. Yet the symbiotic melding of like minds is not there. In New Jersey there are no MITs or Stanfords. So where in New York will this work, Roosevelt Island, in my opinion that is more than highly unlikely.

New York is great for finance and entertainment, for deals and dealers. It would hardly in my opinion be great for high tech start ups. On the other hand there are tremendous opportunities there which can be monetized elsewhere. It is a gold mine of such opportunities, but actually doing a raw start up is more than problematic.
Labels: Technology

SATURDAY, APRIL 13, 2013

HOBBY SHOP

Making something real is often the best way to understand what really works. Thought this video would be of value.

Labels: Commentary

WEDNESDAY, APRIL 10, 2013

A TOASTER WITH A FAUCET

Form follows function, or something like that. Industrial design is I gather an art, and like most art is best seen from the eye of the creator. I have known a few industrial designers in my day and I fear that they all follow the same trend of the belief that their embodiment of reality is the only true path. Sometimes it may work. Apple is an example of a very successful niche market. Microsoft is not in that league, however.

Take Windows 8. I think it is a disaster. Windows 7 works, it is XP upgraded. It is not Vista. It is a utility, it works, it is easy to use and I did not have to change my world views. My Kindle is OK, no great, could be better but compared to Nexus 7 it at least works, Google seems not to be able to get hardware to work, but arrogance does that to you.

Now IDC reports what appears to be a collapse of the PC market. As reported by CBS Newswatch:

Global shipments of PCs fell 14 percent in the first three months this year, the sharpest plunge since research firm IDC started tracking the industry in 1994. The firm said Wednesday that the appeal of tablets and smartphones is pulling money away from PCs, but it also blames Microsoft's latest version of Windows, which has a new look and forces users to learn new ways to control their machines.

Microsoft launched Windows 8 on Oct. 26, hoping to revitalize the PC industry and borrow some of the excitement that surrounds tablets. PC shipments were already falling, but the latest report suggests the decline is speeding up. "Unfortunately, it seems clear that the Windows 8 launch not only didn't provide a positive boost to the PC market, but appears to have slowed the market," IDC Vice President Bob O'Donnell said.

Now let us go back to that form and function thing. Why do I use a PC? Well I write on it, I do spread sheets, I prepare presentations, I store and retrieve massive amounts of data, I use a wealth of special software for various analyses, I use image storage, and the list goes on. It is the engine that keeps me going forward. Now why do I use a pad, like a Kindle. I get email, I can read a document, somewhat, I can get to the web, and it is small and easy to use. I do not play games so that leaves out a tone of usage and I have no use for social media, too distracting.

As the BBC states:

IDC said 76.3 million units were shipped, a figure that underlines the appeal of tablets and smartphones an alternatives to PCs. The firm said Microsoft's latest version of Windows had failed to revitalise the industry. Recession had also led companies to put back renewal of their PCs, IDC said.
The firm's vice president, Bob O'Donnell, said: "Unfortunately, it seems clear that the Windows 8 launch not only didn't provide a positive boost to the PC market, but appears to have slowed the market."

Windows 8 is designed to work well with touch-sensitive screens, but the displays add to the cost of a PC. Together, the changes and higher prices ``have made PCs a less attractive alternative to dedicated tablets and other competitive devices," Mr O'Donnell said. Microsoft was not immediately available for comment. IDC also said that, traditionally, companies replaced PCs every three years, but that during the economic downturn this was more likely to be every five years.

Thus for me the PC is a toaster, you put bread in the top, push the handle, and a few tens of seconds later out comes toast. But what would happen if you decided to add a faucet to it? First question is why? Well, says the industrial designer and marketing folks because the other guys have that on their pads. Well make a faucet and put it on a sink. Don't attach the faucet to my toaster!

But again we saw this tale before. It was Vista. People view the operating system today like a utility. It is an electrical outlet, I just want to plug stuff in and have it work. Microsoft does not want to be viewed that way, it thinks it is much more than that, and every time they try and show us the mess it up again.

The issue is simple. Keep the PC for what it does well. It is a great client and even a server. It has great processing capability and storage capacity. It is not mobile, and for what many people use it for it will never be that way. I have a laptop, it is portable, it goes from one place to another. Yet it is not really mobile. I have my Kindle, it is about as mobile as I want to get. But that is me.

Thus designers and marketing people must understand use and users. What was wrong with Windows 7. It was great. That stupid screen that opens on Windows 8 on a high capacity PC is just an annoyance. Did anyone at Microsoft ever speak to a customer, really? How about listening to the customers also. That's a first. I really do not want a faucet on my toaster.
Labels: Technology

TUESDAY, APRIL 9, 2013

MORE ON CIRCULATING TUMOR DNA

It seems that there is a significant amount of new work being done on evaluating cancers via circulating tumor cells and their DNA. Another paper in Nature states:

Cancers acquire resistance to systemic treatment as a result of clonal evolution and selection. Repeat biopsies to study genomic evolution as a result of therapy are difficult, invasive and may be confounded by intra-tumour heterogeneity Recent studies have shown that genomic alterations in solid cancers can be characterized by massively parallel sequencing of circulating cell-free tumour DNA released from cancer cells into plasma, representing a non-invasive liquid biopsy.

Here we report sequencing of cancer exomes in serial plasma samples to track genomic evolution of metastatic cancers in response to therapy. Six patients with advanced breast, ovarian and lung cancers were followed over 1–2 years. For each case, exome sequencing was performed on 2–5 plasma samples (19 in total) spanning multiple courses of treatment, at selected time points when the allele fraction of tumour mutations in plasma was high, allowing improved sensitivity.

For two cases, synchronous biopsies were also analysed, confirming genome-wide representation of the tumour genome in plasma. Quantification of allele fractions in plasma identified increased representation of mutant alleles in association with emergence of therapy resistance. ...treatment with gefitinib.

These results establish proof of principle that exome-wide analysis of circulating tumour DNA could complement current invasive biopsy approaches to identify mutations associated with acquired drug resistance in advanced cancers. Serial analysis of cancer genomes in plasma constitutes a new paradigm for the study of clonal evolution in human cancers.

Cancer Research UK commented on the works as follows:

Scientists ... used traces of tumour DNA, known as circulating tumour DNA (ctDNA) found in cancer patients' blood to follow the progress of the disease as it changed over time and developed resistance to chemotherapy treatments.

They followed six patients with advanced breast, ovarian and lung cancers and took blood samples, which contained small amounts of tumour ctDNA, over one to two years.

By looking for changes in the tumour ctDNA before and after each course of treatment, they were able to identify which changes in the tumour's DNA were linked to drug resistance following each treatment session.

Using this new method they were able to identify several changes linked to drug-resistance in

response to chemotherapy drugs such as paclitaxel (taxol) which is used to treat ovarian, breast and lung cancers, tamoxifen which is used to treat oestrogen-positive breast cancers and transtuzumab (Herceptin) which is used to treat HER2 positive breast cancers.

And they hope this will help shed new light on how cancer tumours develop resistance to some of our most effective chemotherapy drugs as well as providing an alternative to current methods of collecting tumour DNA – by taking a sample direct from the tumour – a much more difficult and invasive procedure.

As we noted in a previous note regarding the same set of procedures by others researchers this is a useful method to detect the progression of cancer.

However the following observations are of note:

1. Are these coming or going cells, namely are the cells on their way to a metastasis or the result of one.

2. Can we use these cells to determine the changes in DNA expression as the cells progress.

3. How effective a prognostic tool are these measurements.

4. What therapeutic methods can be applied now knowing this information.

Thus is this data of primary use or secondary. Notwithstanding its clinical use it does represent an excellent tool for genomic progression.

Reference:

Murtaza M et al, Noninvasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA (2013) Nature.
Labels: Cancer

MIT VS HARVARD: LOCATION, LOCATION

MIT is expanding Kendall Square and it has gotten approval for almost 1 million sq feet of new high tech, biotech specifically, office space. As The Tech reports:

The rezoning allows for up to 980,000 new square feet of commercial development and at least 240,000 new square feet of residential development, in addition to the 800,000 square feet currently permitted for academic (including dormitory) uses. In some regions, the rezoning permits buildings as high as 300 feet, taller than the Green Building.

The Green Building is the tallest building on the MIT campus but what one sees looking around is ever increasing building height and ever expanding coverage. The main problem is that there is but on T stop and very poor parking and traffic flow. In fact it is a disaster.

One sees taller and taller buildings and more and more people coming into the area. Frankly that cannot be stopped and if done properly can be a tremendous asset to MIT.

Now what of Harvard? Unfortunately Harvard does not have such a convenient real estate

location, at least in the Square. So does location portend destiny, perhaps in this case. This section of Cambridge is exploding with bio tech, MIT has been the intellectual focus, and frankly this may be the obvious evolution of MIT, from a pure tech school to an expanded bio tech institute. Ironically the driver for this may very well have been real estate.

Location is Destiny, or at least a large part of it. Harvard Yard is a closed 17th century artifact, MIT is an unbounded amalgam of ever skyward buildings. I await the first true skyscraper, a bit of Manhattan, with an attitude to match.
Labels: Commentary

AN INTERESTING NEW CANCER TECHNOLOGY

The challenge is determining of a cancer has metastasized is to find out where and how much. The classic approach is to look at the local draining lymph nodes and see if has gone there. However the cancer cells may often escape through the blood system and not the lymph system. Consider ocular melanoma, there is no lymph system connection and it spreads by hematological means only.

That means that by examining the blood we should be able to find the wandering malignant cells, at least in theory. In a recent release by MedGadget the article relates developments at MGH in Boston as follows:

Circulating tumor cells (CTCs) are shed by primary tumors and allow the cancer to metastasize to the distant sites. While this is a devastating tool in cancer's war chest, it offers clinicians a marker through which to diagnose and monitor progress of the disease. Since the discovery of CTCs over a hundred years ago, researchers have been developing ever more sensitive methods of capturing them since they're extremely rare in whole blood.

In a recent development by Ozkumur et al at MGH the authors state:

Circulating tumor cells (CTCs) are shed into the bloodstream from primary and metastatic tumor deposits. Their isolation and analysis hold great promise for the early detection of invasive cancer and the management of advanced disease, but technological hurdles have limited their broad clinical utility. We describe an inertial focusing–enhanced microfluidic CTC capture platform, termed "CTC-iChip," that is capable of sorting rare CTCs from whole blood at 10^7 cells/s.

Most importantly, the iChip is capable of isolating CTCs using strategies that are either dependent or independent of tumor membrane epitopes, and thus applicable to virtually all cancers. We specifically demonstrate the use of the iChip in an expanded set of both epithelial and nonepithelial cancers including lung, prostate, pancreas, breast, and melanoma.

The sorting of CTCs as unfixed cells in solution allows for the application of high-quality clinically standardized morphological and immunohistochemical analyses, as well as RNA-based single-cell molecular characterization. The combination of an unbiased, broadly applicable, high-throughput, and automatable rare cell sorting technology with generally accepted

molecular assays and cytology standards will enable the integration of CTC-based diagnostics into the clinical management of cancer.

There are several problems here however:

1. As we had demonstrated in some of our prior analysis, blood borne cancer cells are rare, but more importantly they are cells which are coming from and going to organs. Namely they are in transit, from whence and to where we do not know.

2. The genetic states of each of these wandering cells may be a marker of from whence it came. The problem is that we do not fully understand this genetic mutation process, and in fact as we have shown before it may actually be a Markov like chain process.

3. Understanding this change in cells may be of significant therapeutic value. However this again is uncertain given our current state of knowledge.

4. Again we come back to the cancer stem cell and ask if the few cells we find in the blood stream are the right cells to examine.

However this advance could provide significant data to allow us to expand the understanding of mutating cancer cells.

Reference:

Ozkumur, E.,Inertial Focusing for Tumor Antigen–Dependent and –Independent Sorting of Rare Circulating Tumor Cells, *Sci Transl Med 3 April 2013: Vol. 5, Issue 179, p. 179*
Labels: Cancer

MONDAY, APRIL 8, 2013

OPEN ACCESS AND PEER REVIEW

Open Access has been a growing trend over the past decade. In the NY Times today there is a critical article referring to interlopers who pretend to be "Academic" publications and are just fronts for collecting fees.

The article states:

But some researchers are now raising the alarm about what they see as the proliferation of online journals that will print seemingly anything for a fee. They warn that nonexperts doing online research will have trouble distinguishing credible research from junk. "Most people don't know the journal universe," Dr. Goodman said. "They will not know from a journal's title if it is for real or not."

Now a non-expert doing on line research is a characterization that I find difficult to understand. I assume it means the patient who goes to some blog web site to seek out someone who has the same ailment and who then comes to their physician with a "cure" that the physician has not been

previously made aware of.

Now research when published presents results which can be replicated. Thus if we see a paper with procedures and with references to established work should we reject that if it is in an Open Access source? Was it "peer reviewed"? Frankly "peer review" is often a joke in today's world, in reality it is peer favors. You approve my 40 author paper and I will approve yours.

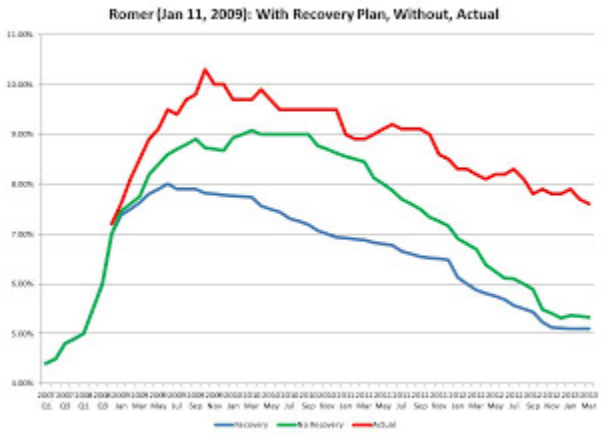
There once was a time of a single author, Einstein, and then it grew to two, Watson and Crick, but now it appears as the whole Professional Society. Who wrote the paper, who did what, and why the 50 or more authors?

Thus Open Access may become a door for re-establishing the author, finally.
Labels: Commentary

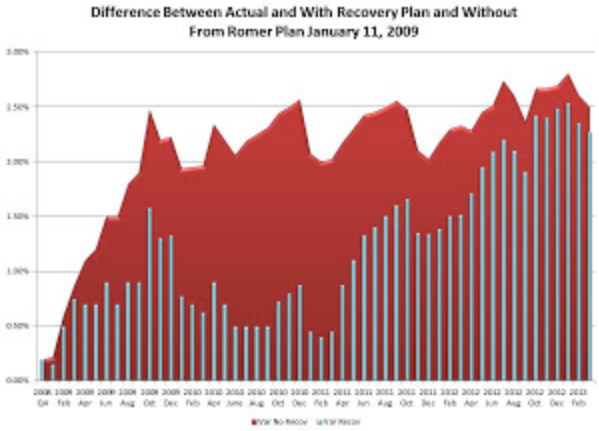
FRIDAY, APRIL 5, 2013

WHAT RECOVERY

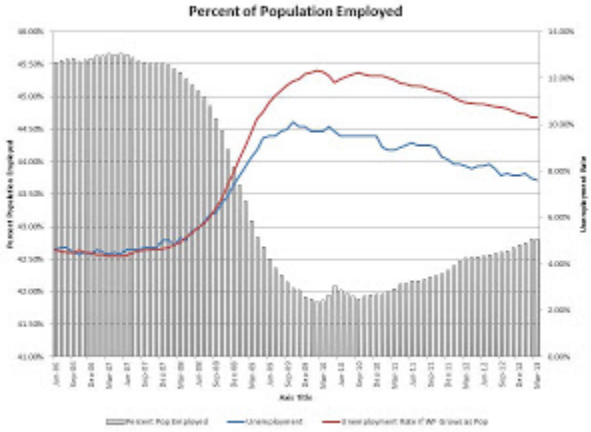
As I go over the employment numbers I am always surprised by some strange issues. Let us begin as usual with the Romer curve or "Why we should not trust any California Economist, Ever!" approach to understanding the world.



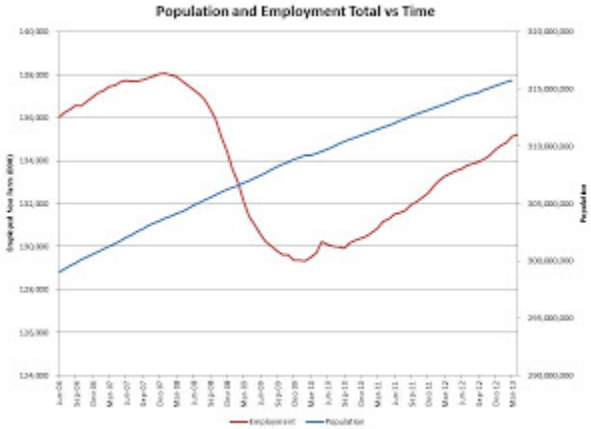
The Romer Curve shows we should be at 5% but we are at 7.6%, or some number greater than 5%. I truly question the 7.6%. Remember the denominator counts. It really counts and the Labor reporting has truly manipulated this on this occasion.



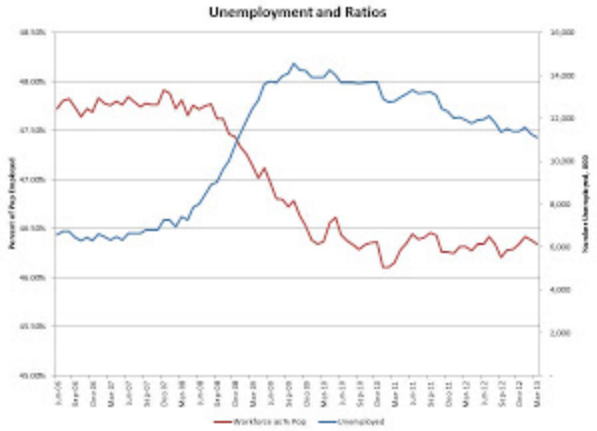
Above are the Romer errors, they still are near all time highs.



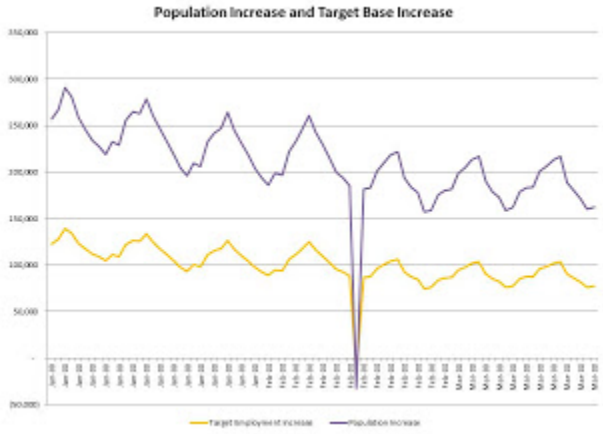
Here we have the unemployment if we had a 2006 economy versus ours now. Note that we have still almost 11% unemployment but they show a greater participation rate than before.



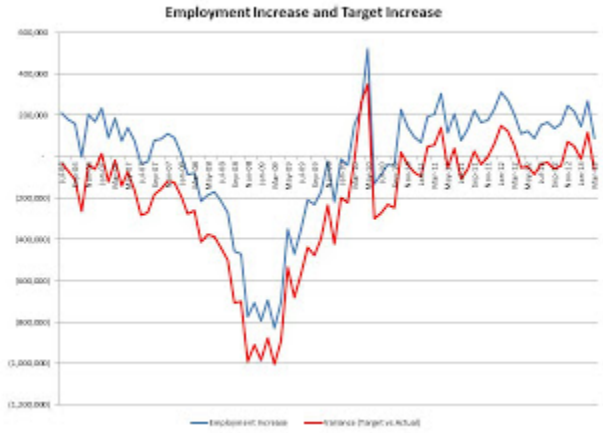
The above shows a beginning to closing the gap but the gap is still substantial. We have had a real systemic change in the workforce.



The workforce as a percent of the population has again dropped and is staying a good 2% points below where we were in 2006. Frankly participation is the true metric no the unemployment rate! We have been arguing that for almost 5 years and I see some of the economic wonders have caught on.



Now this is curious. It is the increase in population versus time and the corresponding required employment increase to match the population assuming June 2006 participation rates. Why the cycle and why the slow drop in population increase!



Finally is we plot the employment increase and then plot the variance from what it should have been from the actual we see that we are negative again and that it has been negative for a long while. There is no improvement! So we have our Government making up an absurd number to make folks feel happy while the workforce goes down the drain!
Labels: Economy

THURSDAY, APRIL 4, 2013

GOOGLE: WHITHER GOEST THOU?

When I was young my father was on the New York Police Department and my life was surrounded by NYPD, FBI, NY State Police and other kinds of law enforcement types. Getting information was at the heart of seeking out the bad guys. So as a young lad I was taught how to get information from the best sources; sales clerks, secretaries, mail men, gasoline station attendants, receptionists, security guards. First they liked the attention and second they were privy to things that contained phenomenal value if you knew what to look for and how to assemble it.

So how does this old way of intelligence gathering relate to Google? Not exactly as you may think. I was at MIT last Saturday and the streets were all blocked. It was a mess. It has been that was for weeks, and will continue that way. Why? Go ask the sales clerk.

Thus when I started to talk with the Coop sales staff the vitriol came out. It was Google! They were building walkways between their buildings across streets so the Google people do not have to go outside and mix with the rabble. They can stay with their own kind, at least that was what I was informed. Arrogance?

Well just look at the NY Times today and some Google employee stating:

"What Google is beginning to do is share some of the knowledge in the world that humans have in their minds," said ... a Google fellow, "so users can begin to communicate with Google in a way that's much more natural to their thinking."

Frankly I have read this a dozen times and really cannot understand what he is saying, but alas it

is my experience that as a company ages it degrades. Now take Google, its search is being disintermediated by "appliances" task specific search systems, that solve a specific problem at a specific time and in a specific place.

Yet when Google tried to expand, it seemed to be successful in Android, an operating system, but the Nexus is in my opinion a disaster due to Asus, a 30%+ failure rate again ascertained by speaking with multiple Staples sales staff. My Kindles and iPads work like a charm, and despite letters to the Chairman at Google, someone who I had worked with extensively on a Presidential Commission with, no response. If it were Hyatt, Honda, Kraft, or Fidelity I would have a reply, if it were Verizon Seidenberg may actually have called. Yet Google is above all that.

So where is Google going, is it still a modified one trick pony, albeit with a lot of cash? Will it become a Microsoft, which is in effect a utility company, the only innovation Microsoft does is akin to the electric utility deciding to install peppermint colored utility polls. So just where is Google going?

After all they appear not to want their people to get cold, wet, or associate with the common person.
Labels: Google

TUESDAY, APRIL 2, 2013

THE ENTREPRENEUR'S SONG

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

Reference: We Must Believe In Magic, Crystal Gayle

Labels: Commentary

THURSDAY, MARCH 28, 2013

KEEN INSIGHT INTO THE OBVIOUS

In a comment by Mankiw at Harvard he notes the obvious absurdity of the new Health Care plan. It was written to cover everything. He clearly notes that all other insurance plans cover big items which can be catastrophic. Health Care should be that was as we had argued in our Book a few years ago.

Our recommendations were simply:

1. Universal Coverage: Others should not have to pay for your problems, especially catastrophic ones. Thus we pool our big risks.

2. Individual Coverage: That means like auto and home insurance you personally foot the bill.

3. Mandated Maximum Risk Coverage: This means that if you want to cover everything you can at your own costs but you are covered for the really big things.

4. Payment Support Coverage: For those who cannot afford coverage then the Government may pitch in.

5. Lifestyle Risk Fees: If you chose to smoke, eat in excess, etc then you get to pay more.

6. No "Somatic" Risk Charge: If you were dealt bad genes then you do not get penalized.

Simple, we worked out all the details, it costs much less, and people are happy. Would Washington buy this? No way, they could not control it. Perhaps Mankiw could follow up on this thread, his observation is spot on.
Labels: Health Care

WEDNESDAY, MARCH 27, 2013

DOES THIS MAKE ANY SENSE?

In a recent posting a Health Care promoter was quoted as saying:

"Over the first two years, costs are going to be higher and (the ACA) is going to be seen as a failure" by some, Paduda said. "Of course costs are going to be higher, because of pent-up demand. ... But after that, demand (for many) procedures will come down significantly."

Pent up demand? The person was waiting for three years to have their lung tumor resected, or was it the glioblastoma, that nasty looking melanoma, that renal failure, what pent up demand. Perhaps the rhinoplasty, the botox shots, the extra birth control pills?

In my opinion this makes no sense at all, but it will become the pitch lines to justify additional cost over runs.

The article further states:

"We're focused like a laser on affordability," American's Health Insurance Plans CEO Karen Ignagni told Modern Healthcare in an interview. AHIP has been arguing for months that premiums will rise because of a new premium tax, essential health benefits required of individual and small-group plans, and a narrower age-band ratio for rates. The new ratio means that an older individual will pay no more than three times more in premiums for the same plan. As a result, younger people will end up paying more for coverage in 2014 than today. Now, most states have a 5:1 age-band ratio.

Some of Ignagni's concerns were highlighted in a study released Tuesday by the Society of Actuaries. The actuaries found that the cost of medical claims, one of the key factors driving insurance premiums, will rise an average of 32% nationwide by 2017 as a result of an expected change in the individual market composition. The study further predicts that as many as 43 states could see claims costs increase by percentages in the double digits.

Premiums will rise because providers are mandated to provide a heap of new services and at no cost. It is not just birth control pills but it is every other service known to man and woman. We are looking at in excess of 10% pa compounded rates of increase. There is no real incentive to drive down costs in such areas as obesity driven Diabetes. In fact the law accommodates that and pays for any related costs.

As we had indicated when this mess began, we expect explosive cost growth going right to the National Debt!

Labels: Health Care

THE INCOMPETENCE OF THE HEALTH CARE INSURERS

First rule of life is: Do Not Get Sick, Ever, Just Die, Neatly.

Otherwise you have to deal with health care providers and insurers. Today I tried to reorder some eye drops. Not real real critical, but timely. So I went off to the website of the insurer to do so;

1. Ten days ago I ordered on line and it seemed simple. Just renew it.

2. Yesterday I found that they cancelled the prescription order.

3. Then I emailed back and forth to see what was wrong but to no avail. First we all know email really does not work in communicating, and second their objective is not to honor the agreement. So obfuscate.

4. Today after 10 min with an electronic operator saying names and numbers a half a dozen time

I go through to a human. Apparently they believe that I can only get so much a year no matter what.

5. The problem, about six months ago they switched from an American supplier to an Indian supplier. The Indian applicator leaks drops all over so one goes through the therapeutic at twice the rate. But the drug is most likely half the price, but if you use it at twice the rate... Do not expect some moron at an insurer to recognize that 0.5 time 2 is still one!

6. The putative solution is to double the dosing, namely have the physician write a script for qid not bid and then hope their computer honors it. Do not count on it.

7. The alternative is to go over into Canada and buy it there. Despite the rumors they really do not ration, that much.

Well this is another sign that we will be seeing a total disaster in Health Care.
Labels: Health Care

MONDAY, MARCH 25, 2013

CANCER AND NEW THERAPEUTICS

There is an explosion of new cancer therapeutics. About ten years ago we saw imatinib for CML and now we have quite a few for metastatic melanoma, once a terminal disease for certain. In the Melanoma case we see some 20% may survive for extended periods of time. However the average life extension may be only 6 months at a cost that may exceed $100K. In addition there may need be several of these therapeutics used at one time.

A former Administration Health Care adviser has written on this of late:

Many cancer patients, after getting a diagnosis of a terrifying disease, pursue any potentially promising therapy, regardless of the price. But the main cost driver is the fee-for-service payment system. The more doctors do for patients, the more reimbursement they receive. Surgeons earn more for every procedure. Oncologists typically make more money if they use newly approved drugs and the latest radiation treatments than if they use cheaper, older alternatives that work just as well. (This is because they get paid back the cost of the drug, in addition to an extra 6 percent of that cost — the more expensive the drug, the higher the compensation.)

His point is the 6% on the $100K charge. That is $6K per patient per six months. Take melanoma. The incidence is about 75K per year. Of that some 12K to 20K it the drug profile. At say $100K per person and assuming all persons, 20K, we would have in any one year $2B in costs and $120M paid to Oncologists. Is that too much? I guess it depends if you are in the 20% or the 80%.

He suggests changes:

First, over the next few years, the payment system needs to move away from fee-for-service

toward a system of bundled payments, in which doctors are paid one fee for all the treatments involved in caring for a cancer patient.

Point well taken. But the problem is the way we compensate people based upon past assumptions.

Second, insurers have to give physicians information about where they are spending money.

I would suggest the patient also be informed. Patients all too often assume that the costs of the medication is low. They have no idea what the costs are. Moreover the basis for the costs should also be known. One must remember that the drug companies have gone through multi-Phase trials of hundreds of patients each at tens of thousands per patients just to the management of the Trial. Recall that the CROs, the Clinical Research Organizations, generate almost $30B in annual revenue just managing the Trials to comply with the FDA. That is not money in the pockets of the Pharmas.

Third, any change in payment methods must be accompanied by rigorous quality monitoring to ensure that there is neither under- nor over-utilization of care.

Quality, now just what do we mean by that? This is what drove the character nuts in the Zen and the Art of Motorcycle Maintenance. Really, is it nothing more than what is in the eye of the beholder.

Fourth, we need more "high touch" oncology practices. In these practices, nurses manage common symptoms before they escalate to the point that they require visits to the emergency room..

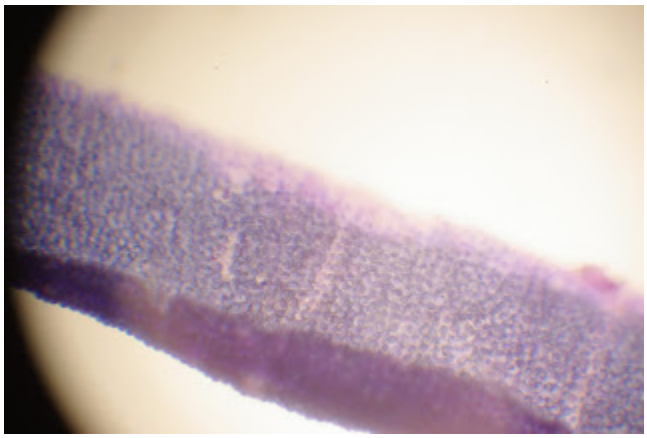
Part of this is that the Oncologists are dealing with a mass amounts of new and different genetically targeted drugs which address pathways that they may have never been exposed to in Medical School. One melanoma drug leads to a new skin cancer, an unexpected effect.

Fifth, we need better incentives for research. Many expensive tests and treatments are introduced without evidence that they improve survival or reduce side effects, and with poor information about which patients should receive them.
Here I would disagree. The Trials are somewhat extensive but when you apply something used over 600 people to 20,000 you get a whole new set of issues. A drug may have to be withdrawn.

One key question is who should receive the new therapeutics? How do we manage them? Cancer is terrifying to the patient. But we now have an environment where people can find out about these new medications and demand them. Physicians are then pressed to use them, albeit with little significant survival benefit, on average. Yet that 20% who do survive contain valuable information for the next step.

Thus do we view use of the new therapeutics as the cost of continuing research or the cost of providing care?
Labels: Cancer

OTHER MODELS FOR CANCER PROPAGATION



As we have described before in our diffusion model and in our Markov chain enhancement, cancer can be modeled as a complex process of; (i) diffusion, (ii) propagation, (iii) proliferation, and (iv) mutation. In each of the above we have defined and measurable processes that result from external and internal physiological and genetic known paths. For example we know that cancer cells when propagated to say the liver will use the liver cells to increase propagation, and in addition will also use liver extracellular factors to potentially suppress gene expression, a factor that appears as a loss of a gene in a pathway.

In a recent paper by Newton et al the authors have developed an alternative ad hoc model, independent of pathways. They state:

The classic view of metastatic cancer progression is that it is a unidirectional process initiated at the primary tumor site, progressing to variably distant metastatic sites in a fairly predictable, though not perfectly understood, fashion.

A Markov chain Monte Carlo mathematical approach can determine a pathway diagram that classifies metastatic tumors as 'spreaders' or 'sponges' and orders the timescales of progression from site to site. In light of recent experimental evidence highlighting the potential significance of self-seeding of primary tumors, we use a Markov chain Monte Carlo (MCMC) approach, based on large autopsy data sets, to quantify the stochastic, systemic, and often multi-directional aspects of cancer progression.

We quantify three types of multi-directional mechanisms of progression: (i) self-seeding of the primary tumor; (ii) re-seeding of the primary tumor from a metastatic site (primary re-seeding); and (iii) re-seeding of metastatic tumors (metastasis re-seeding). The model shows that the combined characteristics of the primary and the first metastatic site to which it spreads largely determine the future pathways and timescales of systemic disease.

For lung cancer, the main `spreaders' of systemic disease are the adrenal gland and kidney, whereas the main `sponges' are regional lymph nodes, liver, and bone. Lung is a significant self-seeder, although it is a `sponge' site with respect to progression characteristics.

Now we believe that this is an ad hoc model because it fails to allow for the inclusion of the cellular pathway dynamics expressly. We believe that it is essential to have the underlying "system model" based on reality as an integral part of the essential model and not just posit an ad hoc model. Our approach has that at its core.

The advantages of including such a model are as follows:

(1) The inclusion allows for the validation based on reality.

(2) The model allows for the inclusion of a model useful for controllability and observability factors. Namely it facilitates the ability to predict usefulness of therapeutics.

(3) A model where the coefficients can be estimated from data and where the estimation is based upon a known physical reality. Thus diffusion is key when say in melanoma we lose E cadherin and thus a melanocyte starts to drift, and where in melanoma we lose RAF control and proliferation begins to occur, or in prostate cancer where in the bone marrow we have excess growth factors and enhanced receptors allowing the malignant prostate cell to proliferate. The nexus with the details of reality are a key and essential factor, a sine qua non, for any such model.

Thus although models of this type may mimic reality I feel that they lack the true essence of reality. One of the essential elements of control theory is the ability to have models of reality which are predicated on essential underlying physical truth.
Labels: Cancer

MONDAY, MARCH 25, 2013

GET A JOB

There is an article on today's NY Times regarding the value of an engineering education. As usual there are the liberal arts types telling us we should be broadly educated as a citizen first and then be productive second.

Their definition of being educated is being told by them what they believe is correct. One can read Locke by one's self, and one does not need some Marxist Professor telling us of the oppression of the working class by the capitalists. After all it was Locke who identified ownership in property with labor.

One Professor of poetry writes:

You are asking the wrong question. Today's students should not be chasing "return on investment." They should be considering a different "R.O.I.," over the longer term: return on the individual. That means a lifetime of skills, like learning how to learn, adapting to a changing economy and society, expressing oneself clearly, solving problems creatively, and acquiring the civic skills to contribute to our democracy.

Colleges and universities want graduates to thrive in their lives, to see the value of the degree. But we must enlarge and enrich our definition of "value" beyond the purely monetary. Students must be prepared for a lifetime of engagement, not for specific jobs that may change or even disappear. The need to innovate goes deeper than the job market; it reaches into how we organize our social and political interactions.

How in God's name can you "thrive" in your life if you cannot support yourself. And your offspring.

Once you have a good job, a sustainable profession, and hopefully independent, then you can be free to do whatever you want. I read philosophy, literature, history, but these became so much more critical when I lived them in my business life. The Thirty Years War became real when the Swedes tried to crush my business and I was saved by the French, despite the fact that I was in Prague but the business was in Poland! Catholics versus Protestants, the Thirty Years War in real life. My ancient Greek became current Greek, since I had to do deals in Athens.

The critical skills to contribute to our democracy is not spending one's life reading poetry but in contributing first hand to is economic survival, and that is done by producing.

Again I recount my road to MIT was from a trash can working as a part time maintenance worker at a New York City school, finding the MIT catalog, and from there the tale is well known. If I did not have my hands in that trash can emptying out the old catalogs perhaps a different life. Perhaps. It was not the poetry, it was not Yeats, it may have been Homer.
Labels: Commentary, Economy, Education

WEDNESDAY, MARCH 20, 2013

MELANOMA AND TVEC

Amgen announced success with Phase 3 Trial using TVEC, Talimogene Laherparepvec, which is an elegant approach to managing melanoma. The simple idea, and most great ideas are simple, is that you use a virus to penetrate specific cells, and then get the virus to do what it does best, multiply, and kill the cell.

Amgen describes TVEC as:

Talimogene laherparepvec is an investigational oncolytic immunotherapy designed to selectively replicate in tumor tissue. Talimogene laherparepvec is injected directly into tumor tissue and then replicates until the membrane of the cancer cells rupture, thereby destroying the cells, in a process known as cell lysis. The virus that was contained in these cells is then released locally in the tumor tissue along with GM-CSF, a white blood cell growth factor that the virus is engineered to express. This is intended to lead to the activation of a systemic immune response to kill tumor cells throughout the body.

As is reported in GEN:

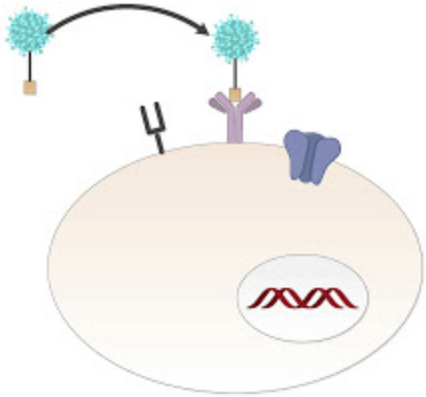
TVEC is based on a herpes simplex virus type 1 (HSV-1) that has been modified to selectively replicate in tumor cells without harming healthy cells. TVEC represents a new class of therapy against melanoma because it combines local with systemic effects against tumors. That effect is believed to be achieved through the functional deletion of two key genes (ICP34.5 and ICP47) from HSV-1, which deprives it of the proteins normally used for circumventing the body's response to infections, followed by the addition of the human GM-CSF gene.

When injected directly into tumors, TVEC selectively replicates until the membrane of the cancer cells rupture or lyse, destroying these cells and releasing the viruses that have been replicated. The released viruses, in turn, invade more tumor cells—a cycle that continues until the weakened virus encounters healthy cells. During replication, TVEC also induces the tumor to produce GM-CSF—a white blood cell growth factor that attracts and activates the cells required for a systemic immune response.

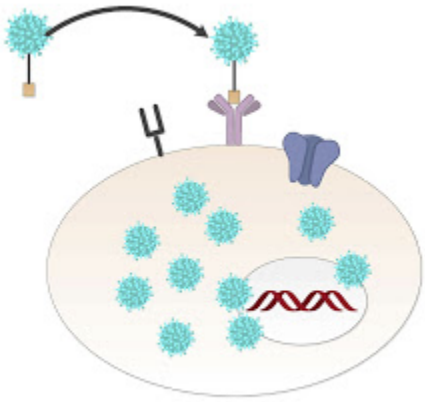
This elegant approach selects a viral carrier which selects the melanoma cell and then enters it and replicates itself until the cell is killed off. This approach may have great applications in many other cancers.

Simply it works as follows:

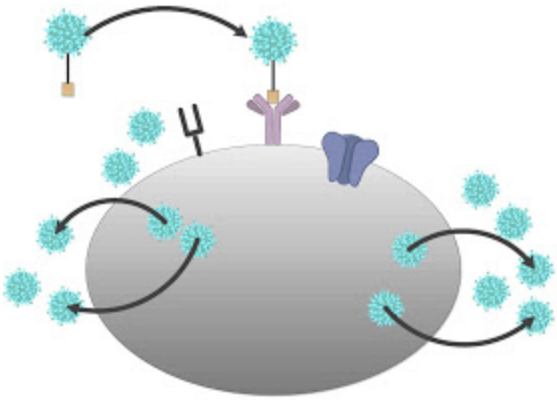
Step 1 Virus is engineered to have attraction to a melanoma cell.



Step 2 The virus invades.



Step 3 The virus kills the targeted cell.



Nice idea and execution. Very interesting execution and great to follow up on. I tried something akin to this a few years ago on plant cells, TMV vector, with some success.

Labels: Cancer

MONDAY, MARCH 18, 2013

CANCER CELL DYNAMICS

We have previously introduced a cancer cell propagation model in earlier discussions which others have also considered. However our model is for a single cell type which grows diffuses and flows. The rates of each are dependent on where the cell is.

In this brief note we add other elements, namely the probability that a cell can mutate and that as it mutates the factors related to the propagation model may also change. We calculate a similar diffusion equation now for the average number of malignant cells by region and by type. That is we demonstrate in the following graphic summary:

Propagation Model: This equation provides a spatio-temporal model for the calculation of the number of specific cancer cells which are propagated by means of: (i) diffusion, (ii) flow, and (iii) proliferation.

$$\frac{\partial n(x,t)}{\partial t} = a\frac{\partial^2 n(x,t)}{\partial x^2} + b\frac{\partial n(x,t)}{\partial x} + cn(x,t)$$

Average Model: This model considers the calculation of the average number of malignant cells in a spatio-temporal manner when the cells mutate into N possible genetic variants. It calculates the average number by variant and thus is a vector equation containing the N variants.

$$\frac{\partial \overline{n(x,t)}}{\partial t} = \bar{L}\overline{n(x,t)} + \Lambda\overline{n(x,t)}$$

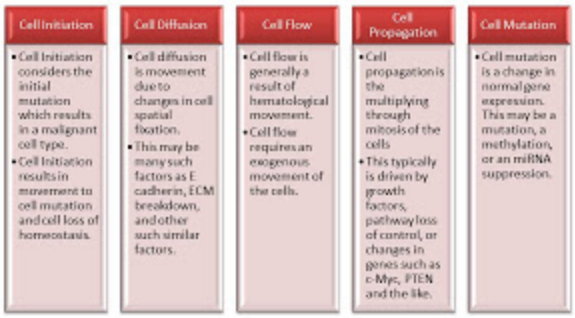
1. The standard diffusion-flow-proliferation model applies on a per-region and per cell type basis. This means that the constants we have developed previously will depend on the specific cell type as well, namely how many mutations have occurred.

2. That we know there are multiple mutations in cancer cells. Some may have a few and are indolent and others may have many and be aggressive. We develop a Markov model for such cell progression.

3. We combine the three element spatio-temporal model with the Markov cell mutation model and this allows us to determine the average number of cells of a specific type in any part of the body at any point in time.

4. We then discuss how one may use this model for prognostic and therapeutic purposes.

The main observation in this brief section is that the average number of malignant cells of a specific mutation state can be determined by the following:



In this equation the n is an NX1 vector of average numbers in spatio-temporal dependent values of each of N possible mutations and the L value is the spatio-temporal dependent operator matrix and Λ is a matrix describing the Markov transition probabilities between mutations.

It should be clear that we can measure all of the constants involved and thus determine the result. As a counter-distinction we can measure the n values and mutation states and determine the constants.

The expanded model considers the issue diagrammed below:
The next issue is the ability to determine what the factors are in the specific model, namely the values of the constants, and secondly the validation of the model itself.

Thus there are two dimensions of issues here:

1. Model Identification and Validation: In previous work we referred to this as the Observability problem. Namely if we have a model and we can identify the required parameters, then can this model be used to determine the end state which will be attained. This is the prognostic problem.

2. Model Utilization: As with the previous cases, if we have this model, and we have identified the constants, can we determine actions which may be taken to control the end state of the system? This is the Controllability problem. It states that perhaps having such a model we can determine methods and means to drive the system, in this case the average number of malignant cells of genotype say G, to a new end state, one where we have reduced the number of bad cells to a de minimis level. This is the therapeutic problem.

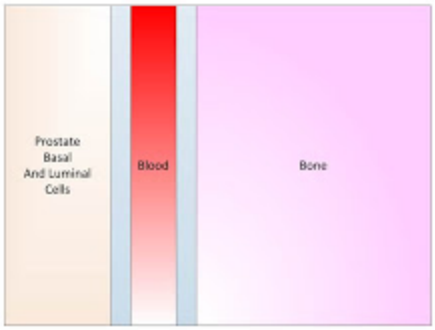
There also is a third element:

3. Identification: In both of the two previous issues we assumed that there existed a method by which we could determine the constants of diffusion et al and furthermore that we could ascertain the list of possible mutations, and also their Markov transition probabilities. This may be accomplished in two ways. First, we can accomplish this by in vitro studies. Second, we can achieve this by using the model itself in a classic system identification model with in vivo analyses.

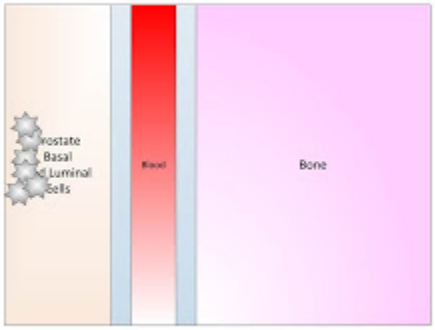
Thus the analysis contained herein is an initiation of what appears to be an innovative way to look at cancer. There have been many studies in more specific and segmented areas but there has not to my knowledge been a study that has examined cancer in such a broad and overarching manner. In essence we have included all of the variables that one may ask for.

To better understand we depict the progression of prostate cancer below.

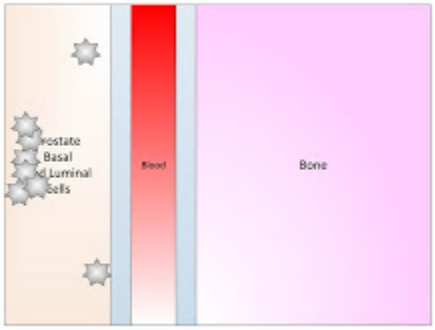
Step 1: Benign State, here we have five segments; prostate, two tissue-blood barriers, blood, and bone.



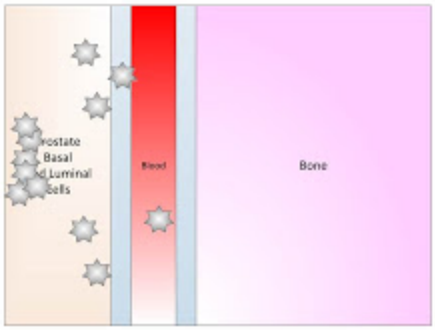
Step 2: We have the beginning of a cancer due to some mutation of the basal or luminal cells. The cancer proliferates and diffuses. It is still localized here.



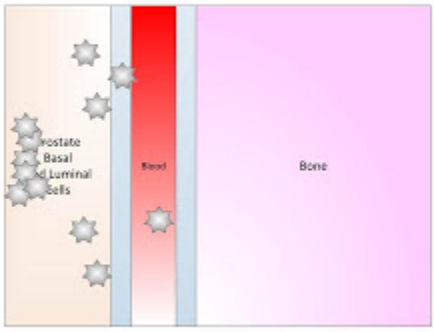
Step 3: Diffusions sends cancer cells to the blood barrier.



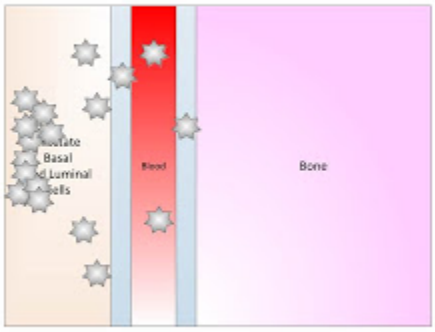
Step 4: The blood barrier is crossed, and we assume by diffusion. Across this barrier there is no proliferation or flow, just diffusion.



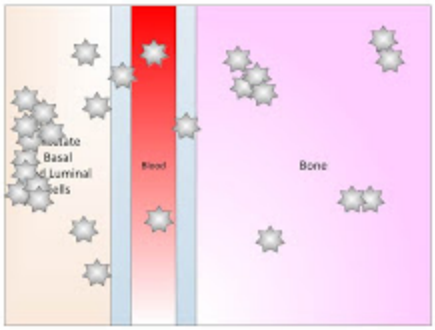
Step 5: The blood barrier is crossed and the cell is now in the blood stream. Here we have flow but no diffusion and no proliferation.



Step 6: The blood barrier is crossed again as discussed above.



Step 7: Metastasis is complete by having the new malignant cells in the bone and proliferation and diffusion predominate.



The above steps are common is almost all cancers. The assumptions here are:

1. The same malignant cell moves across the body.

2. Each separate area, in this case five, has constant diffusion, flow and proliferation constants.

3. That we can then measure the number of cells from this deterministic model.

In the case where they are uniform constants we can solve the equation. In the case where they are uniform constants across uniform spatial domains then we can also solve the equations evoking boundary conditions.

We now want to expand this model to include multiple malignant cell types. Also we want to include their stochastic dynamics as well.

Consider a cell with five possible mutations. We show the genes below. The call may begin with one mutation and then move to a second and so forth. Each path is assumed to be possible and the results of each path are different.

Now we can consider a model for the above simple example. We have 5 possible mutations and they may occur in any order. We assume they occur one at a time. We can identify any number of cells as n(x,t), as the number of cells after one mutation at location x and at time t, of mutation k.

Now we have the following observations:

1. At mutation 1 we have 5 possible cell mutants. Furthermore each may be considered a cancer cell and the growth, diffusion and flow are as described above. Some of the mutations may be indolent and some aggressive.

2. At mutation 2 we have 5*4 possible cells. The question is that some are say PTEN then cMyc or cMyc then PTEN. Are they the same, and this means the difference between perturbation and combination? Are they distinct by have been ordered differently or are they the same? If it is a combination we have 10 instead of 20 different mutations.

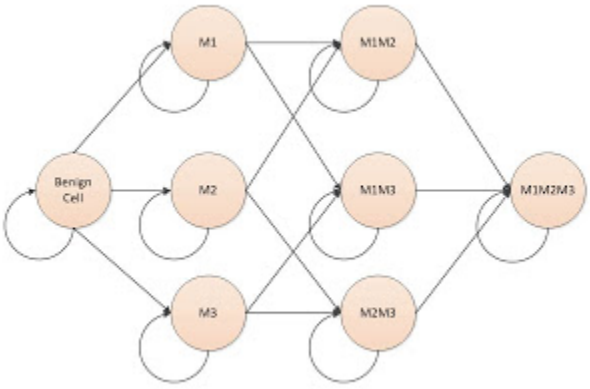
3. At mutation 3 we have 5*4*3 and at 4 we have 5*4*3*2 or 120 permutations.

4. At any location we may have any one or a combination of these mutation types. There are two factors driving their number:

a. A single type will have growth, dispersion and movement dynamics with the above mentioned model but each mutation will respond differently since their coefficients will be different. Some may grow faster and some may diffuse faster. There is no a priori ranking of the coefficients.

b. The surrounding mutant types will also tend to mitigate growth.

For example consider the following three gene mutation case:



We can thus make several important observations regarding this model.

1. Prognostic and Therapeutic: We can determine the transitions and the factors related to diffusion, flow and growth. Thus we can use the result as a powerful one for prognostic and

therapeutic results. As we had indicated earlier, the Observability and Controllability issues are essentially Prognostic and Therapeutic respectively.

2. Variances: The results are for the average. We can determine the results for the variances as well. We have examined the variances on the averages and they are somewhat complex and we do not believe that they lend significant additional information at this time.

3. Solutions: The solutions to these equations are readily obtained using standard techniques. They can, in addition, be determined in closed form results.
Labels: Cancer

WHY I LEFT THE IEEE

The IEEE is the professional organization which represents Electrical Engineers. In 1961 I believe I joined the IEEE and remained a member until 2005. At that point I was quite disappointed in the fact that publications had become group affairs and that worse the articles were just repeats of the same idea, but now promulgated by a group. Further the group was usually headed by some senior faculty member who sat on some IEEE committee.

Now in today's NY Times the representative of the IEEE testifies before Congress seeking gender equality in Visas for Electrical Engineers. It states:

Karen Panetta, the vice president for communications and public awareness for the Institute of Electrical and Electronics Engineers in the United States of America, will testify that "the vast majority of H-1B workers are men," according to her prepared remarks.

Ms. Panetta's testimony points to "a serious gender imbalance in science, technology, engineering and math" as part of the reason that these H-1B visas in high-tech fields skew disproportionately toward men. But she also adds, "If a major immigration program effectively discriminated based on race or national origin, would that be O.K.?"

Let me provide some facts. At MIT the predominant number of Visa eligible students are men. Did MIT discriminate? Hardly! They were the best ones who applied.

Is there a gender imbalance in Electrical Engineering? Perhaps that is the wrong question. You see EE is hard. Yes really hard, and it is competitive, really competitive. So you get out what people put in. We see many Asian students, especially at the PhD level. Of my last 8 Graduate students only one is left in the US, all were foreign students, and some of the best are now in our competitors, and only one was female. Those are facts. What the IEEE is complaining about seems utter nonsense. The problem is not issuing more Visas to men than women, in fact I would be willing to wager that percentage wise of graduates more women get Visas than men.

Let us examine the logic and consequence of her apparent suggestion, in my opinion.

First, if as I suspect, the males in EE represent well over 70% of PhDs and females 30% or less,

Then, if she demands parity in percents in terms of Visas,

One concludes that women will receive twice as many visas as men, and them men will be sent back from whence they came and produce value there and not here.

Engineering is not law or medical school, it still is male dominated. The choice or selection was made decades before graduation. Each and every one of those graduates should be induced to stay here and be creative, not the social engineering selective process of some person at some "professional" society which represents God knows what.

No wonder I left the IEEE! My dues paid for people like this one.
Labels: Commentary

SATURDAY, MARCH 16, 2013

GOOGLE READER AND HOW PEOPLE THINK

I have been thinking and reading a bit about the response to the termination of Google Reader and I have been a bit surprised, but should not really have been, by those who felt it was no loss. For them perhaps. But Google Reader is an artifact of how some people think.

You see my computer screen is organized for efficiency. I have folders in the center of the screen, not just piling up as Microsoft suggests and filling up the screen. Mine are alphabetically organized and then within each is specific applications. Files are organized by topics, subtopics, etc. Google Reader is also organized that way.

I want to watch as topics may come by, I could care less about the images, unless I seek out the specific article. Google Reader let's me know what is new say in a specific area and as some reader may not I often then write upon that in detail, for better or worse. I leave that up to the readers.

But sifting through masses of online data real time to see what has become new and how to fit that in to current research and writings is one of my organized ways. Twitter is totally useless. I have an account, I had to get one for something that I now forgot. I have Linkedin, and it has become the Ginza strip, all bright and useless. I left Facebook years ago, and Google+ makes no sense at all. There just seems to be stuff pasted by others and I have no idea why.

But if you are goal directed, with an organized mental bent, then Google Reader was spot on. If you are a Facebook fanatic, then it would make no sense. Google Reader was for those who did something with what they obtained, Facebook is a narcotic. It is Crazy Bird of the social set.

Google Reader led you to new ideas which made you modify and expand old ideas, it led to challenges, it led to thought. Google Reader was for the organized mind, not the idle mind.

Thus there is a potential wealth of information on how different people think. Social media is for those who want others to think for them. Perhaps a great marketing tool. Google Reader, plain and simple, is for those who want to think for themselves. This tells me something about the folks at Google. They are changing, and perhaps not for the best. Pity!

Labels: Commentary, Google

FRIDAY, MARCH 15, 2013

BEWARE THE IDES OF MARCH

One should remember:

Soothsayer
Caesar!
CAESAR
Ha! who calls?
CASCA
Bid every noise be still: peace yet again!
CAESAR
Who is it in the press that calls on me? I hear a tongue, shriller than all the music, Cry 'Caesar!' Speak; Caesar is turn'd to hear.
Soothsayer
Beware the ides of March.
CAESAR
What man is that?
BRUTUS
A soothsayer bids you beware the ides of March.
CAESAR
Set him before me; let me see his face.
CASSIUS
Fellow, come from the throng; look upon Caesar.
CAESAR
What say'st thou to me now? speak once again.
Soothsayer

Beware the ides of March.
Labels: Commentary

THURSDAY, MARCH 14, 2013

NOW HOW LONG DID THIS TAKE?

In 1967 I had designed a star tracking system used on the X 15 to managed updating the gyro for position location. We used a photomultiplier tube to scan and lock on to Polaris, the north star, and the earth's limb. It allowed precision position updates.

The in 1975 I added an optical, infrared, laser link between two Intelsat satellites as an option. We had designed the system and Bob Kennedy had delivered a detailed system design.

Now in 2013 I see the MIT Lincoln is finally adding an infrared link to a satellite to improve

communications to earth from the satellite. Eureka states:

The LLCD mission will use a highly reliable infrared laser, similar to those used to bring high-speed data over fiber optic cables into our workplaces and homes. Data, sent in the form of hundreds of millions of short pulses of light every second, will be sent by the LADEE spacecraft to any one of three ground telescopes in New Mexico, California and Spain.

The real challenge of LLCD will be to point its very narrow laser beam accurately to ground stations across a distance of approximately 238,900 miles while moving. Failure to do so would cause a dropped signal or loss of communication.

"This pointing challenge is the equivalent of a golfer hitting a 'hole-in-one' from a distance of almost five miles," said Cornwell. "Developers at the Massachusetts Institute of Technology's (MIT) Lincoln Laboratory have designed a sophisticated system to cancel out the slightest spacecraft vibrations. This is in addition to dealing with other challenges of pointing and tracking the system from such a distance. We are excited about these advancements."

The LLCD mission will also serve as a pathfinder for the 2017 launch of NASA's Laser Communication Relay Demonstration (LCRD). That mission will demonstrate the long-term viability of laser communication from a geostationary relay satellite to Earth. In a geostationary orbit the spacecraft orbits at the same speed as Earth, which allows it to maintain the same position in the sky.

My only comments is that 40 years ago we demonstrated this, yes when I was also working at Lincoln. I just wonder what took so long.

Labels: NASA

GOOGLE, I HAVE ALWAYS HAD QUESTIONS

Now Google has a great search engine. Why, because unlike Yahoo it does not fill the screen up with junk. Do I make decisions to go to paid ad sites, yes quite often. But the best element of Google was, yes was, Google Reader. Well not any more.

You see the same morons who brought you Nexus 7, the Asus piece of junk, decided to cancel Google Reader. I use Google+ once a month at best. I am not a social media type. I left Facebook years ago, yes years ago, and I find Linkedin almost impossible to read, even on my 3 grand screens, on my gigantic desk. There is just too much noise.

But Google Reader has little if any noise. The BBC states:

A petition to save the service, which aggregates news content from web feeds, had 25,000 signatures in a few hours. Experts say shutting Reader is part of Google's plan to migrate more people to its social media service, Google+.

Who are these moron experts. I generally do not get this upset. It must be some media savvy twerp from Harvard. No one uses Google+, it stinks, so why close something that works to force people to something that does not. You see Silicon Valley is really filled with intellectual not wits. I bet they paid a fortune for this advice.

So what did I do, as soon as I got the news I ran for an alternative. You see I use Google Reader as a heads up for the latest research in my areas of interest. Get a hit, go to the paper, then write it up, add it to my ever increasing lore of stuff. My last two books would have been near impossible without Google Reader, I would even pay for it. At least until these neanderthals did this colossal misstep.

So what did I do? I went to Microsoft, yes the customer unfriendly Microsoft, and used that antediluvian piece of Microsoft code called Outlook, great little RSS unit. It took some tome, I used Google to get my feeds than loaded them into Outlook. A couple of hours of lost time working on my cancer models but necessary.

Now what did this tell me? First, cloud stuff really stinks. Outlook is not cloud, I have it on my system, thus some evil person cannot randomly remove it. Did I say evil, in reference to Google. Yes I did.

Second, Google seems to have gotten taken over by troglodytes. What happened folks. Are they going to stop the blogs as well, how about gmail, I don't use it anyhow, why not kill off the search engine too while you are at it.

This is clearly one of the stupidest actions taken by any company ever. Just look at the global backlash. Even in the NY Times, which states:

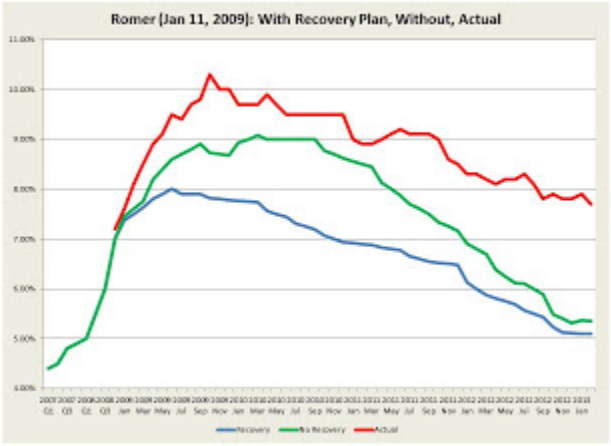
Now people will be out on the news reader street by July 1, and there are few places for them to go.
As BuzzFeed noted, using data from the BuzzFeed Network, a group of sites that collectively have over 300 million users,Google Reader still sends a considerable amount of traffic to these sites. Google Plus, the company's social network, does not.

Remember, if all else fails, listen to the customer!

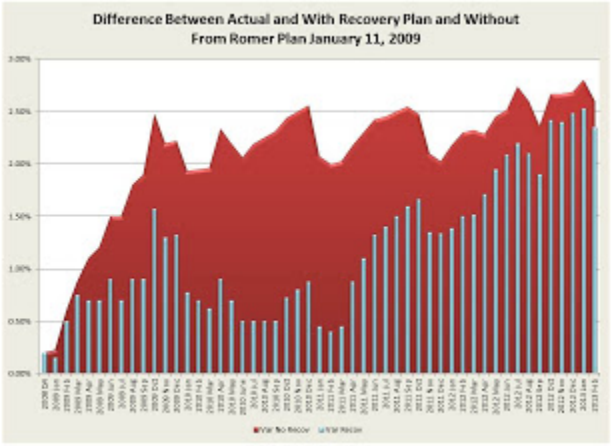
Labels: Google

SUNDAY, MARCH 10, 2013

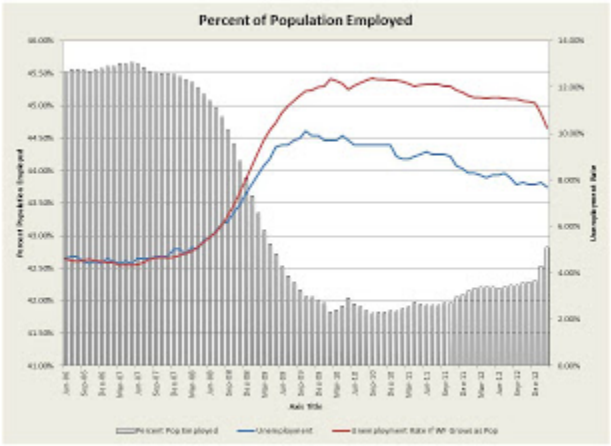
EMPLOYMENT: GETTING BETTER?



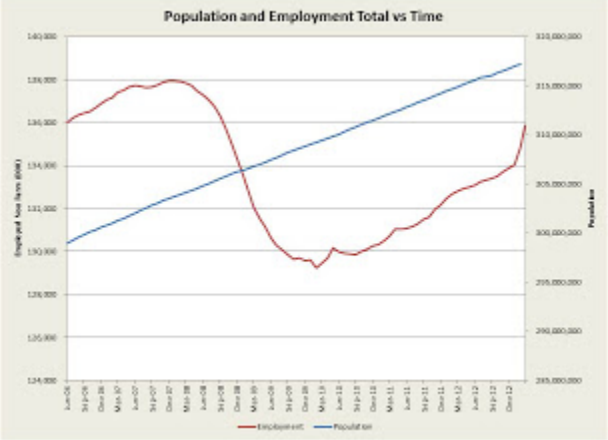
First the Romer Curve. No we have not yet gotten to where she said.



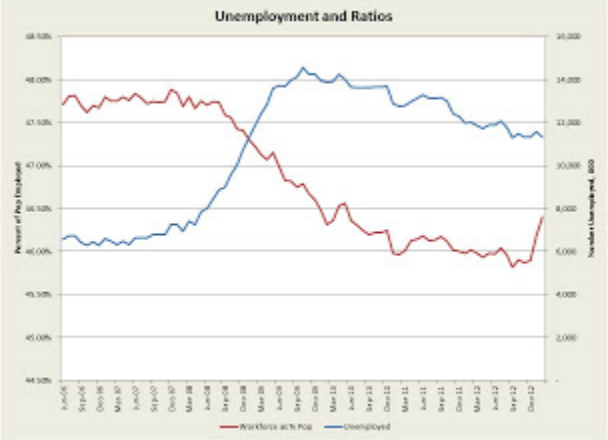
Yes her projections are still way off. And yes she seems to be indoctrinating more minds as to why this has not been the case.



The good news is increasing participation. Notice the upswing as consistent.



If I believe the numbers this actually looks good. We seem to be going back up.



The above reinforces that. Hopefully this is sustainable.

Labels: Economy

SATURDAY, MARCH 9, 2013

BANTING AND BEST, WHAT IS THE CAUSE AGAIN?

Banting and Best where are you when we really need you? I am always amazed by authors such as Basu et al who come out with a new discovery regarding sugar and Diabetes. It is as if they have just gotten some clear insight into the obvious. Obesity drives the suppression of the islet cells which drives down the insulin production which drives up the glucose level. Get the BMI below 22.5 and you drive out the main initiator of Type 2 Diabetes, the inflammatory effects of weight.

Now the authors state[64][1]:

While experimental and observational studies suggest that sugar intake is associated with the development of type 2 diabetes, independent of its role in obesity, it is unclear whether alterations in sugar intake can account for differences in diabetes prevalence among overall populations.

Using econometric models of repeated cross-sectional data on diabetes and nutritional components of food from 175 countries, we found that every 150 kcal/person/day increase in sugar availability (about one can of soda/day) was associated with increased diabetes prevalence by 1.1% (p ,0.001) after testing for potential selection biases and controlling for other food types (including fibers, meats, fruits, oils, cereals), total calories, overweight and obesity, period-effects, and several socioeconomic variables such as aging, urbanization and income.

No other food types yielded significant individual associations with diabetes prevalence after controlling for obesity and other confounders. The impact of sugar on diabetes was independent of sedentary behavior and alcohol use, and the effect was modified but not confounded by obesity or overweight.

Duration and degree of sugar exposure correlated significantly with diabetes prevalence in a dose-dependent manner, while declines in sugar exposure correlated with significant subsequent declines in diabetes rates independently of other socioeconomic, dietary and obesity prevalence changes. ...

In summary, population-level variations in diabetes prevalence that are unexplained by other common variables appear to be statistically explained by sugar. This finding lends credence to the notion that further investigations into sugar availability and/or consumption are warranted to further elucidate the pathogenesis of diabetes at an individual level and the drivers of diabetes at a population level.

Well one would think that to be the case. Sugar, sucrose, is a powerful carbohydrate and Diabetes is a carbohydrate disorder, and Type II Diabetes is exacerbated by obesity and sugar has excess calories thus causing obesity. It is logical causality. We have seen genes, billboards, environment, sugar, and endless excuses for the fact that people eat too much.

Most physicians treating Type II Diabetes sees the patient as obese, having a high carb diet, more than likely smoking and with no exercise. Further if they examine the diet, they find tremendous amounts of carbs, and if they look deeper they are dominated by various sugars. Thus this conclusion is not only obvious but it faces physicians on a day by day basis.

The prototypical Type II Diabetic is a candy eating obese person. Instead of a small candy bar, they get bags of them, cakes, cookies, and the list continues. So what is new?

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[64][1] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0057873

Labels: Obesity

FRIDAY, MARCH 8, 2013

THE CAUSE OF OBESITY: IT IS FOOD STUPID!

There is an article in today's NY Times which states:

OBESITY is a problem everywhere, with significant consequences for personal health and public spending. People weigh more than ever — but why? If we can find the causes of obesity, we can try to eliminate or counter them. Unfortunately, finding causes is easier said than done, and causes we think we see can turn out to be illusions.

The cause, well simple, it is food. Remember 3500 kcal per pound. You basal met rate is say 2000 kcal per day, you eat 2500 kcal per day you gain a pound a week. Simple, End of story. Do not look any further! Input less output is Net Accumulation.

Now here is a real dumb statement:

The gold standard for inferring causation in social science, as in medicine, is the randomized controlled trial, in which people or places are randomly assigned to receive different treatments. In this case, the "treatment" would be the amount of outdoor food ads in an area. But advertisers are unlikely to agree to randomly distribute their signs, nor would people consent to live in a randomly chosen place.

The gold standard is simple physics, in this case energy input and output. The author is a psychologist so I guess I should not be surprised. It is food, too much food. Let me give a few examples:

1. A decade ago when I brought my Czech partners and their family to the US I took them to a lunch restaurant. The plates came out and they were shocked, they at first thought one plate was for all, like a family meal, then they realized that one was for each. In Prague at lunch we had a small plate of food, and even 6 oz of beer, not my choice, but all in moderation.

2. At a day recently of lunches and dinners I kept to my bowl of soup while I saw others with fries and piles of food, well in excess of the 2000 kcal per day. It was not pure choice, but it was choosing Item 9 on the menu. I went off menu. No problem, just ask.

3. The typical business lunch in a conference room contains sandwiches that contain not only bread and meat but a collection of calorie adding stuff. The solution, remove the bread and stuff. Stick with the protein. Also there is always the soda and deserts. Hands off!

The "cause" of obesity is obvious, more input than output. The more I speak with people the

more I am concerned the only way to stop it is through taxation, pure and simple. Especially if those who opine like those in the Times are totally clueless.
Labels: Obesity

THURSDAY, MARCH 7, 2013

AGE OF EDISON: REVIEW

The Age of Edison by Freeberg is a compelling tale of technological innovation and the machinations and creations of all those who participated. At the center is Edison, whose fame was a creation of what he accomplished, what he proclaimed, and what the Press found as good news copy, independent of the reality of what was truly happening. Mr Freeberg has written an exceptionally well balanced and factual book. Unlike the book, The Idea Factory, about Bell Labs, Freeberg looks at each player evenly and based upon facts. His view is expansive and he does not appear to make saints out of sinners. Thus unlike The Idea Factory which is replete with positive statements where the truth may actually be different, Freeberg presents the facts and the result is masterful.

I live but a short distance from Edison's last lab was in West Orange in New Jersey and it is now a National Parks site. Much of what Edison did is memorialized by the many labs, books, and remnants of his hundreds of "inventions". Of course next to this National Landmark is the Edison battery factory which one may suppose is left in a state of total collapse because the cleanup of the site would be astronomical, but those factors are somewhat missing from the tale.

The book is exceptionally well written and it is really a tale of the electric light, with Edison cast as someone who comes and goes, and yet has a lasting influence. Like so many technological advances there is usually not one person, but many competing for the prize. The goal was clear, light, but the path uncertain. The author details the competition between the arc light and the incandescent light, the need for an infrastructure, and the problems of that infrastructure. Power lines grew, collided with humanity, and in urban areas were driven underground. However they remained to be smashed down during hurricane Sandy, almost 150 years after all of this began. Thus the power industry, unlike the electronics industry rapidly grew, and then froze, for almost a century. But this is a tale of the light bulb, perhaps the most significant driver of that industry.

The author opens with the inventing of the light bulb. He wonderfully shows with balance and insight many if not most of the players during this time. Edison was thus one of many, but perhaps the most effective self-promoter. He also had strong financial backers who used their strength as well.

The author then discusses the diffusion of light to both work environments as well as leisure environments. He does a great job showing hos this diffusion changed the way people interacted. This is a critical observation of how technology effects sociological change.

The author discusses the whole issue of patents and patent battles. At the time of Edison there was a strong development of Socialist movements in the US. On p 153 the author discusses the battles over patents. Socialists as he says:

"People invented to satisfy natural creative urge, the socialists insisted, and out of desire to help others. But capitalists bought up the patent rights."

In a sense the author describes the same battle we see today with some on the Internet who feel that content should be free, and that copyright rights are to be trampled.

The author discusses the expansion of applications, some good and some useless. On p 169 he describes certain medical applications, some good some useless. Yet at the same time we see the invention of the X-ray systems, which in a way was a natural step from the incandescent light bulb.

The battle between "standards" is also brought out by the author in the battle between AC and DC. In reading of Edison's views, for he was a DC promoter due to his collections of patents in that space, he never did grasp the basic truth that high voltage AC, using transformers, allowed for very low loss transmission over long distances. Edison apparently just did not understand the theory, unlike Tesla, who was a well-educated engineer. Edison was a technician at best, and when that failed he had a large collection of technicians, but in reviewing his library he had little along the lines of true technology. He had technique, a technique developed by extensive trial and error.

On p 199 the author discusses the issue of municipal ownership of utilities. Specifically he talks of the strong Progressive drive to have municipalities control such vital resources. In fact they wanted to control telephone and telegraph, water and sewer. Again what the author has done is to lay out the issue as the technology evolved and he demonstrates so well the mapping on today's same issues in such areas as broadband. In a sense this book uses the light bulb to demonstrate a near universal development process, sociologically and politically, of almost any new massively accepted technology.

On p 205 the author recounts the development of the technologists, the introduction of electrical engineering into universities such as MIT, Cornell, and Columbia. In this case the universities were followers; they were presented with a pile of technology driven by techniques with no well accepted basis for growth, and then began constructing the basis.

Later in the book the author returns to Government control over the diffusion of this technology. On p 301 is a discussion of the New Deal and the Rural Electrification Administration, bringing light to the farmer. As he says:

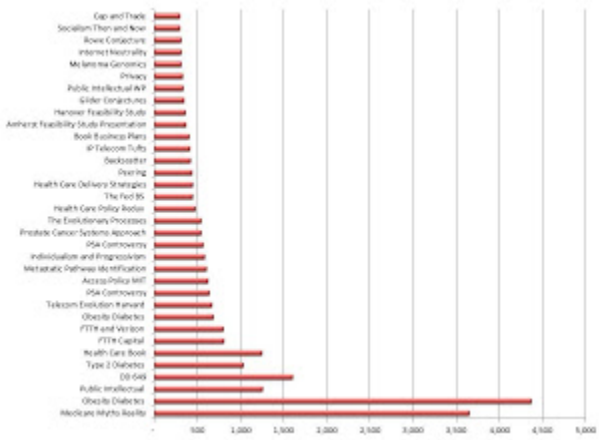
"The New Deal's social engineers believed that rural electrification would do much to ease the burden of farm work…"

Also he notes the FDR administration wanted to bridge what they saw as a growing gap of rural and urban America. Again the author has brilliantly carried the tale to an end point and a point which we can see again today in the broadband arguments.

Overall this book serves two purposes. First it is an excellent summary of the evolution of the light bulb across many facets of society. Second and I believe more important, it represents a paradigm for understanding the development, diffusion and politicization of technological change.
Labels: Books, Technology

WEDNESDAY, MARCH 6, 2013

DOWNLOADS AND WHAT IS INTERESTING



The above is my list of downloads over a recent few months from the Telmarc Web Site. Just thought it is interesting to see what people thought of most interest. I was amazed by the number of downloads of the Obesity and Type 2 Diabetes book. Also almost all are downloaded after a Google search directly to the downlaod, not to the web site.

Labels: Commentary

SUNDAY, MARCH 3, 2013

DARWINIAN DYNAMICS OF CANCER

In the NEJM article by Aparicio and Caldas, the authors make a case for a better understanding and application of clonal genome analysis in diagnostics, prognostics and treatment of cancers[65][1]. As the authors states:

The notion that most cancers are ecosystems of evolving clones has implications for clinical application; we review these, with particular focus on epithelial cancers. Darwin's theory of evolution was originally developed in the context of speciation. It has proved to be a fundamental property of biologic systems, including human cancers. Although tumor evolution has been a foundational concept in cancer biology for decades, a new focus has arrived with the advent of methods that make comprehensive sequencing of cancer genomes tractable for the first time.

Now the authors again and again come back to two premises:

1. Clonal Hypothesis. Namely that cancer is purely clonal and that there is a sing cell that has become aberrant and from that cell all others progress. On the one hand that generally applies to hematopoietic cancers and may apply more broadly, but one may ask where the cancer stem cell theory fits in and further that there are on a cell by cell basis complex and variant genetic profiles.

2. Darwinian Evolution. Namely that cells continue to evolve from the initial stem cells and that it is this Darwinian evolution which drives the difficulty of dealing with cancer.

The authors do raise the need to understand cancer cells not as we do today in some aggregate but in a manner which we can do today, namely o a cell by cell basis. One agrees with this goal, one achievable today, albeit at some substantial cost.

I believe that what the authors are getting at is that to develop better diagnostics, prognostics and therapeutics that we must recognize the following:

1. We must look at cancers on a cell by cell basis.

2. We must know the “age” of each cell, namely how many mitotic changes between the initial precipitating event and the cell we are examining.

3. We must know also the status of the parent cells, the peers and the descendents; thus opening up knowledge to what changes occurred where and when. This opens the door to understanding the dynamics of cancer cell progression.

Thus we need a temporal map of cancer cells.

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[65][1] http://www.nejm.org/doi/full/10.1056/NEJMra1204892

I would argue that we also need a spatial map. The reason for this is as follows:

1. Tumors spread and mutate but besides the somatic genetic failings of a cancer cell we also have the epigenetic failings, miRNA and methylation for example, plus we have the environmental failings, namely cancer cells seem to adapt and prosper in their new environments, oftentimes actually employing the new environment for proliferation advantages.

2. Cancer cells will change as they mutate, and the somatic genetic change can be influenced by their past as well as their current environment.

3. There is a question as to how predictable these changes are. Can we estimate what will happen next knowing the past history of a cell. Is such a change a Markovian stochastic process such that some Bayesian approach may be employed to understand what will happen next and where it will happen.

4. Therapeutics must match not only the current defects, namely kinase inhibitors and BRAF blockers, but most anticipate the next cancer cell break through.

The authors do relate to some of these observation as follows:

Fixed somatic mutations can be used to infer lineage relationships between cells. Large-scale chromosomal aberrations have been used for decades to elucidate clonal structure in cancers. Until very recently, the ability to systematically enumerate single-nucleotide mutations within tumors was limited. However, the advent of next-generation sequencing devices has dramatically reduced the cost and increased the scale of genome sequencing. Moreover, most next-generation sequencing devices can provide a measure of allele prevalence for almost any aberration found in a genome.

As we have discussed before, we can now take multiple samples of tumor cells, from various parts of the body, and then determine both genetic and epigenetic variances. They continue:

In a mixed population of tumor clones, three key concepts relate the prevalence of fixed aberrations measured in the whole population (allele prevalence) to that of the underlying clones. First, clonal-mutation prevalence is a compound measure of the population abundance of the mutation in question and is a function of the size of each clonal population bearing the mutation. Second, a clonal genotype refers to the set of common fixed mutations that define a clone. Third, clonal lineage defines the relationship between clones as they evolve over time. Clonal relationships are usually conceptualized as branched, treelike structures. However, many complex topologies may exist with the potential for extinction events, the independent occurrence of secondary mutations (including identical secondary mutations), and mutations occurring at different scales (from chromosome aberrations to single-nucleotide variants) in the genome.

What the authors speculate about is the use of blood serum to isolate circulating tumor cells and perform the analysis we have discussed. Namely they state:

Even more exciting is the ability to use direct sequencing of plasma DNA to identify the

mutations in circulating tumor DNA (ctDNA), effectively transforming a blood sample into a "liquid biopsy." This approach has the potential to be used, for example, in patients with multiple or inaccessible metastases to characterize the mutational complement in some or all of the metastatic lesions. This has been reported for one gene, PIK3CA, *in which mutations were identified in the plasma of 28 to 29% of patients with metastatic breast cancer. The presence of the mutation in* PIK3CA *in plasma DNA correlated with the mutation status of* PIK3CA *in a metastatic-tumor specimen collected synchronously with the blood sample. The development of ctDNA genotyping for liquid biopsy will depend on the demonstration that mutations are sufficiently sensitive and specific to monitor tumor burden.*

As we know, tumor cells diffuse, flow and proliferate, and that a simple model for this is one where we have a temporal-spatial diffusion like equation which stipulates the number of cancel cells for each location and time point in the inflicted human target. This model, however, fails in presenting ongoing mutations of genes and epigenetic factors as well. Namely it is a pure clonal model, that it, it depicts the single mutated clone going forth and multiplying. We know that such a model is of interest but of limited value. One could enhance the mode by making the unit controlled by the diffusion model a vector, where the vector entities are various genetic states, thus we may start with an n1(x,t) due to BRAF V600 and then have a new n, say n2(x,t) which is MEK, and so forth. This yields a Markovian progression in a diffusion model.

This type of modeling based upon measureable gene expressions are critical for prognostic efforts and therapeutics.

However, back to the authors statement, the use of serum markers is a problem because we do not know if the serum marker is coming or going. Namely is the cell we have selected one on the way to the liver or coming from the liver. We know that most tumor cells in the serum are merely flowing from one place to another, they diffuse through the walls of the blood stream and then multiple in an organ, not the blood stream. Thus the marker may be of some use but is just a single metric. I believe it fails in the goal of the spatio-temporal Markovian model.

The authors conclude:

A greater issue is that most agents are developed to inhibit single targets (or a couple of closely related targets). Targeting the most common driver mutation alone will not succeed if mutations that confer resistance are already present as minor clones in the cancer (see above). The genetic variability of cancer and its capacity to evolve mean that most single-target approaches select for resistant clones, which expand and become dominant. Durable control of viral replication was achieved in HIV therapy only when triple combinations of antiretroviral agents, sufficient to suppress clonal evolution of the virus, were developed. In the context of cancer research, better knowledge of how single targets could be combined from the outset is essential. The ability to follow which clonal genotypes are sensitive and which are resistant could be valuable in both the early stages (xenograft studies) and late stages (phase 1–2 trials) of drug development.

This is of course a critical issue. We know from imatinib and CML that we get a slowdown and regression but it returns and then enters a blast phase. We know with decitabine and MDS we

stop methylation but for just so long, and we know with vemurafenib that we stop BRAF issues but again just for so long.

The previous work make the following clear:

1. When we understand aberrant pathways we can develop a therapeutic to address it.

2. Cancer cells change, just how we may not fully understand, and they do so in a Darwinian manner, and thus we must find another pathway control to stop the next step, and so forth.

The authors have thus raised a critical issue. We argue however that it need a workable paradigm to address its usefulness going forward.

Labels: Cancer

FRIDAY, MARCH 1, 2013

WE NEED A SHAKESPEARE AND DUMAS

I enjoy Dumas, he had a way to tell French history in enough detail, albeit with a twist, so that you could see from the common person's perspective what the often willful incompetence and arrogance of the Monarchy did to the public. Shakespeare did the same, albeit with deference to the Tudors.

We need some authors who can reflect the mess ups of our monarchs, oops, I means Presidents.
Labels: Politics

HARRY HOPKINS: A REVIEW

To say Hopkins was controversial is an understatement. But at the same time Hopkins was an enigma. For someone who rose from the streets as a humble social worker, to the permanent house guest of FDR during the War, as a man who at first became a politically astute distributor of billions to being the voice of FDR between Washington and London, and a man whose health was at best fragile and at worst terminal, this book is a welcome addition. Hopkins was praised by some, feared by others and outright hated by many.

Yet Churchill relied upon him heavily to execute the Lend Lease plan that had allowed Britain to survive. Also, it was Hopkins who made certain FDR chose Nimitz to counter the brash egoist of MacArthur, and provide for a successful engagement with the Japanese in the Pacific.

The book by Roll is a superb presentation of Hopkins in his role during the War.This book focuses on the Hopkins as the agent of FDR, as the advisor to FDR and as a communicator with Churchill and Stalin. It also provides a brief summary of the pre War Hopkins of the New Deal period.

Overall the book is quite comprehensive, is exceptionally readable, and provides an excellent summary and insight to Harry Hopkins, especially during this period. There have been many other works relating Hopkins and his involvement and a few books on Hopkins himself. In reading about Hopkins one sees a man who life in regards to FDR had two clear lives; first as a New Deal bureaucrat and second as an in house personal confidante and advisor to FDR. The first was a distributor of money and an ardent New Dealer, namely one who saw Government as the solution and only solution, and then second as an astute political insider getting involved in all the intimate details as regards to the War and its effective prosecution.

Before commencing with the specifics on the book it is worth understanding that not all though Hopkins was God's gift to the American people. Some saw him as a "Rasputin", some called him "Harry the Hop", and others just outright despised the man. For example, the anti-FDR writer, John Flynnn, one of the "America First" principals, the anti-war isolationist group, wrote of Hopkins:

As soon as Roosevelt got hold of this $3,300,000,000, congressmen, senators, mayors, governors, chambers of commerce, charity organizations from every state and city formed in line. Hopkins saw before Roosevelt did that the President had in his hands on a vast scale what political parties had had in the past on a very small scale. The little local bosses with their pitiful little graft and social welfare benefits from the district clubhouse were pikers. Now all the philanthropy in the country through local politicians flowed from one great boss in Washington. No district leader could satisfy the appetites of his constituents on a scale comparable to the big boss of all the bosses….

Hopkins inhabited an area of moral and ethical life which does not correspond in its standards of behavior to the area in which most normal Americans move. He was pictured to the popular audience as one whose life was dedicated to the welfare of the under-privileged masses. He had married as a young man a fellow welfare worker. They had three sons. In 1930 his wife filed suit against him for absolute divorce in New York State, the charge being infidelity. She secured the divorce and, I am informed, an order for the payment of $5000 a year in alimony. Hopkins was making $10,000 a year at the time.

This meant that one-half his salary would be retained for himself and the other half for the support of his wife and three children. It does not seem to have been an excessive provision. All this, of course, is a matter personal to Hopkins' own life, but it is germane here because of several facets of the incident. Shortly after the divorce, he took a second wife.

He became WPA Administrator at a salary of $10,000 a year. Hopkins himself was a man of very expensive tastes. It took a good deal of money to keep him provided with the forms of amusement to which he was addicted and $10,000 was not enough to take care of his two families and his expensive appetites

Let me now make a few specific comments on certain pages:

p. 14. The discussion of Steiner and the social gospel, social justice, etc is a good way to place Hopkins in terms of his world view. The mid-Western Christian world of the early 20th century

was perfused with social gospel concepts, in many was integrated with progressive thought. Social workers and many progressive politicians obtained their view of dealing with society in the context of the social gospel. It also was a basis for pulling together the Government as a participant in social justice. It would have been useful for the author to have expanded this point since in many ways it is what made the mind of Hopkins.

p. 25. The author recounts the $10,000 per year salary of Hopkins which is brought up many times and the fact that somehow he always managed to let it slip through his hand plus more.

p. 32. The New Deal is Born. The author seems to infer that Hopkins has a prominent role in the birth of the New Deal. That is not clear and the author should have detailed this a bit more.

p. 51. The author recounts the illness of Hopkins and is treatment. The indication was for massive blood transfusions. Ironically for a man who later was diagnosed with hemochromatosis, the added red cells and the iron would just make things worse. Hopkins had allegedly recovered from metastasized stomach cancer, and that in itself was a miracle. Yet his treatment was proper at the time and exacerbated the deteriorating situation. The author clearly delineates this continuing cyclic health issue.

pp 84-85. It was clear that Hopkins had managed to gain the trust of Churchill and that Churchill had high regard for Hopkins. Possibly this was due to the fact that FDR was somewhat incapacitated and that Churchill need FDR and the United States. Notwithstanding this became an essential communications channel.

pp 362-363: The author recounts the less than friendly relationship between Anna, FDR's daughter during the Yalta conference. It appears clear that it was deteriorating and that also FDR was being strongly influenced by Anna as well. The irony was that Anna's third husband, James Halsted, becomes the physician who published the "definitive" medical analysis of the physical deterioration of Hopkins. Hopkins at this time it appears was drinking and the ultimate diagnosis was hemochromatosis, which in 1945 was poorly understood. It is often simply treated today by phlebotomy, removal of blood. Instead for Hopkins it was aggravated by transfusions, increasing his iron load, and consumption of alcohol deteriorating an already depleted liver. On the trip back we again are show the physical depletion of Hopkins combined with that of FDR and their deteriorating relationship. What role Anna may have played could at best be inferred.

pp 366-367. Here one may have room to disagree with the author. He digresses on several points. He brings in G.W. Bush and comments made negatively on Yalta and then he states categorically that the real problem was not Yalta but the plan of Eisenhower in North Africa rather than an early invasion of Europe. There is a great deal of room to argue as regards to Yalta. The author himself had reiterated both the ill health of FDR and more importantly the complaints of Hopkins himself that FDR was ill prepared. Yalta did have consequences and the condition of FDR was a driver of those consequences. Yet the assertion regarding Eisenhower and his mistake is far from correct. The US had a poorly deployed Army and North Africa was a training ground for European entry. The resources were not available and the bombing was just beginning. Germany was strong and any direct assault of an untrained and untested Army on a trained and then still well-equipped German force would have been a disaster. Why the author

makes these points other than perhaps justifying FDR and his actions is uncertain and in the opinion of many baseless.

Overall the book is superb and definitely worth reading, both from the perspective of WW II but also for understanding the dynamics of the Presidency. From time to time the author allows personal views to float through but they seem few and far between. One comes away with another understanding of Hopkins, an elusive but critical figure at this time.

It would have been nice if somehow one could get a better understanding of the psychological relationship between FDR and Hopkins. After Hopkins got remarried and yet stayed in the White House, it seemed to work but when he finally left there appeared to be a break. One wonders just what brought these two people together. FDR was not one to have deep personal relationships. Morgenthau, his Treasury Secretary, did get close during Hopkins absence during the period of Bretton Woods but that was short lived and Hopkins returned.

The question is; what was the relationship between the two men, what did one have that the other did not and vice versa. Why, one wonders, did it seem to work so well at times and then split for short periods. Also one wonders how much of FDR decisions were truly influenced by Hopkins. FDR was a master of playing people off against one another to get that interplay to lead to a decision. He reached decisions by process, a process of "using" people, good people. What was Hopkins role in that effort, if any, or was he just another chess piece on FDRs board?

This book does a good job on many of these issues. It is definitely worth the read.
Labels: Books, Political Analysis

THURSDAY, FEBRUARY 28, 2013

ANOTHER ON LINE EXPERIENCE

I have previously written in the EdX programs and had expressed concerns. Specifically my major concern was that one found problems that could have been mediated by internal directions or by not over relying on external sources. The first problem was lack of discovering how to enter an equation and the second having to download and rely upon third party software, and thus not focusing on the course but some software package which one may not ever use.

I have just complete a Coursera course on of all things Equine Nutrition. Why, well frankly it was a mistake but I thought why not. Well I just finished it today and frankly it was quite useful. Unlike EdX it was simple, a five week course, and despite the Scottish accent of the Instructor it was interesting and enlightening. I actually learned something beside how Coursera works. Yes I passed and did reasonably well, so I found it rather useful. Much simpler than the MIT course, but somewhat akin.

Is there a future here? I now have several benchmarks, EdX, Coursera, and my Harvard Medical CME courses. The CME courses are lectureless, you just had better know or relearn the materials, but they are focused and intense. The Coursera are apparently for a wider intro audience and are just fine.

It will be interesting to see how these evolve but my thanks to the Coursera folks, a fine job well done!
Labels: Academy

NEW INSIGHT ON RAWLS

The book on John Rawls by Thomas Pogge is valuable contribution to the ever increasing body of professional literature regarding this late Harvard Professor and proclaimer of what Justice is. The book is overall a superbly written and presented addition to what is available. It is an excellent interpretation of Rawls' works and has parts of the discussion which present some semblance of balance with other thinkers; here I argue the discussions on Nozick and Sandel, both also of Harvard, are very worthy additions in the discussion. Rawls writings opened up a new dialog for political scientists in the late 20th century by espousing a humanist and communitarian approach to Justice, where Justice meant the sharing of a society's wealth, and inherently assuming that what any individual achieved was done so in the context of the contributions of all those around them.

Let me first begin by providing a summary of the Rawlsian theory. The essence of Rawls' approach to "Justice" is predicated on three elements;[66][1]

Original Proposition: There exists a means and method for a society to establish a Contract amongst and between them. This Contract thus created in this society of the just is one that maximizes the return on every transaction to the least of the individuals in the society.[67][2]This approach to contractarianism is one related to individuals in a non-bargaining environment establishing between and amongst them a "contract" to govern their society.[68][3] There are two elements contained herein.

The first is the essence of a contract, and in fact a form of social contract between the members of society and amongst them as a whole. This is a restatement of the classic contractarian view of a society.

The second element is that of a view towards man as a constrained and unconstrained view of human nature. [69][4]

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[66][1]See Kukathas and Pettit, Rawls, Stanford Press, 1990, for an excellent expository of the Rawlsian theory.

[67][2]Indeed in the Rawlsian world the individual posits their position and does so without any negotiation and thus posits a position assuming that that individual will be the least amongst players in that society. Such a position, to create justice in that society, is a ***maxi-min*** position.

[68][3]This is the same in many ways of the Social Contract envisioned by Rousseau.

[69][4]See Sowell, Conflict of Visions, Basic, 2002, pp. 18-24. Sowell does present an interesting a simple analysis of several of the issues.

The unconstrained view states that man, individually and in concert, has the capabilities of feeling other people's needs as more important than his own, and therefore we all act impartially, even when the individuals own interest are at stake.

The constrained view is to make the best of the possibilities which exist within the constraint.

For example, the constrained view of universal service is one which would state that if it costs a certain amount to provide the service, an there is a portion of the society not able to purchase the service, then there is no overriding need to provide it if such a provision is uneconomical and places a significant burden on the other member of society. The unconstrained view, as a form of socialism, states that if there is the least of us in want then they should have access to it at whatever cost.[70][5] Rawls approach to this contract is one wherein the individuals in the society collect themselves as individuals, and agree to a plan for the operations of that society, and they accomplish behind some veil of anonymity. That is no one has the benefit of knowing who may be getting more or less, including themselves.

First Principle of Justice: each person shall have equal rights and access to the greatest set of equal fundamental personal liberties.

Second Principle of Justice: social and economic inequalities are to be arranged so that they both, (i) provide the greatest benefit to the least advantaged. and (ii) attached to positions available to each individual under conditions of fair equality of opportunity.

This latter element of the Rawlsian world is often viewed as a Schupeterian form of socialistic control. If we were to define the public welfare by a function as some measure W, and each individual listed as a variable I, then the policy choice, which we would call P, is chosen such that the welfare is maximized for the least advantaged. What this states is that we want to maximize the society welfare subject to the constraint that no individual suffers due to the change or execution of a policy P.

We can compare this to the utilitarian school which states that we seek the maximization of the average welfare for all of society, sort of a raising of all the boats approach which is not constrained on what happens to any one individual, but to society as a whole. This approach is the basis of the Ramsey tax policy. The Ramsey approach is Rawlsian whereas the approach of an Adam Smith or other utilitarians is the average approach.[71][6]

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[70][5]See Schumpeter, Capitalism, Socialism, and Democracy, Harper, 1942, pp. 167-186. Specifically, he defines socialism as; "*an institutional pattern in which the control over the means of production and over production itself is vested in a central authority- or, as we may say, in which, as a matter of principle, the economic affairs of society belong to the public and not the private sector*."

[71][6] This is the Baumol Willig theorem in economics which uses the first Rawlsian approach to maximizing the return subject to a single constraint; namely that the monopolist suffers no harm.

Now let me address several of the specific sections of the book. This is in no way inclusive; it merely highlights some of the worthwhile parts of the book.

pp 11-15. The involvement of Rawls in WW II is a major turning point in his life. He fought in the battle of Leyte in the Army as an enlisted man, albeit a college graduate. His decision, frankly a wise one to not obtain a commission, since if he had he could and most likely would have been drawn into Korea, did place him in places of significant carnage. I had written a book on Navy actions during Leyte, my father was there, and the brutal land as well sea engagements left lasting change on all the men involved. Although the author does reflect this it clearly is of interest to have explored this seminal event on the part of Rawls and better understand how this set the path for his future views of human existence and the relationships he would suggest imposed on society. In my experience interviewing dozens of men who fought there the effect was lasting and world view changing. Although presented, it truly deserves deeper understanding.

p 20. The author presents some of the conflicts during the 60s which further made for his world view, especially the perceived draft inequity. For example, for Rawls, he could not understand education deferments, that is, those, say studying engineering, being deferred while those, not in college, being drafted. In essence this was a utilitarian approach, in that it was assumed that the draft scheme benefitted society on average better than equality in the draft. To Rawls, the very poorest student or person should have equal treatment. One sees a kernel of his theory of Justice emerging.

p 28. The author starts with the statement: “Justice is the first virtue of social institutions.” My concern here is several-fold. First, it is declaratory without a basis. Second, fails to define Justice, virtue, and social, and I will assume I understand the term institutions. This is a Rawls statement, the beginning of his work. The second part of the sentence missing is “as truth is of systems of thought.” Yes Rawls uses this in almost a Marxian declarative manner, or like Rousseau, man and his chains, but it leave one wondering what this justice thing really is. The author does begin defining it and his use of social justice for Rawlsian Justice is telling. For social justice had already had a long history in Progressive movements for almost a century by the time the book was published. Again one wonders how much of this also influenced Rawls.

p 29. The author discusses somewhat the origin of the Theory of Justice. One would like, as I have stated before, to have seen a more expansive overview, one linking a bit more of past social justice thought. I did find his analysis on this page reminiscent of Scholastic thinking and methodology.

p 30. There is a discussion of happiness. One is left asking what happiness is. This of course is a problem with many who approach this area, use of terms like happiness, fairness, all too often

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This is of course a different twice to Schumpeterian socialism, wherein a monopolist usurps the power of the state for its own benefit.

are in the eye of the beholder and have long histories of use by different people for different purposes. However the author will return to this important issue later.

pp 43-44. This is an excellent introductory approach to Rawls. The author clearly discusses the concepts of (i) consequentialism, (ii) humanism, and (iii) normative individualism, all elements of the Rawlsian theory.

pp 48-48. The discussion on the anonymity issue, the veil of ignorance, is reasonably well done. My only difficulty was the detailed discussion was less than fully descriptive.

pp 53-54. Here the author does go into some detail on Rawls own objections to happiness. This I found quite enlightening and exceptionally well done. The two objections to using happiness are clear and to the point and definitely worth spending some time on.

pp 67-67. This is the maximum versus average argument, it is my argument from Mill and the Utilitarians to Rawls and the Redistributionists. Rawls wants to consider the least of us in his use of Justice, Mill just wants to make sure on average we are all just fine. Mill and the Utilitarians have a more "democratic" metric, namely the group on average, and Rawls want to make certain that we do not disenfranchise anyone.

p 75. The author has an interesting discussion regarding the allocation of goods, redistribution and society. It is a critique of certain elements of Rawls but clearly worth examining.

pp 178-185. The author compares Rawls to some of his critics. He considers two at length, Nozick and Sandel. The Nozick opposition is characterized by three objections: (i) that Rawls is a redistributionist, and this violates fundamental property rights, (ii) that Rawls in his redistributionist view demands a sharing on equal basis denying individual contributory differences, and (iii) the Rawlsian view of collectivism, namely that any single individual benefits from the contributions of all in society and thus no individual stands alone, only on the efforts of all others in society. In essence Rawls is an anti-individualist, and Nozick is a libertarian. This is not exactly at total odds, but it is fairly close.

pp 185-188. Here the author does a comparison with Sandel and his communitarian views. Although, not at as great a set of odds as with Nozick, the author does a superb job in making these contrasts.

Overall the author provides a professional, articulate, accurate and highly readable and accessible overview and analysis of Rawls. As I have indicated the deeper analysis and understanding of Rawls the man would be exceedingly useful. For example, what led him to evolve these ideas, what resonances helped him along the way, why did he believe that he was right and others were in error? Understanding Rawls as a philosopher I believe requires understanding Rawls as a man. I have yet to fully see that task achieved. Yet this book is a very valuable contribution to that effort.

Labels: Books, Individualism, Political Analysis

THURSDAY, FEBRUARY 28, 2013

OFFICE OR NO OFFICE, WHAT SHALL IT BE?

The Yahoo CEOs demand to return to the Office strikes a chord. I have mixed feelings on offices, having spent about half my career in one and the other half away from one. Large Corporations waste so much time at meetings that one wonders how any work is accomplished. I recall as I moved up the NYNEX/Verizon hierarchy how I spent more than three fourths my time at such meetings as Quality, Ethics, "Planning". and the like that I could never see how work got done, and in fact it did not. It was the Phone Company.

As the NY Times recounts:

A memo explaining the policy change, from the company's human resources department, says face-to-face interaction among employees fosters a more collaborative culture — a hallmark of Google's approach to its business.

In trying to get back on track, Yahoo is taking on one of the country's biggest workplace issues: whether the ability to work from home, and other flexible arrangements, leads to greater productivity or inhibits innovation and collaboration.

In my experience the answer is a bit of yes and no. First of all Yahoo seems in my opinion to be a dying entity, just is no one seems to have told the patient. But that aside, it is nice to have key people accessible, but that can be accomplished in various ways. But again leadership is essential, if you demand certain performance from your troops you must be out in front doing ten times more. If you do not lead by example then people immediately see you as a self centered egoist. Not a good thing when you are trying to right a sinking ship.

The other side of this argument is that if you want people in the Office then when they are away from the Office the corollary is that you leave them alone; no cell phone calls, no emails, no video conferences, no instant messages, no nothing. Yet I suppose that this side of the equation

will not be honored.

Productivity can be quite high "at home" or not in the Office. I can be ten time more productive. Yet my group productivity demands face to face contact, not even a video conference makes it. So I travel to Boston, Washington, etc to "meet" people since effective collaboration is contact intensive. Thus one must separate the two functions; collaboration versus concentration. Programmers, writers, etc may function better alone and at "home". Executives must meet, but then again they are on the road frequently.

Bottom Line: It all depends and no one size fits all. But again one leads by example. I spent a portion of my life doing "turn arounds" and that demands up front leadership, leadership that has people follow, not be ordered to do so.

Labels: Commentary

WEDNESDAY, FEBRUARY 27, 2013

THE IDEA FACTORY: A REVIEW

It is frequently said that history is written by the victors. This is a history written by the defeated. It is a hagiography of a select few who were at Bell Laboratories (Also Bell Telephone Laboratories, BTL). It also is a paean for the return of structures like Bell Labs despite the overwhelming evidence of the technical and economic success of the entrepreneurial and "creative destruction" mode which has been a dominant driver of our economy since the breakup of AT&T, and even slightly before.

This is a review of The Idea Factory by Gertner. It is placed here rather than on Amazon due to the negative attacks.

Let me commence this review with some bona fides. From 1964 through 1972 I spent a considerable amount of time back and forth from MIT and Bell Labs. I worked in Electronic Switching and in the Defense side; I worked at West Street, just before it closed, then Holmdel, then Indian Hill and finally Whippany. I saw many sides of the business as an MTS during that period. Then again from 1986 through 1990 I became Head of R&D at NYNEX, now Verizon, and thus had to manage parts of Bellcore, the residue of some of Bell Labs. In between I have run CATV companies, Satellite companies, fiber companies, wireless companies, here in the US and in over 20 other countries. I have written over 125 papers and fourteen books, many relating to telecom. Thus my approach to this book brings the "distinct disadvantage of experience", unlike the author, who appears to have none in this space.

Now as to the many principals in this book I have known some personally. John Pierce taught a semester seminar at MIT, I believe the spring of 1971 when I was finishing my degrees, and I was strongly advised to go. I did and it was an hour of hubris each and every time. At that time the world was already changing, I had worked on Apollo and was essential to its guidance system; I had even worked my first start up the end of 1969, albeit as a consultant yet I saw the future. Pierce was stuck in the past, and the longer he spoke the more I saw that. Big monopoly R&D was still his mantra while we were seeing small startups in the back yard buildings around

MIT, companies like DEC. I would see Shannon, a ghost like person, in Building 26 from time to time. He was a total contrast to Wiener, who wandered around with his cigar, listening and speaking to whoever would listen. I never heard Shannon utter a word, and I was teaching Information Theory at the time.

I believe that there is a story in Bell Labs, but that this book grossly fails to tell it. The story is one of a monopoly controlled entity whose actions actually set our technology back, perhaps a decade. Add this to the NASA boom in the 1960s and you had a perfect storm which diverted American entrepreneurialism back for a lost decade, thus it led to the Japanese bubble in the 1980s, but by 1990 the US caught fire again. That is a story worth examining.

Page by Page Comments

The following are some page by page comments and then I will provide some overall observations.

p. 3 The author starts by contemplating how ideas begin. He uses wireless communications and computer networks, and he then uses these two areas as exemplars of what Bell Labs produced that our present and future depend. Unfortunately that is not really how it worked. Let me begin with computer networking. That began with ARPA, first Larry Roberts and then Bob Kahn. Add Vint Cerf, Irwin Jacobs, Kleinrock, and yes even yours truly, I did the satellite connections, and we have the beginning of a new world. But what of BTL? As told to me by one of the principals at ARPA, they went to Murray Hill to seek support to use a Bell modem to test out the ARPA net. A couple of folks from ARPA enter a room filled with BTL executives. Before they could talk about their needs, the BTL Execs told them that if they wanted anything then just give BL an open ended contract, they will decide what is needed, develop it, operate it, and they, ARPA may then determine whatever they want with the data. Fortunately ARPA folks did not comply, the thanked their guests, and went out and assembled a team that in a highly entrepreneurial manner developed the Internet. An Internet that did away with AT&T. It was hubris that led to their ultimate collapse. It was the hubris of the monopoly, of the very structure that the author praises, never asking to see the other side.

p. 5 The author denigrates the entrepreneur by lauding the colossus of BTL. The very nature of technology development is the continual “creative destruction” that is required, the change of the past with the replacement of the new. The typical example is when BTL developed and implemented the Electronic Switching System, ESS No 1, it was a computer controlling massive amounts of mechanical switches, fereeds. Fred Kappel was the CEO of AT&T at the time and he wanted to see this progress to a fully electronic system. Fred tried to get the Labs to develop such a system but the rigidity of the Labs management said that he would get it in due time. So Fred went to Canada. You see ATT owned a large interest in Bell Canada, and they owned Bell Northern Research. He then asked them on the sly to develop an all-digital switch. They did, the first one was sold to New York Telephone and from that came the competitor to Western Electric, Northern Telecom. It was my way or the highway at BTL, even to ATT. Yet one person at ATT said no, and sought a “creative destructive” manner to solve th problem.

p 81 The statement that “it would become a kind of received wisdom that many of the revolutionary technologies …” One must ask by whom was this wisdom received. There were other voices, many other voices. In fact in the 60s there was an explosion of other voices, in many ways driven by the Cold War demands for innovative technologies. Places like MIT Lincoln Labs, developing technology well beyond what Bell Was doing. Silicon Valley was just starting, large Defense contractors were seen many offshoot startups, like Linkabit, STI, and others which were pushing telecom well beyond limits at BTL. Satellite companies like COMSAT had developed TDMA technology, and even developed spread spectrum for use in enhanced telephony, key to all mobile systems today. ARPA was doing packet radio. There was an explosion of technology, much from outside BTL. In contrast when one of my Czech partners, the former Communist head of the Czech PTT, Moscow educated, told me they use Bell System Technical Journal designs to try to reverse engineer systems until they found out Erickson was much farther ahead!

p. 118 The author again and again brings out the mid-west origin of many of the people. This stylistic approach of using the same facts over and over can and does become a distraction.

pp 122-123 Again we have a mid-west hero. But this time it is BTLs adventures in radar. In reality there was a battle between MIT, BTL, and MIT won with the Rad Lab. However BTL learned a lesson and tried to be certain this would not happen again. At the bottom of p 123 the author alludes to Shannon and his work on fire control systems. In reality there were many independent contributors to the enhanced fire control in WW II< and one of course was Norbert Wiener and his use of random processes with control theory. Wiener was a true mathematician, Shannon was at best an applied mathematician. Wiener’s problem was he all too often made certain the answer was acceptable to the best of the best, Shannon gave simple and highly readable descriptions available to the many.

p. 128-129 The classic Shannon papers were so successful not only because of the insight but more importantly because of the presentation and simplicity of paradigms. Before his peers one had complex pure mathematics or hand waving engineering. What Shannon did brilliantly was two things. The block diagram in the book and the one missing, the binary symmetric channel, BSC. From the BSC came innumerable advance in information theory and communications. But Shannon also took the reader through the problem as if it were a simple novel, it was not a challenge until you got to the end. It clearly was one of the most brilliantly written papers ever, beyond its ideas. It made the reader comfortable, you could sit down and become engaged.

p. 130-131 The problem with many non-technical authors is how best to explain Shannon’s results. Simply they were threefold; first, any signal can be defined in terms of some measure call information. Second, knowing the information at a source, then one can also determine the information transferring capacity of a channel, the stuff between source and sink, and this delimits the rate at which you can transfer the information. Third, this is often overlooked, the source coding theorem, which states that you can compress the stuff that you send. The author did not discuss this.

p. 153-154 The author discusses Kelly College and the Techs. Kelly College was a way to educate the people inside. However one thing I could never find was how a Number 1 Crossbar

worked. I could do that when speaking with craft folks but not at Kelly College. I did get queuing theory, but from a BTL perspective, namely looking at trunks and overload trunks. Kelly College turned into a Master's Degree program first at local Universities and then at major Institutions. We had a large group at MIT. Now for Techs, they were good, they had been trained typically in the military and could advance to AMTS, Associate Members of the Technical Staff. But there was a glass ceiling. If you got your degrees after starting at BTL you were almost always never going to become MTS. I always found that disturbing.

pp 184-185 The author's reference to the Organization Man is quite on point. BTL was a hierarchical system, it made the Catholic Church look like an interloper. Everyone knew their position and if you had a godfather you could make it, otherwise you became a "40 year man" In addition you had no ability to move about unless they asked you to do it. The entrepreneur was anathema. You were told what to do and you did it their way. Kelly clearly was a top down manager. The tale the author tells of his public termination of supervisors after WW II, apparently lauded by the author, is one of the most demeaning and demoralizing acts I have ever seen. You just do not do that, it is not gentlemanly.

p 191 Pierce is introduced with the accent on his being an only child. That characteristic is brought out several more times. It would have been useful to have explored some of these issues: poor families, only child, mid-west, and on and on. In my observations a strong New Yorker would most likely not fit well.

pp 216-219 This is a long discussion regarding Pierce and the satellite. It appears that Pierce was enamored with the technology and not the system, service, and economics. As I will show later he decided on a design to provide excellent voice quality, albeit economically infeasible.

p. 225 This is classic Pierce and accepted by the author as gospel. The author states:

"He (Pierce) doubted satellite engineering could advance at the same rate without Bell Labs …"

That was in reference to the establishment of COMSAT, even though ATT owned some 25-40% of the new entity. The author fails to seek the veracity of such a statement. For by this time NASA existed and NRL and other Government entities have extensive satellite experience. In fact the experience well exceeded anything within BTL. This approach by the author again and again accepting statement at face value is a true and basic failing of the book.

p. 250 The author by this point is becoming annoyingly repetitive. We have heard multiple versions of Shannon stories or Shockley tales.

p 252 The development of the integrated circuits was a massive loss for BTL. It was done by entrepreneurs outside the Bell System. The author's comment by Ross that "it could never be reliable" is again a reiteration of the not invented here syndrome. But by the time this happened the very foundations of BTL were crumbling. DoD was demanding more advanced systems, technology, and the industry and more importantly the people, were finding new ways to deliver this in a more efficient and cost effective manner. Not the Labs way.

pp 302-303 The discussion about the Drucker paths is worth some note. The alternative of going into business for itself and making money from its patents what in reality is what companies like Qualcomm actually did in the very same time period. When at NYNEX I was the instigator in our venture fund investment in Qualcomm, for after all Irwin Jacobs had been my faculty advisor at MIT.

Specific Observations

Let me make a few detailed observations using the words of people who were there. I choose two, Jack Harrington who was my boss at COMSAT and Paul Rosen who was my boss at MIT Lincoln Labs. I find their observations regarding Bell Labs on point and reflective of some of the serious issues the author failed to consider.

Let me begin by looking at Pierce and his satellite program. He had the big balloon, a jump the shark act, to put BTL out in front. It was good PR but poor technology. Out of that came COMSAT, I was there for six years, and that became the focus for satellite and other communications technologies. COMSAT was set up by law in 1962 and was incorporated with an IPO in early 1963. But they raised some $500 million in anticipation of having to build the satellite system proposed and designed by Pierce and the BTL team. Yet that was a low orbit system requiring tracking antennas and dozens of satellites with many launches to keep them up there. It was the most expensive design ever considered. In 1961 Pierce had written a detailed article in Scientific American detailing his design. He concluded:

The cost of a global satellite communication system will be large-on the order of $500 million-but no larger than the cost of undersea cables that could provide the same geographical coverage. (One cannot say the "same service," because undersea cables do not yet provide the band width needed for television.) Assuming that the experiments of the next few years are encouraging, there should be no lack of capital, domestic and foreign, to share the cost of a world-wide satellite communication system.

Pierce's proposal was:

A system of 40 satellites in polar orbits and 15 in equatorial orbits would provide service 99.9 per cent of the time between any two points on earth. A.T.&T. has proposed that the system contain about 25 ground stations so placed as to provide global coverage. Bell Telephone Laboratories is building an experimental satellite to test the feasibility of such a system; NASA has agreed to launch it early next year for a fee of about $6 million, to be paid by A.T.&T.

The technical problems were tremendous, many of which I suspect Pierce had no clue about. But just after COMSAT raises the necessary $500 million Harold Rosen and his Hughes team launch Syncoms 1 and 2, synchronous satellites (February and July 1063). Much less expensive and much more effective. They just need simple antennas and they only require 3 for global coverage.

From oral histories at COMSAT Jack Harrington, a former MIT Professor but head of Engineering at COMSAT when I got there states[72][1]:

NGS: Although just the fact that you knew that you could in fact launch the satellite, put it into geosynchronous orbit, didn't necessarily mean that it would be a commercially viable system because of the time delay.

JH: Yeah, there were time delay effects which under certain circumstances can be troublesome. The Bell people [Bell Telephone Laboratories] made a big issue of that.

NGS: The "Bell people" meaning John Pierce?

JH: Yeah . The Bell Labs people in general and the AT&T people in general. I wouldn't particularize it, but John Pierce was certainly one of the strong spokesmen of the time delay effects on satellite communications.

NGS: Now, do you feel that there was pressure on the part of the engineering staff by the people at AT&T? Obviously, who had TELSTAR, had had success with TELSTAR.

JH: I think it was clear that if one left it up to the Bell System to specify the nature of the satellite system, the specification would have gone to a medium-altitude satellite, and the reason was to control the delay. Which is annoying, no question. It's very annoying.

Pierce it appears designed the satellite system to meet delay issues and not cost. This was a pandemic issue at Bell. Cost and any tradeoff were thrown out the window if the "best" in their sole opinion could be delivered.

Now to the issue of computer networking. In an oral history with Paul Rosen, one of the MIT Rad Lab team, he states[73][2]:

At the time Bell Labs had great men working on this, and they said if one drives a telephone line over 600 bits per second, one has arrived at the end of the flat earth, and you've had it. With my simple device I did 1800 bits per second consistently. That was a big deal, because they were going to install thousands of miles of transmission. They (the Bell Labs people) adopted my modem – initially. Jack Harrington and I got a patent on it. I did the grunt work and Jack did the analysis post facto that it would work. One of my colleagues said, "Oh, you're going to get rich on this." We had an incompetent attorney at MIT. You have been with academics. I think you may know that some the administrative people associated with academic institutions believe that they have tenure until ten years after they die. This attorney was terrible. The problem was that he let me write a patent application that was much too constrained.

[72][1] http://www.comara.org/legacy/oralhistory/

[73][2] http://www.ieeeghn.org/wiki/index.php/Oral-History:Paul_Rosen

Much, much broader claims. The result was that when this system ultimately went into the field indeed my design was the one that Western Electric (under Bell Labs aegis) built for its early stuff. There was an Air Force contracts officer who thought that Harrington and I should have gotten something out of it. We got point-triple-O nothing because no one would buy the patent and it belonged to the government. The government gave it to Western Electric and that was the end of it. In the meantime, having worked at these sites first on the components that made up these machines, and second on these machines and third on installing them at sites we began to make a system. I became the leader of the group that built and installed these pieces of equipment at the various sites.

Now what is most startling about this is that Rosen did this in 1945! BTL was still only providing 300bps modems as late as 1980. It was this very 300 bps modem that the ARPA folks wanted to upgrade gratis and that they already knew could and had been done. Where BTL had competent patent attorneys Rosen is quite clear as how MIT just lost a tremendous opportunity. Yet it would be again in the early 1970s when ARPA folks, many from MIT, went to BTL again, they in their normal arrogant manner dismissed them, and the ARPA folks took their demand to people like Linkabit, Codex and others, and thus we had a Hayes modem of the early 80s, and now we have modems of 10s of Gbps on silicon chips. Creative destruction at work, and a missed opportunity for the author to have grasped an important observation and made it worthwhile.

Overall Observations

Let me now make some overall observations than that I have delineated some of my concerns as well as having provided a background of facts which counter the overall theme.

The Message is a Hagiography: This is one continual praise after another for a small portion of what was BTL. There were at times upwards of 15,000 people at the Labs and many just worked away in the tombs of technology. They were buried in routine and endless tasks and creativity was often stifled. I am reminded of an office mate of mine for a shot while at Whippany. I suspect he was mid to late 40s and had PhD in mechanical engineering. For twenty plus years he had been with the underwater cable group, an area praised by the author. He would come in at 9 promptly each day, open his door, then go down get coffee, read the Wall Street Journal, call his broker, then do some work, then go to lunch at 11:30, then go off to a Bell Labs club of some sort till 1:30, return with another cup of coffee, do some work, the call his broker, then read the Journal again, then leave at 5 PM on the dot! He did this every day! It was like a prison sentence, nothing new, and nothing different. For he was the stress-strain expert on the underwater cable and thus he was good for the next twenty years, he was what we called a “forty year man”. He was the guy who had done X and X had a 40 year life in the Bell System so he was stuck with it forever. I saw hundreds of grey 40 year men! They do not come out in this book.

The Style is Overly Repetitive: As I have noted above the author tells the same tale a dozen different times and a dozen different ways. He tells and retells Kelly, Shannon etc.

It is a Paean to Pierce: One must ask why so much on Pierce. His claim to fame was an analysis of the Travelling Wave Tube, a microwave amplifier. Nice job but sooner or later some PhD

student would have done the same thing. Pierce was abrasive, arrogant, and frequently in my opinion wrong. One needs look no further than the satellite tale. Shannon was elusive, Pierce arrogant, and Kelly abusive. Nice group of folks to hang around with.

It Fails to Tell the Other Side: The Rad Lab at MIT made seminal developments in radar and communications. The Labs, according to many writers, always was trying to shut them down and take over the work. One needs look no farther than Norbert Wiener and his feedback systems for fire control. The Labs had invited Wiener solely to pick his brains and then to do an end around run. Fortunately Wiener was smart enough. The other side would be to tell what MIT Rad Lab had done. One needs look no further than the classic Rad Lab Series of books, each of which must have started a dozen new companies over time. I use the Servomechanism Rad Lab book to design Apollo guidance systems, and Antennas for designing satellite systems. There were no such products from Bell. Take Shockley's book on semiconductors. I tried it a few times but there were much better documents from those outside of BTL.

BTL Was Set Up to Preserve the Monopoly: The Kingsbury Decision made ATT a legal and untouched monopoly. In fact it was written into the Antitrust laws and thus it could do fairly whatever it wanted to and the Labs was a means to preserve that bulwark against any intruder. Their portfolio of patents was a protective measure, less a technological platform to deliver the best available. It was a bulwark against competitors and innovation. The author never seems to be even aware of these issues. Somehow he gives the impression that they actions were purely and always benevolent.

What of the Other People: To understand BTL and to opine on it being the proper paradigm for research one must look at it in its entirety. Not as a single set of a few "strange" people, albeit creative. What of the thousands of "40 year men" who when the Labs went bust were thrown into a world they could not understand. The outside have moved centuries forward and these rejects were cast asunder.

BTL Publications: There were two BTL publications; The BSTJ and Bell System Journal on Economics. The BSTJ seemed to serve two purposes: an in house technology release organ and a vehicle for publishing interesting technical desiderata. The Economics journal was different, it was the house organ attempting to gain peer acceptance in economics addressing issue which were related to justifying ATT positions with regulators. The economics justified the ATT filings but the people were at Bell Labs. One would have liked the author to explore these publications, what they did, how influential they were, and what the staff thought of them.

The General Executive Instructions, GEI: There was a manual, in fact a book shelf of them, called the GEI. It told you what size office you would have the desk type, the chair, the phone, travel restrictions, vacations, the tiles on the floor, the promotion and salary scales, the organizations structure. It was all regimented to a fine point, and it applied to all. It surpassed anything one could think of even in the Federal Government. It was suggested that this was Kelly and his heavy hand but I was not there long enough to truly understand. But it was pervasive, and no entrepreneurial company could ever exist under such binding regulations.

Thus in my opinion the author had a wonderful opportunity but totally missed it. In my opinion,

true historical writing requires both sides, the writer must be competent to understand when they are being used and by whom. Was Bell Labs a sine qua non of R&D. Not really. It did insure the monopoly control over telecom for decades but it also became the seed of its very destruction. Today there is not a single US manufacturer of telephone switching equipment. So this is a legacy?

Labels: Books, Telecom

TUESDAY, FEBRUARY 26, 2013

TAKE THE CHILDREN AWAY!

I have been reading the proposals for pre-K Federally mandated education. As the White House States:

Study after study shows that the earlier a child begins learning, the better he or she does down the road. But here's the thing: We are not doing enough to give all of our kids that chance. The kids we saw today that I had a chance to spend time with in Mary's classroom, they're some of the lucky ones -- because fewer than 3 in 10 four-year-olds are enrolled in a high-quality preschool program.

Most middle-class parents can't afford a few hundred bucks a week for private preschool. And for the poor children who need it the most, the lack of access to a great preschool education can have an impact on their entire lives. And we all pay a price for that. And as I said, this is not speculation. Study after study shows the achievement gap starts off very young. Kids who, when they go into kindergarten, their first day, if they already have a lot fewer vocabulary words, they don't know their numbers and their shapes and have the capacity for focus, they're going to be behind that first day. And it's very hard for them to catch up over time.

The Federal Government now wants to extend public education down to the infant, it reminds me of the old Soviet Union and child indoctrination. Parents cannot be trusted, they may create an independent thought. Public School teachers will tow the Party line. When does the Great Leap Forward occur, when do we send the Harvard Faculty to the fields, working rice along side the new immigrants, keeping the cotton mouth snake at a distance?

Parental responsibility should not be shoved off on all the taxpayers. Especially from someone who apparently does not afford themselves of the public school system.
Labels: Politics

ARE THE SHIPYARD WORKERS BEING PAID?

There is a piece about the current President at Newport News shipyard bemoaning the cut in the allowed expenditures. The Hill has a description. But a question when I saw the crowd. It appeared that hundreds if not thousands stopped work on "vital" ship work to stand idle as stage props. Were they still on the clock, and if so how much money was wasted there? If we had say

1,000 for 4 hours at a fully loaded salary of say $100 per hour, then that is $400,000 just standing around! What if there were more?

You see, this just makes no sense. It is not a real cut, it is a cut from an increase. The increase was more than the cut! Why all the fighting, why not negotiate. One would like to see Grammar School Report Cards, "Works Well With Others". D!
Labels: Politics

SATURDAY, FEBRUARY 23, 2013

TRUST, STAELIN AND MACROECONOMICS

Dave Staelin was a prominent Professor at MIT who I had the good fortune to know since my first days as a Grad student in the early 60s. In fact I believe I was in his first class as a Faculty member, Radio Astronomy if I recall. Towards the end of his life, unbeknownst to me at the time, we had many long conversations regarding the economy, economics, and what the problems were. Dave was a great thinker, a big thinker, and at the time I was just coming up the ramp of understanding what was afoot. It was 2009 and 2010, just before he passed away, we would have lunch and trade papers.

In one of his papers he wrote:

To summarize, today's dilemma arose from the dramatic successes of modern technology in spreading knowledge and capital across the globe. Rich nations built plants and exported both knowledge and aspirations around the globe, generously enabling poor nations that organized properly to bootstrap themselves into the restricted capital-rich sector of the global economy. These same rich nations failed to recognize that such open exports of capital would weaken their own ability to produce and retain liquidity. As such rich nations became dependent on others to provide goods, they first paid with other valued goods and then increasingly with credit based on trust—credit and trust that became overextended. But loss of trust is a two-edged sword affecting both creditor and debtor, for the creditor also needs liquidity, and liquidity losses due to reductions in local or national exports propagate across the entire global trust and credit network. Such losses force both creditors and debtors to reorganize, and if they must reorganize rapidly the resulting human displacements can further erode trust in government and self, which are the fountainheads of trust.

Trust is key to both economic and social liquidity, for trust alone binds us locally and nationally in both our economic and social structures. Absent trust, both are in jeopardy.

At the time I did not fully understand what was being said. Now I believe I do have a better grasp and feel it is worth sharing. You see, for Dave, Trust was what was Quality to Pirsig. Trust was the underlying element of a stable economy. Trust was what created the AD and AS that we see the macroeconomists talking about, the basis of arguments between nations. Trust is engendered by a good leader. Mis-Trust is a bad leader. A growing economy is based on Trusting the leader, or leaders, a collapsing economy is based upon mistrust.

Dave had hist upon a true piece of insight. He was fundamentally and engineer, an engineer in the true sense of the word. He believed in facts, in modelling and demonstrating the results, which is why perhaps my missing what he was saying on Trust was so easy to do, I was looking for the quantitative answer, instead he laid out an existential answer. Now as I have read and watched some of these macroeconomists I have a deepened grasp of what Dave meant. Too bad we could not continue the conversations.
Labels: Economics

WHAT IS MACROECONOMICS?

What is macroeconomics? All too often I read detailed analyses, in texts, the literature etc, which are the basis for the policies postulated. All too often these policies just do not work. Again and again I come back to Romer and her fallacy regarding employment and the Stimulus. Perhaps I have been the only one holding her feet to the fire.

I just spent a few days helping my grandson in Prep school understand physics, 5th former, but the fact is that I could explain by demonstrating. I can demonstrate a pulley, I buy a few at Staples, then connect them and then measure. Predictions equal experiment. It happens each and every time. Not so with anything in macroeconomics.

I wrote recently regarding the observation that the economy is all too often driven by people's opinions and beliefs. The question may be whose beliefs and opinions but that is irrelevant just now.

I saw a piece today in The Money Illusion which reinforces my point:

Most of us macro teachers work with some sort of new Keynesian model. This is roughly the AS/AD model, with an upward sloping SRAS curve.We teach the model by repeatedly lying to our students.

Yes indeed, they are lying, lying but having convinced themselves that somehow the math makes it all true. AD is really a belief system, consumers are happy, they believe, we have a Reagan recovery. They do not believe, Johnson and Carter, and we have inflation and recession. Do fundamentals matter? Somewhat, but I am afraid not much. Trust is key. Trust was something that an old friend Dave Staelin had been trying to get me to believe in before he passed. I was not getting it at the time, now I do, thanks Dave.

The article continues:

If oil shocks are going to raise inflation, they should lower RGDP. Yet even during the worst of the oil shock period (mid-1973 to mid-1981) RGDP rose by 2.6% per annum. So the inflation was almost all monetary, even if you generously assume RGDP growth would have been 3.6% in the absence of the oil shocks. In fact, growth slowed sharply after 1973 for reasons mostly unrelated to oil; the rapid improvement in products like jet airliners and home appliances came to a screeching halt. We shifted toward a slower growing service economy. We couldn't even

average 3.6% growth in the 1990s, when oil got cheap and the computer revolution took off. Are these lies justified? It's nice to give students some real world examples of fiscal shocks and supply shocks. But what if the message they take from this exercise is that monetary explanations of inflation and NGDP determination are "just a theory," just as evolution or global warming are "just a theory." What if the public doesn't realize that the Fed drives the nominal economy? Might that lead to less effective public policies? Might that have contributed in some small way to the fiasco of 2008? I think our students can handle the truth. Why don't we stop lying?"

Now again Trust in the leaders are essential. I think Reagan understood that, not clear of Clinton, perhaps he was just preoccupied elsewhere.

Now my favorite economist, Nick Rowe, has a posting today regarding teaching of monetary policy in macro. He states:

I always suffer self-doubt when I teach the Money part of Intro Economics. Perhaps I'm over-thinking it, and it would be better for my students if I told myself to shut up, and just give them some simple clear story. But how to get it simple and clear, yet not horribly wrong or incomplete?

Sense a theme here folks? The Gnome from the South who blasts his instant thoughts to us from the Times would never make a statement like these two. The Blob from the West would never have such humility. But here we have two clear statements.

As Nick states when speaking of the meaning of money:

Words don't really mean anything either. But people use "cat" to mean cat, because everybody else does too. Sometimes which equilibrium we are in depends on history.

A bit of Ockham and nominalism, but money is just easy to hold, unless and until there is a replacement, and we have been using it for a few decades now, agreed upon credit.

As Nick finishes his piece:

Because once you start talking about "the demand for money", in the same way you talk about "the demand for apples", you end up with (orthodox) nonsense like the idea that the stock of money is determined by the quantity demanded at the rate of interest set by the central bank. Which makes sense for a good like apples, which is traded in only one market, and which people either buy or sell. But doesn't make sense for a good like money, which is a medium of exchange traded in n-1 markets, that everyone both buys and sells. The quantity of money will be determined by the demand for loans at that rate of interest, but the demand for money is not the same as the demand for loans. But that's a topic for another post. ***This is far too complex and too abstract.*** *How is a first year student supposed to understand all that?*

Yes it is far too abstract. I have been tracking the FED Balance Sheet for four years plus now, watching it explode, as a result of the debt. It should make me terrified of inflation since most of

that stuff has a duration and when it expires one hope they roll it over as they seem to be doing. But what if they don't, what if people believe they will not, what if people lose Trust in their Government? You see Trust really counts, it is the AD, it is the ability to "believe" in money, and it is not really measurable, you cannot come up with a stochastic differential equation defining Trust. Even at MIT, I have seen it tried.

Labels: Economics

FRIDAY, FEBRUARY 22, 2013

HAVE THEY NO SHAME?

The upcoming "cuts" in Government spending are not only necessary but are an exercise in ferreting out those whose hold of any semblance of reality is questionable.

Take the Secretary of Transportation ans the comments in today's NY Times:

The U.S. air travel system faces widespread disruptions if automatic government spending cuts go into effect next week, Transportation Secretary Ray LaHood said on Friday, as the administration kept up a steady drum beat of pressure on congressional lawmakers to delay the cuts.

Now I know the Department of Transportation quite well. They are the same group who could never upgrade the air traffic control system. It is still working in a manner designed in the early 1930s! They could cut well more than any amount required by just firing every SES and GS 15 in the place! And we would actually see things get better. Imagine if they got the GS 14s and 13s as well. Why the transportation system could just go rolling on.

No, the person in charge is more interested in scaring the folks, playing the political game, and not taking one step to improve anything. Watch closely folks, what the do is what will impact the taxpayers the most while protecting the internal folks the least. So why do we have these folks in the first place? Does anyone remember?

Thus would anyone believe this person when the Times continues:

However, LaHood and other administration officials have repeatedly denied that they have any discretion in applying the cuts or that they are exaggerating their impact.

"The idea that we're just doing this to create some kind of a horrific scare tactic is nonsense," LaHood said. "We are required to cut a billion dollars. And if more than half of our employees are at the FAA ... there has to be some impact."

I would doubt so!

As an afternote I did the calculation of what we would save by just dropping all GS14-14s from the payroll. Salary alone is $26 Billion, the details are:

Salary	Number	Total ($000,000)
$136,771	121,531	$16,621.92
$155,500	61,404	$9,548.32
		$26,170.24

Now if we recognize benefits etc we would save at least another 50% or a total of about $40 Billion. Well there goes the Sequester.
Labels: Politics

MORE DETAILS ON ACA

The HHS issued some more of the rulings on the ACA implementation today:

Today's final rule implements five key provisions of the Affordable Care Act that are applicable to non-grandfathered health plans:

- **Guaranteed Availability**
  Nearly all health insurance companies offering coverage to individuals and employers will be required to sell health insurance policies to all consumers. No one can be denied health insurance because they have or had an illness.
- **Fair Health Insurance Premiums**
  Health insurance companies offering coverage to individuals and small employers will only be allowed to **vary premiums based on age, tobacco use, family size, and geography**. Basing premiums on other factors will be illegal. The factors that are no longer permitted in 2014 include health status, past insurance claims, gender, occupation, how long an individual has held a policy, or size of the small employer.
- **Guaranteed Renewability**
  Health insurance companies will no longer refuse to renew coverage because an individual or an employee has become sick. You may renew your coverage at your option.
- **Single Risk Pool**
  Health insurance companies will no longer be able to charge higher premiums to higher cost enrollees by moving them into separate risk pools. Insurers are required to maintain a single state-wide risk pool for the individual market and single state-wide risk pool for the small group market.
- **Catastrophic Plans**
  Young adults and people for whom coverage would otherwise be unaffordable will have access to a catastrophic plan in the individual market. Catastrophic plans generally will have lower premiums, protect against high out-of-pocket costs, and cover recommended preventive services without cost sharing.

We have estimated that the costs of these plans will be significantly higher. Why not vary costs on such things as weight, a major health cost, and drug usage, also significant, STD status, and other sets of well accepted metrics?
Labels: Health Care

THURSDAY, FEBRUARY 21, 2013

HHS ISSUES RULES

The HHS has issued (see Federal Register)another set of rules regarding the implementation of the ACA. These are:

Essential Health Benefits

The Affordable Care Act ensures Americans have access to quality, affordable health insurance. To achieve this goal, the law ensures that health plans offered in the individual and small group markets, both inside and outside of Health Insurance Marketplaces, offer a core package of items and services, known as "essential health benefits." Under the statute, EHB must include items and services within at least the following 10 categories:

1. Ambulatory patient services
2. Emergency services
3. Hospitalization
4. Maternity and newborn care
5. Mental health and substance use disorder services, including behavioral health treatment
6. Prescription drugs
7. Rehabilitative and habilitative services and devices
8. Laboratory services
9. Preventive and wellness services and chronic disease management
10. Pediatric services, including oral and vision care

The Affordable Care Act also directs that EHB be equal in scope to benefits offered by a "typical employer plan." To meet this requirement in every state, the final rule defines EHB based on a state-specific benchmark plan. States can select a benchmark plan from among several options, including the largest small group private health insurance plan by enrollment in the state. The final rule provides that all plans subject to EHB offer benefits substantially equal to the benefits offered by the benchmark plan. This approach best strikes the balance between comprehensiveness, affordability, and state flexibility. The final rule also gives issuers the flexibility to offer innovative benefit designs and a choice of health plans.

These are still defined as a process not as a fait accompli. The costs of these mandated coverages we suspect will be significant. One must remember that they apply to all coverage and thus include an expansion of Medicare not only to those covered but to the added 40 million to e covered.
Labels: Health Care

TUESDAY, FEBRUARY 19, 2013

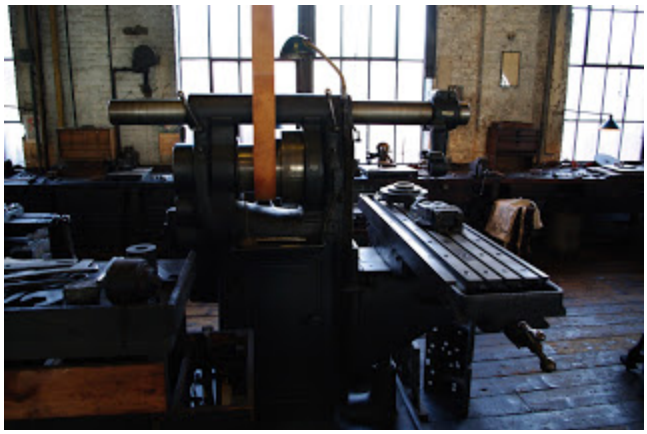
PATENTS, INNOVATION AND 3D PRINTING

I spent some time at Edison's Lab a couple of days ago and saw the massive number of things he had patented, for better or worse. He personally amassed some 1,000+ patents, a feat allowed by having lots of lawyers.

I was then interested to see a piece in Wired on the 3D printers bemoaning the number of blocking patents in existence which will make consumer based 3D printing a thing of the distant future. That frankly is a shame. You see Edison had lots of machinists who could make from metal anything he dreamed up. At the time they machinists were cheap and the technology was expensive. But he could crank out anything. 3D printing could do for our economy what the PC did in the early 80s. But due to the Patent office it will not. Apparently the Patent office will patent anything, thus creating massive road blocks filled with litigation. We have created the seeds of our own destruction.

To quote Wired:

If you're waiting for desktop additive-manufacturing technology to move closer to professional-level results, be prepared to wait for a very long time....We've uncovered 10 patents that could severely stifle innovation in the low-cost segment of the 3-D printing market and keep you from making colorful, smooth-finished figures and precise, articulating parts. These patents cover core technologies and ease-of-use features, and could take momentum from the upstarts and return it to the entrenched companies.



Indeed, the patents will block any such innovation. The tool would have allowed for the explosion in 3D product and technology creativity. The 3D printer is what programs were in the 80s, we had millions of new applications, and the 3D printer would facilitate millions of new "things", things which could create considerable prosperity. Yet if not here in the US, it will more than likely leak to other less controlling countries.

I am not a fan of patents. I understand them and have been through the process. Some are beneficial but all too often they become trolls under the bridge, bringing no true value, just fees.
Labels: Innovation

THURSDAY, FEBRUARY 14, 2013

DOES THIS MAKE ANY SENSE?

I am often amazed by the nastiness and smugness of the left. Perhaps it is just me, but MSNBC folks have the smirk on their faces that is pandemic amongst the left, that look like we are right and you are just dumb, real dumb.

Now there is a chubby economist on the left coast who for reasons known only to him, has this habit of making snarky comments about those he opposes. I can see this on some electronic instant messaging but from an accredited full professor type, it is unbecoming. It is akin to the gnome from the South upon whom I had placed some remarks recently.

The issue is Say's Law. Say I gather was some economist, or so they so tell, and his "Law" is either believe or doubted. Frankly it is irrelevant. The fact is that people respond to what they believe, and belief is a stronger driver than all these facts. That is to some degree the essence of Nick Rowe's soul searching and it is at the core of what I termed the Rowe Conjecture. It is a battle between belief and fact. Belief drives so many things, despite the facts. The collapse of the housing market was as much driven by the belief that made it grow and then tore it down.

Now economists have no real way to measure belief. And, yes, people believe different things, so there is no one belief. Just go to the racetrack. That is the heaven of belief.

Thus if someone makes a statement which flies in the face of the "Law" of whatever economist stated it, one should always remember that belief tops any law. And, yes, we have not yet figured out how to measure that o less change it. Although true leadership can often do so. Sadly we have none.
Labels: Economics

TUESDAY, FEBRUARY 12, 2013

USPTF, CCE, MELANOMA, AND SURVIVAL

Screening for melanoma should be a simple task, especially with the recent use of dermoscopy, but somehow it is not. The USPTF is one of the many bodies under the ACA which will create limitations on patient care, namely a means to reduce costs. Melanoma is an all too tragic disease, one which should and can be militated against. Unfortunately the death rate from melanoma has not decreased and with the current recommendations it may very well increase.

Let us begin by reviewing the current Government ruling on skin examination. One should remember that this is the basis for Comparative Clinical Effectiveness, CCE. We discussed this issue just a few postings back. We have also been concerned since the beginning of the ACA debacle about its negative impact on Health Care. The USPTF has presented a set of at best non-recommendations[74[1]].

[74[1]] http://annals.org/article.aspx?articleid=744253

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for skin cancer by primary care clinicians or by patient skin self-examination. (I statement)

Namely the recommendation is that primary care physicians are not trained to make a correct diagnosis. However it does not admit that Dermatologists do so as well. One may envision a great opportunity for Teledermoscopy allowing the capture of in office dermoscope images and then referral to a Dermatologist. Reading the dermoscopic images takes less than a minute by a trained Dermatologist and the specificity of such a reading can be quite high.

The USPTF Report continues:

Primary care physicians are moderately accurate in diagnosing melanoma, with a sensitivity of 42% to 100% and a specificity of 70% to 98%. A large systematic review analyzed the evidence on diagnostic accuracy of primary care physicians and dermatologists; most of the studies used images of lesions that had been histologically confirmed. The systematic review included 11 studies with primary care physicians and found a sensitivity of 42% to 100% and a specificity of 98% in the diagnosis of melanoma. The authors concluded that the evidence was insufficient to determine whether dermatologists and primary care physicians differed in accuracy . However, most studies on the accuracy of diagnosis of melanoma by primary care physicians evaluated the ability to identify melanoma from images of lesions of a known diagnosis; the applicability of this evidence to a whole-body skin examination in the setting of screening for skin cancer is not clear.

In a recent Editorial in Investigative Dermatology the authors state regarding recent and currently standing USPTF recommendations the following[75][2]:

….. incorporating new policy initiatives is paramount. The USPSTF recently gave a B-level recommendation for behavioral counseling to prevent skin cancer in patients 10 to 24 years old, an upgrade from the previous I rating (insufficient evidence). Such ratings indicate at least fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms. Results from the well-executed German screening and educational program (albeit not a randomized study) should now be proactively shared with the USPSTF, which has previously argued that there is insufficient evidence to support the recommendation of population- based skin cancer screening. In its most recent report on screening, the USPSTF noted that "no studies of the benefits of screening have compared a screened population with an unscreened population with respect to appropriate health outcomes"

This is recommendation is vague and to some degree flies in the face of the obvious. Screening, especially with a dermoscope, works in most cases. The specificity is high, and even if in doubt the removal of a questionable lesion is hardly traumatic.

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[75][2] http://www.nature.com/jid/journal/v133/n3/pdf/jid2012360a.pdf?WT.ec_id=JID-201303

A study of potential harms of screening is key—although the USPSTF has expressed concern that false-positive results may lead to biopsies and unnecessary treatment, they have acknowledged that the evidence to back up this theory is limited. Screening should be lodged within closed health-care systems that have experience in large screening trials and the demonstrated ability to follow up on all participants.

They would also need to be capable of capturing melanoma thickness, mortality, and other relevant data. In addition, there may be the potential to seek funding for a Medicare demonstration project, possibly in a state with high melanoma mortality rates and physician networks lodged in underserved areas. Lessons can be learned on obtaining cost estimates for broad-scale public health efforts from the Assessing Cost-Effectiveness– Obesity group and its important contribution to obesity prevention programs.

The authors of the Editorial conclude:

In summary, in the United States, melanoma remains the only preventable cancer for which mortality rates are not dropping. Nevertheless, population- wide screening rates remain low. As melanoma rates continue to rise and patient demand for screening accelerates, the current deficit in the dermatology workforce will become even more apparent. However, a confluence of new developments holds much promise. Web-based technology affords the potential to teach standardized skin cancer examinations to physicians, physician extenders, and high risk patients in multiple settings. Digital dermoscopy offers clinicians new options for distinguishing between benign, atypical, and aggressive lesions.

The Affordable Care Act has the promise of providing screenings to the majority of the US high-risk population that has yet to be screened. Finally, the results of the German screening program provide new and important evidence for the value and benefits of visual examination for melanoma.

Thus we believe that although such screening is possible, and highly productive in reducing morbidity and mortality, the way the USPTF phrases its results will have a negative impact on patient survival.

References

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Labels: Cancer, Health Care

TUESDAY, FEBRUARY 12, 2013

PASSING ON THE MISINFORMATION

I gather that there is some inside the Beltway rumor mill which maintains urban legends for long periods of time. Furthermore they are reproduced without anyone ever asking if they are true, or what the basis is of the legend.

Klein in the Washington Post reiterates the fallacy when he states:

7. "Two married recent retirees who had typical earnings over their lives will have paid about $88,000 in dedicated Medicare taxes through the payroll tax, according to a calculation by Eugene Steuerle, Stephanie Rennane and Caleb Quakenbush, all of the Urban Institute. That sum includes the portion of the tax that employers pay and is expressed in today's dollars (adjusted for both inflation and the interest the money would have earned over the years). In return for the $88,000 in lifetime taxes, that married couple can expect to receive benefits worth more than three times as much: $387,000."

8. "Patients and doctors alike gravitate toward the latest, most expensive treatment, regardless of whether it is the most effective. Common treatments for prostate cancer, for example, range from about $25,000 to more than $100,000. "No therapy has been shown superior to another," an analysis by the RAND Corporation concluded. But which therapies are growing the most rapidly? The most expensive ones, like proton radiation therapy. "

Klein has allegedly obtained these from some book by Leonhardt at the NY Times. Now let me comment on both, and my comments are based upon verifiable facts, generally primary research.

First, the hypothetical couple mentioned in the first paragraph are in the bottom 20% of the income base. For the upper 80% of the folks, why they contribute a great deal more, and in fact the top 40% contribute well in excess of what they get in return. In fact, the lower the income the sicker the person, thus the lower incomes use most of the services and pay least of the funds. I did an extensive analysis of this about 4 years ago, updated it 2 years ago. Thus it would help to understand the facts and not merelt parrot what they find to validate their opinions. But alas it is the Press, and we really have such a poor Press.

Now for the second. Here I wrote a detail draft book on Prostate Cancer. The statement that no therapy has been shown to be superior is not quite correct. It all depends and the details must be examined. In fact there is a gross distortion of the underlying evidence to condense the result in such a statement. For aggressive yet localized PCa, surgery can be quite effective. For indolent PCa, one might just leave it alone. The problem is we have not yet determined the nest way to split the two. That is the real answer, not what is quoted above.

The Press all too often never does due diligence on what they believe are facts. They are all too often just urban legends.

The (New) New Republic, Croly may be turning in his grave, has written a piece which is rather down on the young man making the statements from his beloved economic writer.

Notwithstanding the long piece, and the critique from the left leaning economists, failing to validate facts is a valid criticism.
Labels: Health Care

SEVEN "DEADLY" SINS

The seven deadly sins include: gluttony, lust, greed, sloth, wrath, envy and pride. Now for gluttony, we now call it obesity, which is the end result of gluttony. There has been a mass of recent evidence as to the negative effects resulting from obesity.

In Prostate Cancer Journal it is reported[76][1]:

Obesity and hypertension were each associated with an increased risk for BCR of prostate cancer after RP, independent of age at diagnosis and tumor pathological features. Given the increasing rates of obesity, hypertension and prostate cancer, a better understanding of the relationship between these entities is of significant public health importance. Elucidation of the involved pathogenic mechanisms will be needed to establish causality.

They conclude:

The pathogenic mechanisms potentially linking obesity and other components of the MetS to prostate carcinogenesis are poorly understood. The central derangement of MetS—a defect in insulinstimulated glucose uptake with secondary hyperinsulinemia—may in fact be present in patients with prostate cancer. Hyperinsulinemic men have been shown to have higher circulating levels of insulin-like growth factor 1 (IGF-1), a putative prostate cancer mitogen.[36] IGF-1 has a role in cellular proliferation and apoptosis reduction; thus, increased bioavailability of IGF-1 may be relevant to prostate cancer incidence and aggressiveness, though data demonstrating causality is lacking. ...

Thus, obesity and MetS likely affect prostate carcinogenesis via a complex interaction between altered androgen metabolism, insulin resistance, and chronic inflammation. Further study is needed to clarify these pathways.

Now at the same time in JAMA we have an article which states[77][2]:

Relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality. The use of predefined standard BMI groupings can facilitate between-study comparisons.

Thus despite the objections related to personal attacks by certain politicians, the facts are undeniable; they are put at risk by their behavior. If they were using illicit substances, abusing

[76][1] http://www.nature.com/pcan/journal/v16/n1/pdf/pcan201232a.pdf

[77][2] http://jama.jamanetwork.com/article.aspx?articleid=1555137

alcohol, or even engaging in highly risky sports, we would be concerned. They are public figures, namely they have personally agreed to put themselves out to the public for examination. Further they are on the public expense; we will pick up the tab for their excesses. Thus they have an affirmative duty to respect the public purse.

Perhaps the seven deadly sins are deadly because they lead more swiftly to than end. Politicians have a duty to present a positive image, albeit that all too often they fail. Yet on this point they generally do not yell at those recognizing their failures, failures which are personally selected and which continue.

References:

1. Asmar. R., et al, Hypertension, obesity and prostate cancer biochemical recurrence after radical prostatectomy, Prostate Cancer and Prostatic Disease (2013) 16, 61–65.
2. Flegal, K., et al, Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories A Systematic Review and Meta-analysis, January 2, 2013, Vol 309, No. 1

Labels: Health Care, Politics

DOING DEALS?

Deal making is both art and science. It is the art of knowing the right people. You must be able to get to see people with money and people who can facilitate your business. You must be able to be a "dream merchant". selling to the right buyers you vision. It is a science because you must deliver on the facts, the elements of the business, and the numbers.

Now the NY Times business writer extols some web based entity that has a database that tells one who is connected to whom and ultimately tells you how you can through your own connections ultimately get to the person you seek.

For example, say I want to pitch Mr. X at entity A. It tells me that I know Ms. Z at B and she knows Ms. Y at C and she knows Mr. X at A. Thus I should speak to Ms. Z and ask her to speak to Ms. Y who will of course speak to Mr. X. Yeah, like it really works like that!

The problems are as follows:

1. Often Mr. X prizes his channels of communications and if one is close to Mr. X, well you just do not tell too many people, and if they know, you really do not bring them to Mr. X. If you do then Mr. X will soon cut off the relationship.

2. If you want to get value from Mr. X, and Ms. Y and/or Ms. Z know it, they will most likely want a piece of the deal. What do they look like, chopped liver?

And the problems go on. Deal making is complex, and often there are unexpected twists and

turns. It is often based upon years of building trust and success, of trading favors, of having a track record, and of mutual benefit. It is not accomplished via another Facebook like app.
Labels: Business

MONDAY, FEBRUARY 11, 2013

NOW WHO IS REALLY IGNORANT?

Now I really try not to be a name caller. On the other hand when one deals with economists one's best intentions are all too often strained. Let me briefly comment on that rather stilted mind from just a bit south of me here in New Jersey.

He writes:

But Mr. Cantor's support for medical research is curiously limited. He's all for developing new treatments, but he and his colleagues have adamantly opposed "comparative effectiveness research," which seeks to determine how well such treatments work.

What they fear, of course, is that the people running Medicare and other government programs might use the results of such research to determine what they're willing to pay for. Instead, they want to turn Medicare into a voucher system and let individuals make decisions about treatment. But even if you think that's a good idea (it isn't), how are individuals supposed to make good medical choices if we ensure that they have no idea what health benefits, if any, to expect from their choices?

Now is CCE really great or as Mr. Cantor infers is it a Trojan Horse. I am a great fan of medical research. But the CCE we are speaking of is not really research. It is effectively a bunch of Government paid people who may loosely be affiliated with the topic at hand, say prostate cancer, and who are "supported" by some mass of Government staff, who have the agenda at hand.

You see, I have served on may such committees and what I saw was often appalling. The appointees were politically chosen and worse the real work was performed by the staff of the related Government agency, whose agenda was to be verified. It was often not the best people

who did the work but the staff who were young, inexperienced, managed by bureaucrats, and driven to produce some pre-ordained result.

Thus, one need look no further than the Prostate cancer analysis on PSA testing. The group coming to a conclusion did not appear to have the best of the best in the field, but some amalgam of folks who may know something and they had the staff collect data that seems in my opinion to justify the pre-ordained result that there should be no PSA testing.

Again as I have demonstrated the best results were even flawed, fatally I may say, because they asked the wrong question. Perhaps in my opinion they started out well intentioned but after fifteen years one learns more and the initial question is no longer relevant, as was the case with the PSA test.

Well to answer the gnome from the South, the fear my good man is that we have the wrong people, with an agenda, misinterpreting the clinical results, and doing so with no trained clinical understanding, and reaching a conclusion which will result in death! Is that clearer. The gnome from the South's opinion in economics will just send us all back to the Middle Ages, dependent on Edward II and his incompetent rulings. But the gnome from the South's opinions on Health Care may kill off a large portion of the population, kind of a plague of the 21st Century.
Labels: Health Care

SUNDAY, FEBRUARY 10, 2013

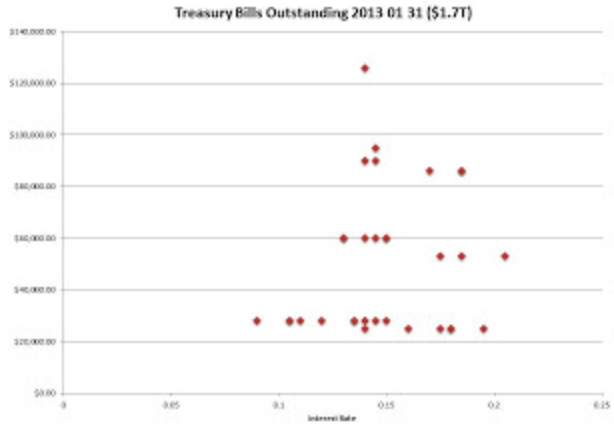
TREASURY DEBT

The current Treasury Debt is $11.1 T and it is composed of:

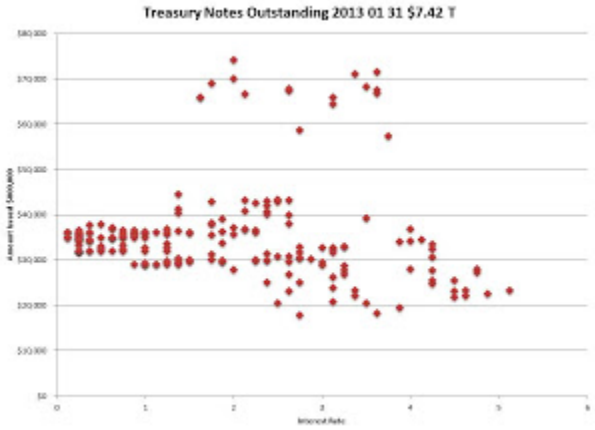
1. $1.3 T Bonds
2. $7.4 in Notes
3. $1.6 in Bills

and the remaining in TIPS.

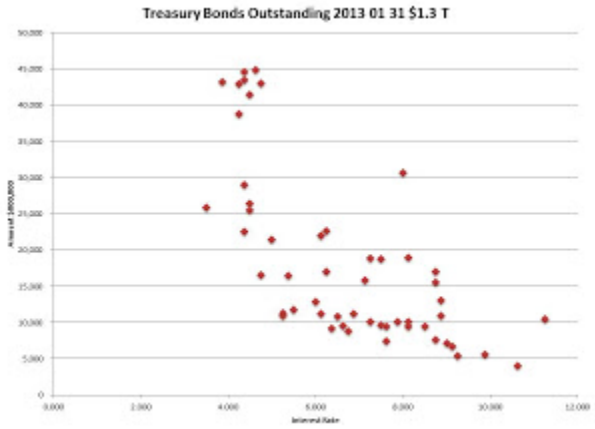
Now the distribution of the interest rates is of interest. First the Bills are:



The Notes are:



And the Bonds are:



We examined this two years ago and the good news is a shift to lower interest rates. The bad news is that the FED bought most of this junk. What happens when this stops!

Labels: Economy

SATURDAY, FEBRUARY 9, 2013

PSA, SNPS, AND PROSTATE CANCER

In a recent PLOS article there was an analysis of obtaining better diagnostic results using PSA and SNPs from germline cells[78][1]. The authors conclude:

The present study aims to evaluate the reproducibility and performance of a genetic risk prediction model in Japanese and estimate its utility as a diagnostic biomarker in a clinical scenario. We created a logistic regression model incorporating 16 SNPs that were significantly associated with PC in a genome-wide association study of Japanese population using 689 cases and 749 male controls. The model was validated by two independent sets of Japanese samples comprising 3,294 cases and 6,281 male controls. The areas under curve (AUC) of the model were 0.679, 0.655, and 0.661 for the samples used to create the model and those used for validation.

The researchers focused on the set of 16 Single Nucleotide Polymorphisms, SNPs, and those nucleotides which are different in a single spot. The authors calculated an odds ratio using logistic models. Specifically they posited:

log (OR) =b0+b1x1+b2x2+b3x3+…

and here the bs are the regression coefficients and the x the number of the risk alleles at each SNP locus. The result was a ROC, receiver operating characteristic, whose area under the curve was nearing 0.7, a reasonable number.

Now the authors state:

PSA is a protein secreted specifically from the prostate gland, and has been widely accepted as a serum biomarker for PC. However, other medical conditions, such as benign prostatic hypertrophy and inflammation can cause serum PSA elevation. Hence, the diagnostic specificity of PSA is quite low, especially at boarder-line levels of PSA, or 'gray-zone'. Patients suspected to have PC by PSA screening usually undergo prostate needle biopsy, which is an invasive procedure that accompany complications, some of which are severe. In addition, ***recent randomized controlled trials have shown no or little benefit of PSA screening in extending cancer-specific survival****, Economic burden of prostate needle biopsies, followed by overdiagnosis and overtreatment for PC, is another serious issue since it is estimated that each*

[78][1] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0046454

year, more than one million patients undergo prostate needle biopsies in the US, a procedure which costs $500–1,000 for each. Therefore, there is a world-wide controversy over PSA screening, and additional biomarkers which can better identify the patients that need prostate needle biopsies are definitely required.

As we have discussed before, the "recent randomized controlled trials" were not really that good of a trial. We refer the reader to our analysis of this issue.

The authors state:

There is still a large debate over the clinical utility of genetic risk prediction models. The overall predictive performances of genetic risk prediction models as assessed by ROC analysis are usually modest, since the distribution of the ORs between the case and controls largely overlap. However, it has been implicated in breast cancer that genetic risk prediction models could be clinically useful among a subset of high risk patients. In case of PC, patients can be risk-stratified using PSA, and genetic risk prediction models can be a useful compensatory marker at gray-zone PSA, where patients have relatively high risk of PC, and the diagnostic ability of PSA is the lowest. Furthermore, PCs are generally slow growing, and even if patients with PC are false negatively classified as low risk by a genetic prediction model, they can still be followed with serial PSA measurements, and can have prostate biopsy with increasing PSA before reaching advanced stages except in rare cases of very aggressive tumor. Identification of aggressive PCs is another important issue in PC diagnosis. Most of the PC susceptibility variants identified by GWAS have fallen short of discriminating aggressive from non-aggressive PCs, and there was no significant difference in the distribution of ORs between the aggressive and non-aggressive PCs in our genetic risk prediction model as well. Additional biomarkers that can discriminate aggressive and indolent PCs should be explored.

The above is another generalization which can result in serious complications. Yes, many PCa are slow growing. We see the 85 year old patient who we have been watching with a Gleason 7 for fifteen years. The PSA may now be 20. But he most likely will never die of this disease. On the other hand we all have seen the patient with a PSA of 4, then two years later it is 40, and two years later after painful bone mets he is dead. How do we tell the difference?

They conclude:

We have shown that while the genetic risk model may not be helpful clinically in all the patients with gray-zone PSA, it may largely influence decision making in a portion of patients. In our clinical simulation, 24.2% of the patients had OR,0.5, and these patients had 10.7% chance of being positive after prostate needle biopsy. Considering the complications of prostate needle biopsies, these patients might chose serial PSA follow-up rather than immediate prostate needle biopsy. On the other hand, 9.7% of the patients with OR.2, who have more than 42.4% chance of being positive for prostate cancer, may choose to undergo immediate prostate needle biopsy. Although the genetic risk prediction model should further be evaluated prospectively in clinics, our data suggests that it can be an additional biomarker that can risk stratify individuals at gray-zone PSA in Japanese, leading to personalized medicine.

Yes, this is a form of personalized medicine. Yet the key question is still what does the somatic cell have that the germ line does not and why. We want to control the somatic, not the germ line. Causality, and causality relationships are essential, they are the *sine qua non* of understanding cancer.

Observations

This paper raises several compelling issues:

1. The SNPs are germ line not somatic. They are there from the very beginning. The question then should be "why these SNPs" and "how do they create the malignancy?" The authors just thrown them in the pile with so many others and causation is totally neglected. Unlike what we seen in more main line analysis, we see a PTEN problem, an AKT issue, and AR fault. We then know what these do and we can then do something to reverse the process.

2. These are genome wide surveys, GWAS, and what we have seen is that one may catch a lot of things in a GWAS; they just seem to sweep everything in. Is that good, or is it just a distraction? I really do not know.

3. Personal genomics has become a new catch phrase. This raises the issue that in the germ line gene we can predict our medical future. It is not at all clear that such is the fact.

4. Just what do the SNPs do? What makes the changes causative, if at all?

Notwithstanding my concerns here, the work is of substantial interest.

Labels: Cancer

SATURDAY, FEBRUARY 9, 2013

HERE IS WHY I THINK HE IS THE SMARTEST, AGAIN

I keep scanning the economics blogs for insight, but I often know that it will not be there, except for Nick Rowe, again and again. What insight, from a recent one he states:

My guess is that price controls may be a good thing in the short run but will be a bad thing in the long run. I can explain why I think that, but I can't build a model to show that. That's the trouble with models.

If the real world really were as simple as my simple model, then price controls really would be a good thing, in both the short and long run. But the real world is much more complicated than my ability to model it, so I think that price controls will be a bad thing, at least eventually. But I can't model it, because it's too complicated for me to model.

I think that it is thoughts like this that drive Austrian economists to distraction. I sympathise. I think they are right. The, um, medium of modelling biases the message.

In fact it goes back to something I tried to analyze decades ago. Namely systems where the system changes to oppose anything you try to do to change it. Consider some dynamic system, yes it is stochastic, but even more so, it has some form of perverse intelligence. So try to exert some external force to change it but then it decides to modify its internal dynamics to oppose the change. But you cannot determine that until after it does it.

That is the nature of the human economy. It is really hard. Humans a smart, if you put up a mountain they will go around it or under it but the seem to get to the other side. Just look at the Tax Code. Now many economists believe that they have ultimate wisdom. In fact they do not, they are just arrogant, and alas dumb. But they tell our Government what to do. Is that bad? Only if they all align in the same direction. If they just wander around in some form of Brownian motion then their actions will cancel out.

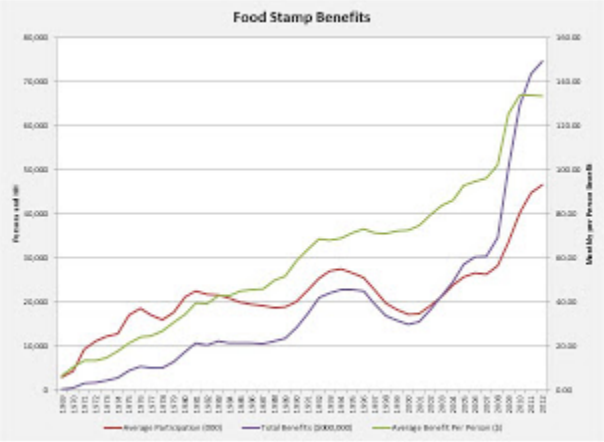
The blog, The Money Illusion has an interesting piece relating this to quantum physics. In fact this is where I got the Rowe piece. Worth a read.

Labels: Economics

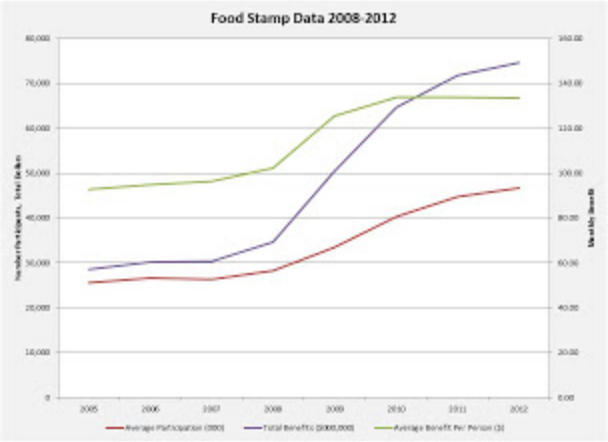
MONDAY, FEBRUARY 4, 2013

FOOD STAMPS

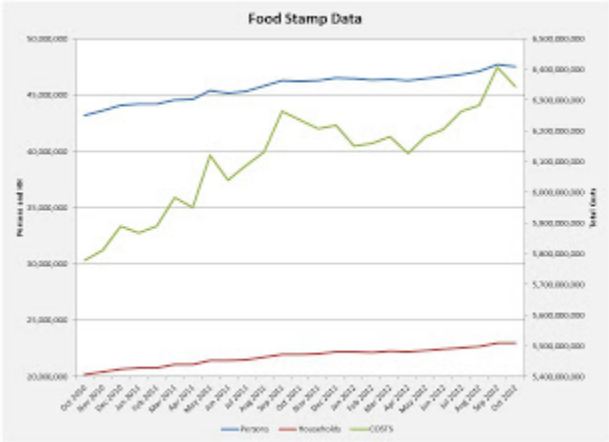
We always look at the Department of Agriculture data. It is cumbersome, not even in pdf, and never in xls, but after a bot of effort we get the following on Food Stamps.



First we see a long term historical growth.



Now above we have 2005-2012. Note we almost a tripling in total benefits, approaching $80 Billion per year and a total number of beneficiaries approaching 50 million. That is almost 18% of the population on Food Stamps!



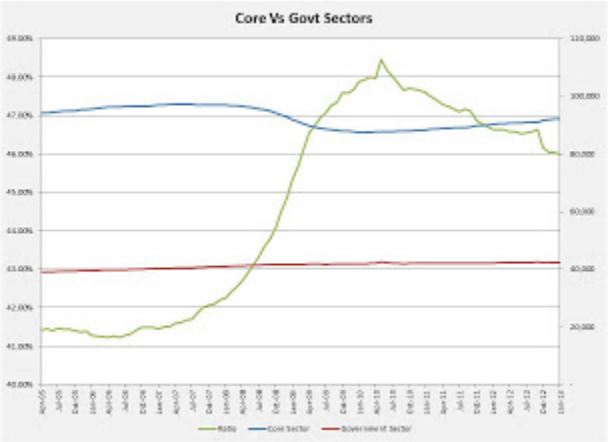
The above is from October 2010 through October 2012, a two year window. Note the cost increase.

DoA is one of the largest Government agencies. It subsidizes everything from Food Stamps to almond growers. We must remember this as well as DoD.

The above is the Participation Rate, namely the percent of total population getting Food Stamps. It has exploded. It normally runs 8% but this year, 2013, it will near 18%. Despite the bias of Gibbon, Rome fell because of reliance on bread and circuses. It seems we are going that way.
Labels: Economy

SUNDAY, FEBRUARY 3, 2013

AN INTERESTING RATIO



The above shows the total employed in core industries, namely those producing something, and those in non Core, namely Government, Health, Education, those we pay for now out of taxes.

The ratio of Non Core to Core is now 46%, it had peaked at 48.5% during the peak of the Recession. That means we have almost one person being supported by two workers. But we have gone from 41% to 46%. That in just five years!

This is a metric that causes me great concern. Especially since the only time I was in the funded by Core part was as a Lifeguard working for the City of New York.
Labels: Economy

100 YEARS OF COLLECTING

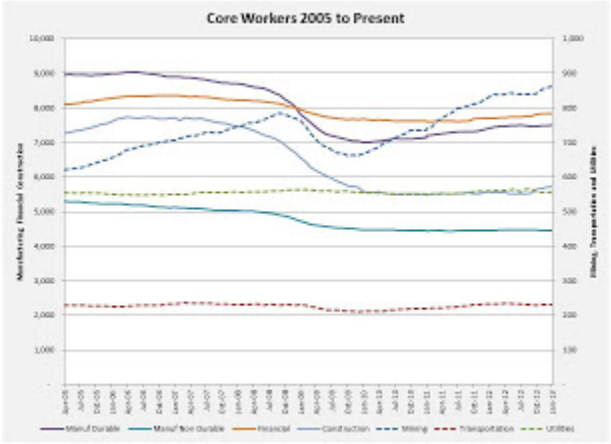
Today is the 100th Anniversary of the Ratification of the 16th Amendment, the Income Tax.

Article XVI.

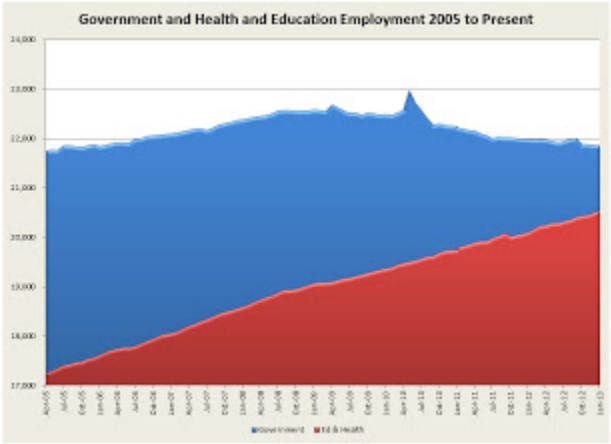
The Congress shall have power to lay and collect taxes on incomes, from whatever source derived, without apportionment among the several States, and without regard to any census or enumeration.

Thirty words and it is now the core of our Health Care as well. Happy Birthday.....
Labels: Politics

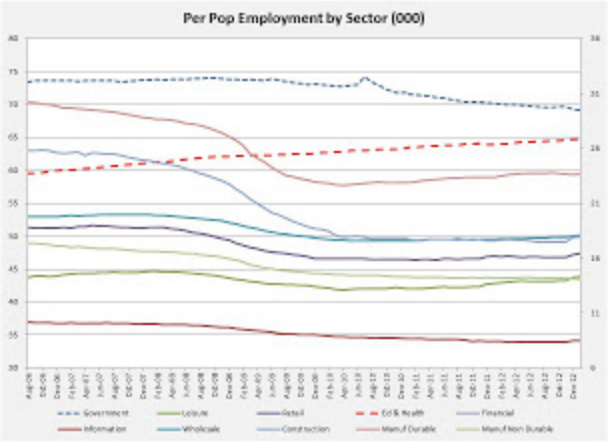
MORE EMPLOYMENT DATA



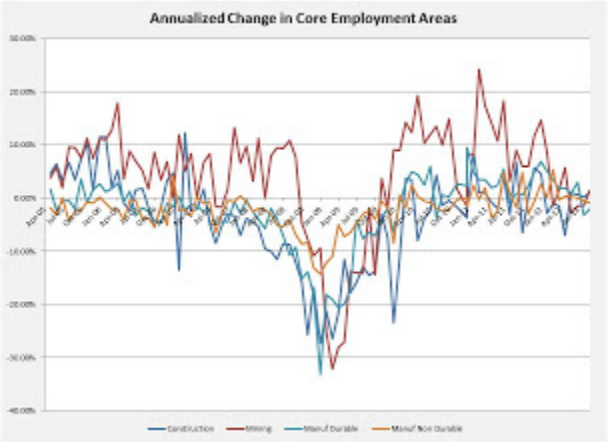
The above is the Core Worker count since 2005. It is raw numbers and does not account for population growth. The Mining element is the only one with any substantial growth. Manufacturing of Durables has some. Construction saw a bit of an up tick.



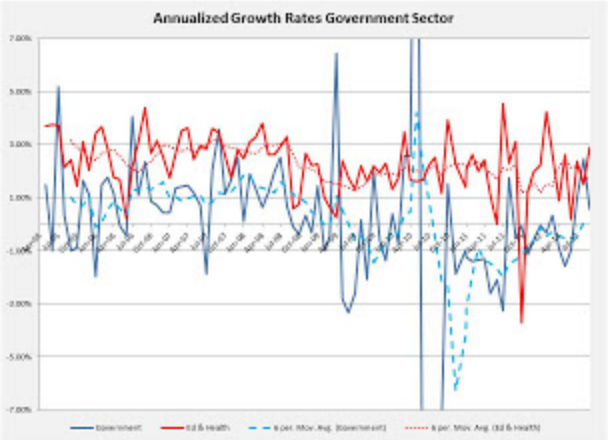
This is the gem. State and Local Government is slowing but Education and Health care still sees a steady rise. One should expect a Health Care moderation but not really.



This is a telling chart since it recounts employment per PoP. Again the only strong increase is Education and Health Care! One would assume as we become more productive the ratios would decrease. That itself is a cause of unemployment. However Education and Health Care has negative scale economies. They have gone from 59 to 65 as a ratio in eight years.



The above is the annualized percent change in Core. It is fundamentally around 0%.



The above is the annualized change in Government Services. It is running well above 3% in Health Care and Education.

Labels: Economy

SATURDAY, FEBRUARY 2, 2013

THE NEW MARINE?

I truly respect the Marine Corps, many have kept me out of serious trouble from time to time, and many have come to my rescue. I could never be a Marine, not the physical part, but the team thing, because there are true team players like Marines and then there are single players, and I seem to have fallen in the later. But often that is what makes an entrepreneur. Yet again and again I am impressed with current and former Marines, somehow to become a Marine is truly transformative. Also they are in my opinion and experience the true backbone of our Armed Forces. When you are in a stressed situation, it is always good to have a Marine around.

Now in today's NY Times is a piece on the expansion of the Corps to women in combat. Again I have no problem here, Israel has had it for years, and it works well. But what was somewhat disappointing was the picture of so many obese individuals which I assume was at a marine boot camp, Paris or Pendleton. This is not what I ever remember, but I gather it is becoming pandemic. In WW II the weight of the average inductee was about 135 pounds, now the weight of the average Midshipman male is near 195 pounds. And it tends just to get higher, except in the Corps, but not in the picture.

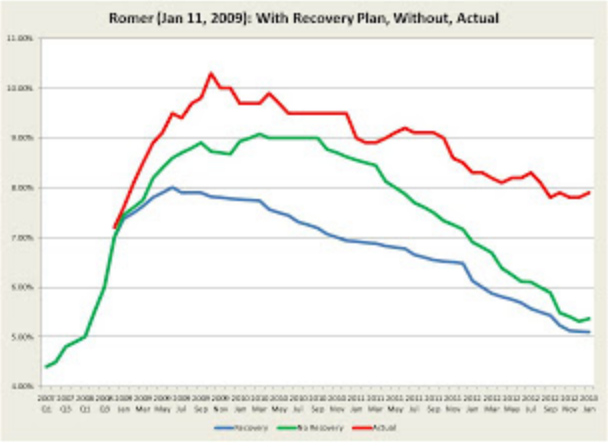
The challenge is to get them fit, make them fitter, and keep them the fittest. It will be interesting to see how this evolves.
Labels: Military

FRIDAY, FEBRUARY 1, 2013

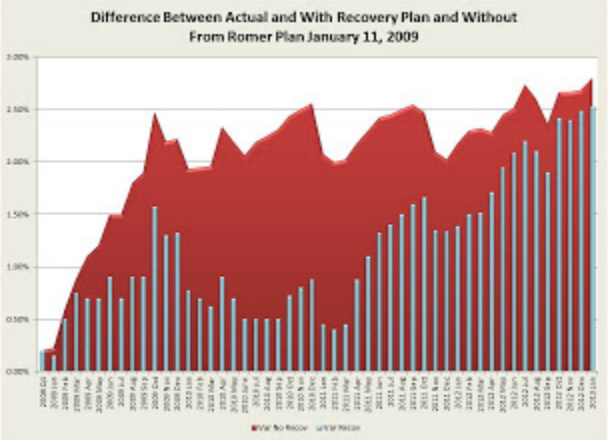
EMPLOYMENT CHALLENGE

As we noted yesterday, the economy is a mess. It is over four years since the wonderful economists from the West predicted great things. Have not noticed many of them. But let us go through the numbers.

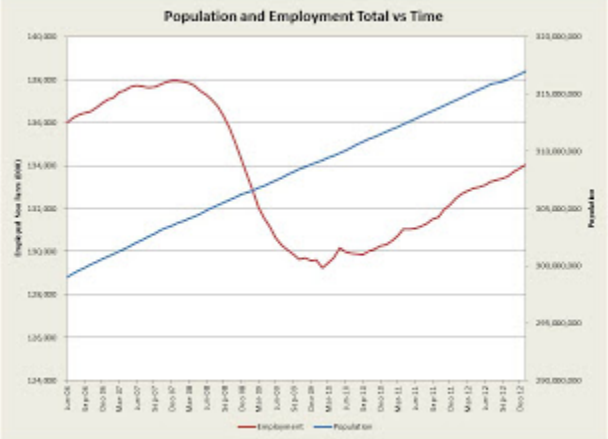
As usual we start with the Romer Curve. I can't avoid going back to this one. It is important to note that she not only had unemployment at 5% by now but the employment base was to be greater than what it was originally. If it had happened we would most likely have little if any deficit. How far can you be wrong.



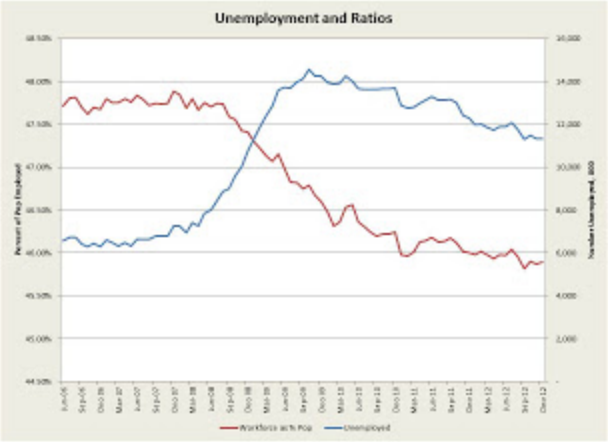
Looking at the above month after month can those people have no shame.



The Romer errors are above. Not a splendid job one could say.



The above is the truly troublesome chart. The gap of some 12 million people to possibly 15 million who are forever out of the workforce is horrible and never spoken of. We have been pointing at this for years!

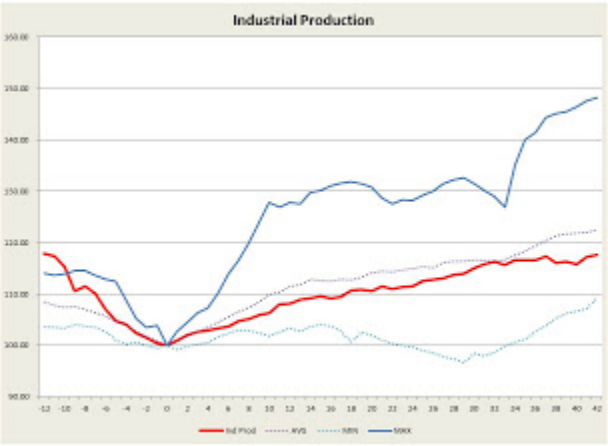


The above is the announced and actual unemployment. We are still near 12% and flat. There is no movement to change this at all. I guess we must just wait and pray!
Labels: Economy

THURSDAY, JANUARY 31, 2013

WORST RECOVERY EVER, OR IT MAY NEVER END

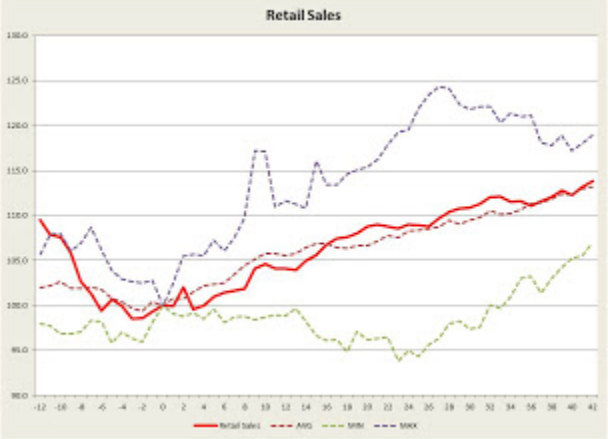
We have been tracking the Recession using the St Louis FED statistics and comparing them to past recessions. This one is a mess, and as I have indicated it is due completely to the incompetence of economists and the current Administration. Let me recount the stats.



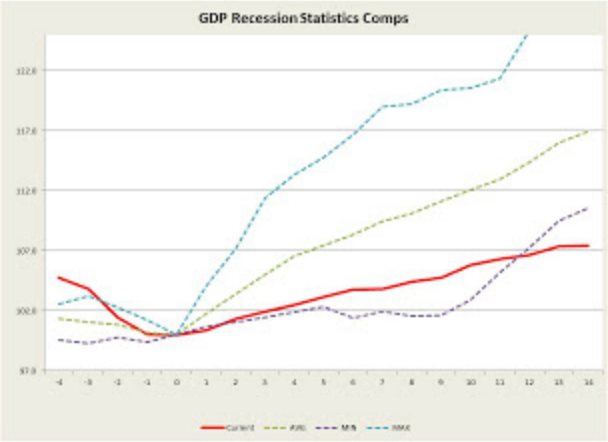
Industrial Production is slowly improving but with increased productivity there will most likely be little or any increase in employment.

Income is just collapsing. Not only is it below the past recessions but it is widening.

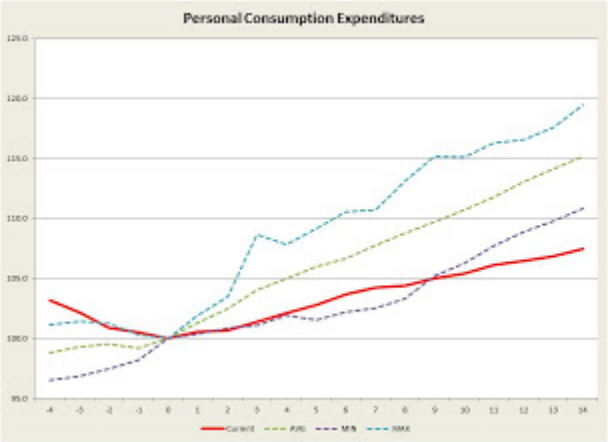
Employment is heading back down again. This is a result of the lowered production and the increased productivity.



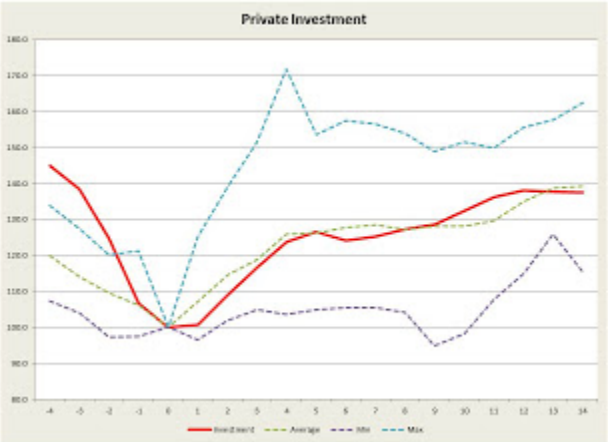
Retail Sales remains fixed at the average most likely driven by Government supports but these will diminish and drive them down also.



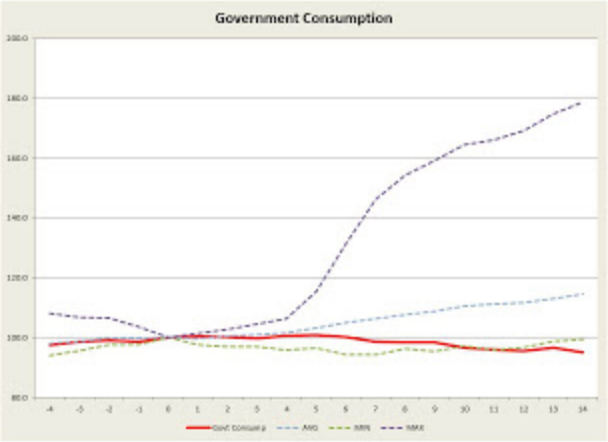
The GDP Stats are horrifying. We are now consistently below what was the worst. This sets a new low. There is minimal improvement from a year before the beginning of the Recession.



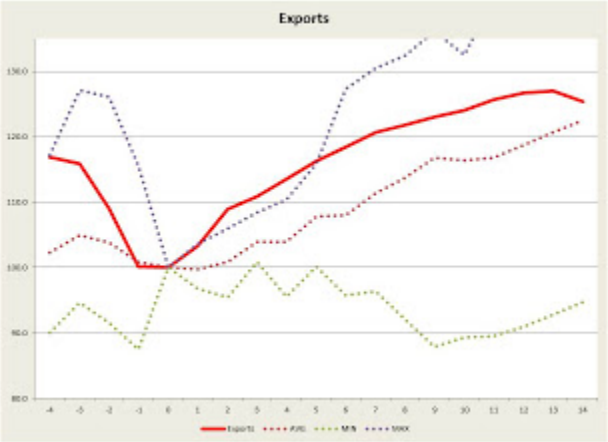
The PCE portion of the GDP is above. It is dropping quickly. That is a sign that the non-government sector is starting to fall off.



Private Investment remains on average, but it may also start to stall.



Government Consumption is now below the start of this process. Not unexpected since we are out of 2 wars.



Exports are doing well as are Imports.

Overall this is still quite a mess and they folks keep going off the cliff with no notice of what is happening.
Labels: Economy

YA THINK! THE ACA IS JUST BEGINNING

The web site Zero Hedge has a telling commentary on what the Unions are now realizing about the ACA. Worth a read, it is based on commentary from the WSJ, unless you pay a fortune it is not worth getting to in my opinion these days, but the point is that Unions now see how costly it will be.

Well as one of the dozen or so who actually read each and every draft of that hellish document I can tell you that you have not seen anything yet. It is not the Bill, that just empowers the moronic Government workers and their consultants to write the Administrative code. For every page of Law expect dozens of pages of code, typically 50 or so.

That means for the 2,000 page law we will have 100,000 new pages of un-understandable regulation. It will put the Tax Code to shame! Just wait. It may create a totally new profession, we have lawyers for law, accountants for tax codes, and what for this massive mess.
Labels: Health Care

WEDNESDAY, JANUARY 30, 2013

OH IF ONLY A GARDEN

A write for the NY Times praises gardens and bemoans lawns.

Now I tried this on my front garden, but alas to no avail. The rodent deer ate every plant, every one, no matter what I did, no matter what I used. I even got a Daisy BB gun but NJ gun laws were so strict I left it in New Hampshire. There we have wolves so no worry. But in New Jersey the monsters eat everything, except grass. So we have lawns.

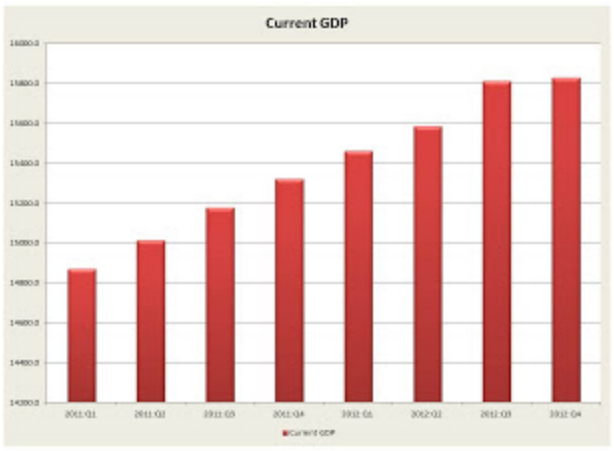
So when I read some writer denigrating lawns and praising the gardens I know he is no real gardener. He has not gone to war with the deer. As he says:

But when it comes to the eye of the beholder, weeds are the same thing as beauty: to a gardener, grass is a weed; a row of lettuce surrounded by dark, grassless soil a thing of beauty. To some gardeners, including me, dandelions are a crop.

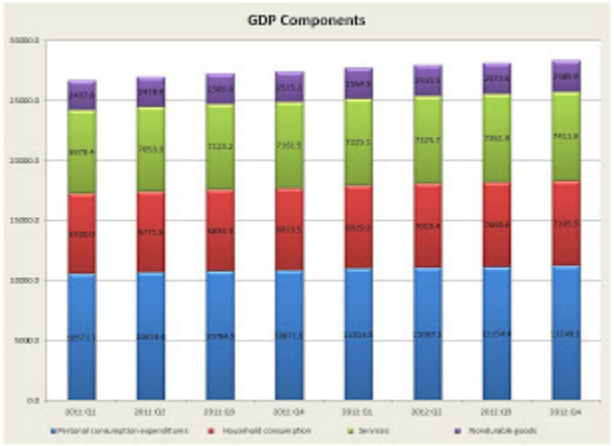
No my friend, grass is a sign of defeat, I have the town approved fence, the barrier between me and total evil. I let the squirrels in and the chipmunks, rabbits, but not the deer. There are days when they sit outside the fence, their evil eyes peering through, those deadly teeth just waiting to munch, to destroy, to eliminate. Do they eat grass, NO! So let them eat grass.
Labels: Commentary

GDP DATA Q4 2012

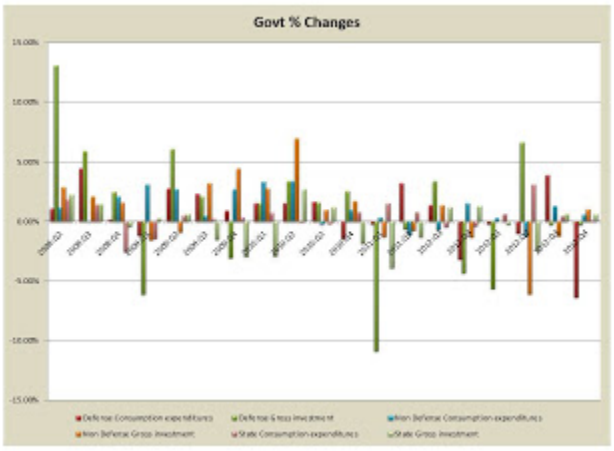
Things are not going so well, and that is an understatement. Over the last four years we have been tracking the projected recovery which has not appeared, despite the wonderful economists we have.



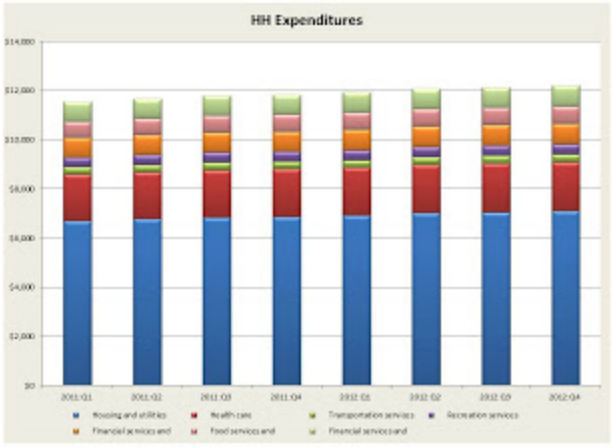
The GDP is stalled at best and declining slightly in reality. One more decline and we are back in a Recession.



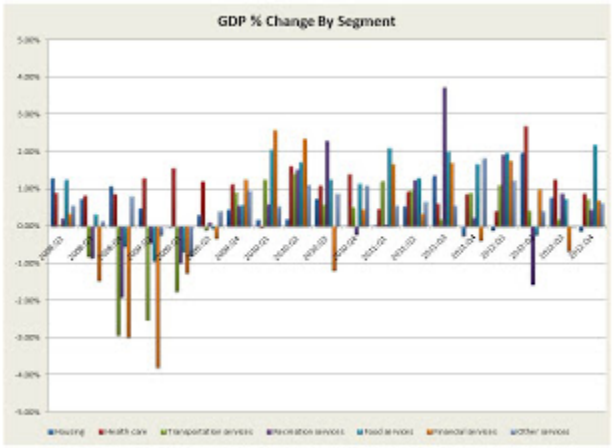
Government spending is as above. The changes by quarter are below:



Yes Defense is cutting back but that is what we anticipated. But nothing else is really growing here. On the consumer side we have:



and its percent changes are below:



These are somewhat better but not really a recovery.

The overall trend are downward and we are fearful of a 2013 collapse.

Labels: Economy

TELOMERES AND MELANOMA

Telomeres are those ends of DNA which have the tendency to be lost each time a cell reproduces leading eventually to a loss of function. Cancer on the other hand may have mastered the loss of sections of the telomeres and thus may have an ability to prolong their life to many reproductions, namely unlimited. There has been significant interest in targeting telomeres and especially the related enzyme, telomerase, to control cancer cells. In a recent pair of papers the authors have focused on this process in melanomas and especially on UV activation. The authors have discovered somatic mutations in TERT genes which are used to produce Tert and control

the Telomeres during cell reproduction. In addition they authors argue that these mutations result from UV radiation.

The focus on telomeres and cancer has been an area of active interest for almost two decades. As Shay et al (2012) state:

To grow indefinitely, human cancer cells must counteract the progressive loss of telomeric DNA that universally accompanies cell division. To do this, about 85 to 90% of cancers use telomerase, an enzyme that synthesizes the tandem 5′-TTAGGG-3′ hexanucleotide repeats of telomeric DNA by reverse transcription using its own RNA subunit as a template. Because telomerase is not expressed in most normal human cells, telomerase inhibition is considered an almost universal oncology target, and several clinical trials are under way

The above focuses on the critical importance of telomerase. Before continuing it is worth reviewing the telomere. As Shay and Wright state:

Telomeres are tracts of repetitive DNA (TTAGGG/ AATCCC for human telomeres) that protect chromosomes from degradation and loss of essential genes, and allow the cell to distinguish between double-strand breaks and natural chromosome ends. Human telomeres at birth contain 15–20-kilobase pairs of the repetitive sequence TTAGGG followed by a 3′ single-strand overhang on the G-rich strand, which is believed to be inserted within the double-stranded region to give a lariat-like structure called a t-loop.

Telomeres progressively shorten in most human cells with increased age, and telomere length in almost all middle-aged human tissues is approximately half that of the new born length. Telomere-specific proteins (such as protection of telomeres-1 (POT1), telomeric repeat-binding factor-1 (TRF1) and TRF2) bind directly to the single- and double-strand telomere regions to form a complex, providing a cap over the ends of the chromosomes that protects chromosome termini from degradation, recombination and end-joining reactions.

The authors further state that telomeres are somewhat maintained in humans via the use of telomerase as follows:

Telomere length is maintained by a balance between processes that lengthen telomeres, such as the activity of the cellular ribonucleoprotein enzyme complex telomerase, and processes that shorten telomeres, such as incomplete synthesis of the lagging DNA strand and end processing events. Telomerase stabilizes telomere length by adding TTAGGG repeats onto the telomeric ends of the chromosomes, thereby compensating for the continued erosion of telomeres that occurs in its absence. Human telomerase contains two essential components, a telomerase reverse transcriptase *catalytic subunit (hTERT) and a functional* telomerase RNA *(hTR, also known as TERC…*

Other earlier authors such as Campisi et al state:

Telomeres are the repetitive DNA sequences and specialized proteins that form the distinctive structure that caps the ends of linear chromosomes. Telomeres allow cells to distinguish the chromosome ends from double strand DNA breaks. The telomeric structure prevents the degradation or fusion of chromosome ends, and thus is essential for maintaining the integrity and stability of eukaryotic genomes. In addition and perhaps less widely appreciated, telomeres may also indirectly influence gene expression.

The length, structure and organization of telomeres are regulated by a host of telomere-associated proteins, and can be influenced by basic cellular processes such as cell proliferation, differentiation, and DNA damage. In mammalian cells, telomere length and/or telomere structure have been linked to both cancer and aging. Here, we briefly review what is known about mammalian telomeres and the proteins that associate with them, and discuss the cellular and organismal consequences of telomere dysfunction and the evidence that cells with dysfunctional telomeres can contribute to cancer and aging phenotypes.

As reported in the Harvard Gazette we have[79][1]:

Two mutations that collectively occur in 71 percent of malignant melanoma tumors have been discovered in what scientists call the "dark matter" of the cancer genome, where cancer-related mutations haven't been previously found….

This non-coding DNA, much of which was previously dismissed as "junk," accounts for 99 percent of a cell's genome. A large number of oncogenic mutations in cancer have been identified in the past several decades, but all have been found within the actual genetic blueprints for proteins….
"In addition, this represents the discovery of two of the most prevalent melanoma gene mutations. Considered as a whole, these two TERT promoter mutations are even more common than BRAF mutations in melanoma. Altogether, this discovery could cause us to think more creatively about the possible benefits of targeting TERT in cancer treatment or prevention," Garraway said.
The mutations affect a promoter region — a stretch of DNA code that regulates the expression of a gene — adjacent to the TERT gene. TERT contains the recipe for making telomerase reverse transcriptase, an enzyme that can make cells virtually immortal, and is often found overexpressed in cancer cells. A promoter region of DNA controls the rate of a gene's transcription — the copying of its DNA recipe into a message used by the cell to manufacture a protein….

The researchers said the same mutations are present in cell lines from some other malignancies, and that preliminary evidence showed they might be unusually common in bladder and liver cancers. They also noted that the discovery of these important mutations in DNA previously not linked to cancer-causing alterations highlights the value of whole-genome searches of tumor DNA.

Another report on Science 2.0 states[80][2]:

They analyzed the genomes of family members and found an identical mutation in the gene for telomerase, an enzyme often called 'immortality enzyme', in all persons studied. Telomerase protects the ends of chromosomes from being lost in the process of cell division and, thus, prevents that the cell ages and dies. The inherited gene mutation leads to the formation of a

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[79][1] http://news.harvard.edu/gazette/story/2013/01/mutations-drive-malignant-melanoma/

[80][2]

http://www.science20.com/news_articles/familial_gene_mutation_immortalizes_malignant_melanoma-101871

binding site for protein factors in the controlling region of the telomerase gene, causing it to become overactive. As a result, mutated cells overproduce telomerase and hence become virtually immortal.

This finding prompted the scientists to also look for mutated telomerase genes in non-inherited (sporadic) melanoma, which is much more common than the familial variant. In most of the tissue samples of melanomas of all stages they found alterations in the telomerase gene switch, which the researchers clearly identified as typical consequences of sun exposure. Even though these mutations were not identical to those found in the melanoma family, they had the same effect: overactive telomerase…

This is also confirmed by the surprising incidence of this alteration: The telomerase gene is the most frequently mutated gene in melanoma. "This is something we hadn't expected, because malignant melanoma has been genetically analyzed thoroughly. But this mutation always seems to have been overlooked," says Kumar.

It should be noted in the above the reference to sun exposure. The argument is that the telomerase change is a direct consequence of the UV exposure. We will focus on that observation later. The "overlooked" nature of this gene and its product is also of issue in that many researchers have examined telomerase extensively so frankly it is not truly new, even as a target for control.

Before continuing it is worth a quick summary of TERT, the telomerase that maintains the telomere. TERT is located at 5p15.33. From NCBI we have[81][3]:

Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, encoded by this gene, and an RNA component which serves as a template for the telomere repeat. Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres. Deregulation of telomerase expression in somatic cells may be involved in oncogenesis.

Studies in mouse suggest that telomerase also participates in chromosomal repair, since de novo synthesis of telomere repeats may occur at double-stranded breaks. Alternatively spliced variants encoding different isoforms of telomerase reverse transcriptase have been identified; the full-length sequence of some variants has not been determined. Alternative splicing at this locus is thought to be one mechanism of regulation of telomerase activity.

The observation can be made that if we do not have adequate TERT then the Telomere ends decay and ultimately the cell line dies off. This is the typical case. Therefore take a malignant melanoma cell. If it has in its pathways and receptors been activated to mitotic duplication then if the TERT is inadequate then the Telomere ends get cut shorter each time it goes through mitosis and at some point it just stops. For example, and this is just for exemplar purposes only, we have

[81][3] http://www.ncbi.nlm.nih.gov/gene/7015

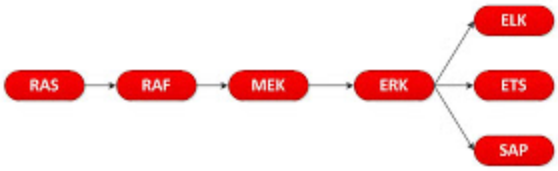
a malignant melanocyte, then it goes through mitosis say 10,000 times but each time it would lose a piece of the Telomere until they are all gone, then th cell cannot go again. But if there is an overabundance of TERT, then the TERT resupplies what may be lost and this cell has no way of stopping, at least due to this factor.

The ETS family of genes is positive or negative regulators of gene expression. They can up or down regulate expression. They are named for the initial gene discovered, the E26 Transforming Sequence, where E26 was the oncogene v-ets characterized in 1986 of an avian transforming virus called E26. It is also called the erythroblast transforming specific family, as discussed by Zong et al.

The ETS family is a large family of over 20 such genes, and we will focus on ERG specifically. The Table below is from Watson et al.

	Subgroup	Name	Unigene Name	Alternative Names	Locus	Size
1	ETS	ETS1	ETS1		11q23.3	441
2		ETS2	ETS2		21q22.3	469
3	ERG	ERG2	ERG		21q22.3	462
4		FLI1	FLI1	ERGB	11q24.1-q24.3	452
5		FEV	FEV		2q36	238
6	PEA3	PEA3	ETV4	E1AF, PEAS3	17q21	462
7		ERM	ETV5		3q28	510
8		ER81	ETV1		7p21.3	458
9	ETV	ER71	ETV2	ETSRP71	19q13.12	370
10	TCF	ELK1	ELK1		Xp11.2	428
11		SAP1	ELK4		1q32	431
12		NET	ELK3	SAP2, ERP	12q23	407
13	GABP	GABP α	GABPA	E4TF1	21q21.3	454
14	ELF1	ELF1	ELF1		13q13	619
15		NERF	ELF2	NERF1, NERF2, EU32	4q28	581
16		MEF	ELF4	ELFR	Xq26	663
17	SPI1	SPI1	SPI1	PU.1, SFPI1, SPI-A	11p11.2	264
18		SPIB	SPIB		19q13.3-q13.4	262
19		SPIC	SPIC		12q23.2	248
20	TEL	TEL	ETV6		12p13	452
21		TEL2	ETV7	TEL-B	6p21	264
22	ERF	ERF	ERF		19q13	548
23		PE-1	ETV3	METS	1q21-q23	250
24	PDEF	PDEF	SPDEF		6p21.3	335
25	ESE	ESE1	ELF3	ESX, JEN, ERT, EPR1	1q32.2	371
26		ESE2	ELF5		11p13-p12	255
27		ESE3	EHF	ESEJ	11p12	300

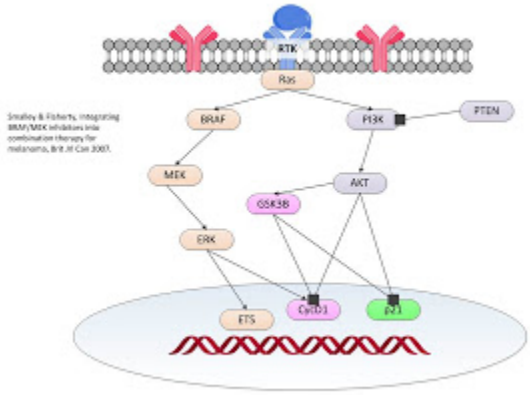
The ERG gene was first presented in the paper by Shyam and Reddy et al in 1987. There the authors identified it and set it in the ETS family. From Weinberg, we see that the ETS are transcription factors driven by the RAS/RAF pathway along with other such factors.



ETS also plays a significant role in the process. We briefly review that as well. ETS is located at 11q23.3. From NCBI we have[82][4]:

This gene encodes a member of the ETS family of transcription factors, which are defined by the presence of a conserved ETS DNA-binding domain that recognizes the core consensus DNA sequence GGAA/T in target genes. These proteins function either as transcriptional activators or repressors of numerous genes, and are involved in stem cell development, cell senescence and death, and tumorigenesis. Alternatively spliced transcript variants encoding different isoforms have been described for this gene

From Smalley and Flaherty we have the following pathway for ETS:



The mutations we discuss here are somewhat new and they are present in a relatively large number of samples, at least percentage wise. We know that ETS has transcription control and we

[82][4] http://www.ncbi.nlm.nih.gov/gene/2113

can see from above the relationship to BRAF as well. Thus there are many points of loss of control in a melanoma cell. Specifically, as Chudnovsky et al note[83][5]:

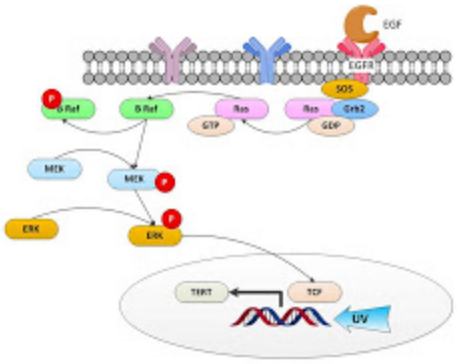
Multiple genetic alterations occur in melanoma, a lethal skin malignancy of increasing incidence. These include mutations that activate Ras and two of its effector cascades, Raf and phosphoinositide 3-kinase (PI3K). Induction of Ras and Raf can be caused by active N-Ras and B-Raf mutants as well as by gene amplification. Activation of PI3K pathway components occurs by PTEN loss and by AKT3 amplification. Melanomas also commonly show impairment of the p16(INK4A)-CDK4-Rb and ARF-HDM2-p53 tumor suppressor pathways. CDKN2A mutations can produce p16(INK4A) and ARF protein loss. Rb bypass can also occur through activating CDK4 mutations as well as by CDK4 amplification. In addition to ARF deletion, p53 pathway disruption can result from dominant negative TP53 mutations. TERT amplification also occurs in melanoma. The extent to which these mutations can induce human melanocytic neoplasia is unknown. Here we characterize pathways sufficient to generate human melanocytic neoplasia and show that genetically altered human tissue facilitates functional analysis of mutations observed in human tumors.

As Horn et al state:

Cutaneous melanoma occurs in both familial and sporadic forms. We investigated a melanoma-prone family through linkage analysis and high-throughput sequencing and identified a disease-segregating germ line mutation in the promoter of the telomerase reverse transcriptase (TERT) gene, which encodes the catalytic subunit of telomerase. The mutation creates a new binding motif for Ets/TCF transcription factors near the transcription start and in reporter gene assays, caused up to 2-fold increase in transcription. We then screened the TERT promoter in sporadic melanoma and observed recurrent UV signature somatic mutations in 125/168 (74%) of human cell lines derived from metastatic melanomas, corresponding metastatic tumor tissues (45/53, 85%) and in 25/77 (33%) primary melanomas. The majority of those mutations occurred at two positions in the TERT promoter and also generated binding motifs for ETS/TCF transcription factors.

Horn et al conjecture the following pathway:

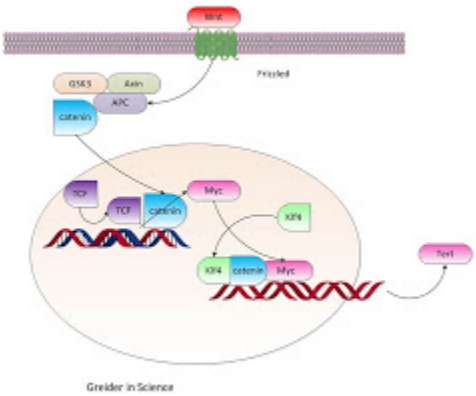
[83][5] http://www.ncbi.nlm.nih.gov/pubmed/15951821?dopt=Abstract



As Huang et al state:

Systematic sequencing of human cancer genomes has identified many recurrent mutations in the protein coding regions of genes but rarely in gene regulatory regions. Here we describe two independent mutations within the core promoter of TERT, the gene coding for the catalytic subunit of telomerase, which collectively occur in 50 of 70 (71%) of melanomas examined. These mutations generate de novo consensus binding motifs for ETS transcription factors, and in reporter assays the mutations increased transcriptional activity from the TERT promoter by 2 to 4-fold. Examination of 150 cancer cell lines derived from diverse tumor types revealed the same mutations in 24 cases (16%), with preliminary evidence of elevated frequency in bladder and hepatocellular cancer cells. Thus, somatic mutations in regulatory regions of the genome may represent an important tumorigenic mechanism.

We have discussed before the Wnt pathway connection to TERT as well. As shown below we have discussed this option as well.



This has been discussed by Hoffmeyer as well as by Greider. As Greider states:

Recent studies have proposed that the Wnt pathway is linked to TERT in a quite different way. Constitutive overexpression of TERT in mice activates the Wnt pathway, suggesting that TERT may also function as a transcription factor. Although one study did not observe Wnt pathway activation in response to TERT overexpression, other studies have raised questions about the physiological relevance of the constitutive overexpression of TERT. Deletion of TERT in mice does not affect expression of target genes in the Wnt pathway, nor give rise to the cellular phenotypes that loss of Wnt signaling induces, indicating that TERT regulation of Wnt signaling may be limited to situations where TERT is overexpressed.

It is reasonable to propose that Wnt regulates TERT given that Wnt signaling plays an essential role in stem cell self-renewal and that TERT is needed for the long-term growth of stem cells. TERT regulation seems to require not one, but two master transcriptional regulators to assure that there is neither too much, which may allow the growth of cancer cells, nor too little, which might lead to stem cell failure. The finding by Hoffmeyer et al. that both β-catenin and Klf4 are required to activate TERT expression puts the horse (Wnt) before the cart (TERT) and provides a foundation for linking telomerase levels and self-renewal.

Thus TERT regulation is truly a complex process. We have examined the impact of Wnt on melanoma previously. This recent work is on mutations on TERT genes yet we also must consider the influence of Wnt as well.

Observations

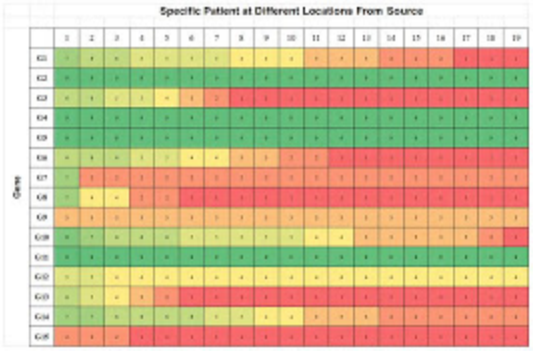
This discovery leads to several observations of note:

1. One could have imagined something of this happening with Telomeres. It would almost be necessary to allow ongoing uncontrolled mitotic activity. Thus, despite the fact that there is no surprise here we do have a specific target, namely the activator of TERT.

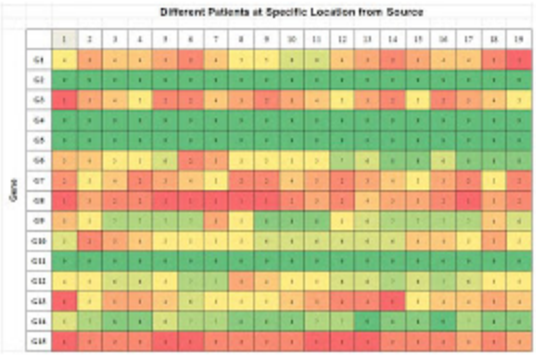
2. Melanoma, as most other cancers, has a multiplicity of changes to genes. There are ligands, receptors, pathway elements, transcription factors, and the telomere issues as well. It is clear that no single factor is the dominant one as of yet. BRAF as a target works for a while and then there is a work around. Thus cancer is an evolving process, and one which may be highly adaptive.

3. A Conjecture: As we have learned more and more as to aberrant genes and their products, as well as miRNAs, and their effects, one could envision several uses of malignancy profiling. We consider that in two steps.

Step 1: Profiling a Specific Patient at Various Locations. As shown below we consider a specific patient and then profile gene expression as a function of distance from the site of initiation, if such was possible. Then we can see how various aberrant genes are being expressed over the distances measure from the source. One would suspect that distance must be measured in some normalized manner but we leave that as an exercise for the student at this time. This gives us a profile for a specific patient, perhaps one for developing therapeutics.



Step 2: The Same Location but across a Large Pool of Patients: Again we look now at the same distance from the source, perhaps at the same time, again an exercise for the student, and we get profiles of the expression of aberrant genes. This allows us to understand the between patient differences.



3. Is Seventy Enough? The study did an analysis on 70 lesions. Perhaps that is not enough. Furthermore based upon our previous comments perhaps a correlative study is demanded as well, by patient and by distance.

4. One of the problems I see is the continually hyping of the results as if this is finally the right answer. Anyone even slightly familiar with the field will understand that each input is vital but assembling them in a cohesive whole is essential. The systems approach is the sine qua non, but that cannot be done without the continual bench work required to understand the details.

For example in an article in the Boston Globe the reporter states[84][6]:

[84][6] http://www.boston.com/news/science/blogs/science-in-mind/2013/01/24/boston-researchers-discover-mutations-that-underlie-melanoma-junk-dna/mNIYVavGfVsvstVj5eNfzO/blog.html

Now scientists working independently in Boston and Germany have made a surprising discovery: a set of genetic mutations found in most melanomas, the deadliest skin cancer. The presence of these mutations in the vast majority of tumors studied suggests that the researchers may have stumbled upon a fundamental mechanism involved in a hallmark trait of cancer cells—their ability to live forever—that could one day be targeted by drugs.

Outside researchers said the work, published online Thursday in the journal Science Express, is exciting because the conclusion is the opposite of what many exhaustive studies of cancers have shown.

In reality as we have discussed, it was imperative that the Telomeres be preserved in metastasis. Millions of rapid mitotic changes in a stem cell must survive and that means keeping Telomeres and that means lots of TERT. Somehow the conclusion was logical, consistent and not at all unexpected especially given what else has been found in the past decade.

The article continues:

Both teams zeroed in on mutations in a part of the genome called a promoter, which acts like a volume knob on a stereo to control gene activity. The gene that the promoter controlled happened to be one that has long been of interest in cancer because it creates part of an enzyme called telomerase, which enables cancer cells to continue to divide indefinitely as one of its key jobs. Still, it wasn't easy for the researchers to convince themselves that what they found, underlying more than two-thirds of melanoma cases, was real.

One would expect this and if one looks at say the miRNA discoveries, they all add up to what controls the ultimate expression of mitotic survival.

5. Theraputics: Can we expect therapeutics from this understanding? Good question. Kinase inhibitors are now well understood, one could in theory build an inhibitor here as well. Is this the target, another target, necessary, helpful, we can only guess. Yet the above Conjecture may allow for the development of a therapeutic profiling plan for melanoma and other malignancies.

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Labels: Cancer

WEDNESDAY, JANUARY 30, 2013

WHAT RECOVERY?

As the Department of Commerce Reports:

Real gross domestic product -- the output of goods and services produced by labor and property located in the United States -- decreased at an annual rate of 0.1 percent in the fourth quarter of 2012 (that is, from the third quarter to the fourth quarter), according to the "advance" estimate released by the Bureau of Economic Analysis. In the third quarter, real GDP increased 3.1 percent.

This is hardly anything to cheer about. One wonders what keeps stocks afloat?
Labels: Economy

TUESDAY, JANUARY 29, 2013

REMEMBER WHAT BUSINESS YOU ARE IN

As I have mentioned before, I purchased one of the first Nexus 7 units off the line. Software wise is was phenomenal. Hardware wise if died after about ten weeks. I have been going around to Staples, a seller of the Nexus, asking what their experience was. The sale folks open up when you say that you hear a failure rate of 30%. They agree that it is around that number. Imagine Boeing or Dell have such a failure rate. Yet Google finds that acceptable.

As I mentioned I sent my back to Schmidt, the Chairman and long ago colleague with a nice letter. Never heard back. In fact that is the Google way apparently, total abject arrogance. Had I sent Ivan Seidenberg a note, he would and have called personally. Ivan and his folks are professionals, Google seems in my opinion and experience to be a collection of dilettantes. That may indeed be their long term undoing, but not too soon.

I saw the recent note of a new Nexus which states:

The next Nexus 7 may increase the resolution of its display to 1080p and maintain the relationship between Asus and Google, according to a report from Digitimes. The follow-up has been rumored for some time, but now Digitimes suggests Google will tweak the device with updates while maintaining the starting $199 price.

Google scarcely promoted the Nexus 7's IPS display, which was an impressive 7-inch 1280×800 and rivaled the screen of the Kindle Fire HD. If Google preserves the aspect ratio of the Nexus 7 in its follow-up, the new display would be 1728×1080; if it conforms to a standard HD display, 1920×1080. Digitimes also suggests Google and Asus may slim down the bezel surrounding the screen, which might allow an aspect ratio change.

Reports on sales of the first Nexus 7 have been rare outside of the ballpark figures from Asus CEO David Cheng suggesting Google had sold about three million units in the four months following its launch. Digitimes indicates Nexus 7 sales have remained steady and that six million units will have shipped by the end of January. Reports on the success of the Nexus 10, or a successor to it, have also been scarce.

With a 30%+ failure rate Google should have dumped Asus in my opinion. But it is not Asus. They have a poor product in my opinion but Google has a horrible Customer Service. I recall calling them and was told that they feel my pain and the approach was to frustrate the customer so much that they just went away. And away the customers went, to Kindle. The Asus product in my opinion is cheap and fragile, and in fact most likely a poor rushed deign. Thus the alleged massive failure rate. Will Google learn? I really doubt it, they are software people, ad they just do not understand, or even want to understand, hardware. Compete with Apple, I think not. Also Asus is ruining its own reputation as well. Perhaps they should reconsider this venture.

TRANSLATION AND CULTURE

The NY Times has an excellent piece today about the trials of translating. The author rambles on, very positively I must say, with statements of the like:

In my opinion, you don't have to be mad to translate, but it probably helps. Take, for instance, the case of the late, great Gilbert Adair. He was translating into English the brilliant novel by Georges Perec, "La Disparition" – a lipogram written entirely without the letter "e." (I had had a tentative go at eliminating the most frequently occurring letter in both English and French and failed utterly.) Adair even succeeded, for a while, in deleting "e" from his vocabulary. I met him for tea in London, while he was in the midst of it, at the Savoy hotel (it had to be the Savoy, not Claridge's or the Grosvenor, obviously). When a waitress came around and asked if he would

like "tea or coffee," he frowned, gritted his teeth, and replied, "Lapsang souchong."

But I am reminded of several events in my life of translating. I have managed about six languages, plus classic Latin and Greek, but they are in varying degrees. I am not too bad in French, that is after a couple of weeks in France, and can manage a bit of Greek, current that is at a Diner or two, and Spanish, yet it is New York Subway Spanish, a language I have found which is truly New York. Then my Italian is just short of the God Father thanks to my being brought up on Staten Island.

But my translating was crowned by two events. In the mid 90s I wanted to create a Term Sheet, about two pages, for a French Canadian company. Thus I sat down and transliterated from English into French and emailed it. Well! I was told that a second grader could do better, but they all got a big laugh out of the document, and when I discussed it with them so did I. You see you just cannot transliterate.

Second, I held a meeting in Prague of my company heads, I believe it was January 2001. I had a new US employee who was to talk and I told the employee many times not to use sports metaphors, football, US that is, and baseball, but since this was the employee's first time out of the US it was hopeless. My other country heads thought that the employee was a typical American of shall we say lesser talents. But then I soon had my chance.

I got frustrated over some issue, cannot recall just what, and in my frustration I declared: "I don't give a rat's ass!".

You should have seen the room. The Russians were transliterating into Russian, the Germans into German, Czechs into Czech, Greeks into Greek and so forth. I saw the process, the contorted faces, trying to word by word make some sense of what I said. They In called a stop and spent a few minutes explaining that it was an outburst of frustration and that I also had no real idea of either what I said or from whence it came. Then I started to collect in about twelve languages similar outbursts, and tons of laughter.

Thus translation is an art, an art which must have the capabilities to transcend both languages and culture. The transcendence is not necessarily one to one, it is not unique, it is a blending of the personal. But the piece in the Times is quite telling. So too was my rat.
Labels: Commentary

SUNDAY, JANUARY 27, 2013

PIGOU, TAXES, HORSES, AND NONSENSE

As many of you know I am not a great fan of Pigou Taxes as sold to us by some left wing "Republicans". In essence they tell us that by placing a tax on say the purchase of gasoline, albeit inelastic in demand, that by the Government collecting the money it will be good for the economy. Never got that idea.

As promoted by a famous Harvard economist, who must get to Harvard by means which are quite elastic, an article in the National Journal by some writer who appears to have in my opinion

only half of the idea states:

But Pigou realized that if a producer wasn't paying for the full cost of producing a good, they would produce too much of it anyway and everyone else would foot the bill. Imagine that making glue is expensive because it costs a lot to cart away all the horse carcasses used in its production. There's not going to be a lot of glue because only people who really like glue will be willing to pay to produce it.

Now imagine that instead of carting away the dead horses, glue factories realize they can dump them in nearby rivers for free. All of a sudden, it becomes a lot cheaper to make glue, so the price goes down. At a price like this, you can't afford not to buy glue, so people consume more of it, and new glue factories pop up.

It all looks like economic growth, until the dead horses start piling up, and people start getting sick. Then they get a bunch of medical bills and the government has to spend money cleaning up the river. The sticky-fingered glue barons don't mind much, because they can afford to buy the expensive houses upriver, and when the cost of cleanup gets spread to everyone, the cost to them is a pittance compared to their newfound glue fortunes.

Meanwhile, the tape users are fuming. They're getting sick from glue they don't even use, and the horse-dredgings are driving up their tax bill. And because a bunch of the former tape-makers have jumped on the glue bandwagon, there's now a tape shortage. It's a mess.

When you account for the costs of sickness and cleanup, each tub of glue costs $20 to produce. But the glue factories don't pay for this, so they can sell glue at a going rate of $12. Glue that's only worth $12 is being made at a cost of $20, so $8 is being wasted on each new tub of glue.

In this case, Pigou would prescribe an $8 tax on glue. Now, it costs glue factories $20 to produce glue, and only people willing to pay that much for glue will buy it. Less glue is produced, so fewer dead horses end up in the river, and the revenue raised from the tax can be used deal with the problems caused by the ones that do.

Now let us examine this logic, I am being kind of course.

1. If we can determine that the cost of picking up the carcass of the deal horse is $8 per bottle of glue soled, then we could collect that from a variety of ways. We could tax the producer, namely we could invent a way to have the town or State pick up the horse and then to tax the glue producer for the carcass removal. Or we could put a tax on the sale of the glue, and then have the buyer expressly pay. In either case it should add to the cost. But alas what may have happened is that we taxed everyone, glue users or not, for the removal, then as any good Government entity does, it over spends, and we get that allocation of an added tax. Like CATV and sports. In either case the dead horse is gone and someone is paying.

2. Now we have argued that a Pigou like fee, let's not call it a tax, can be determined for certain externalities; obesity and dead horses. We can also find an allocation process to collect the right fee. Namely we know the seller or buyer or user and then we can allocate directly; glue buyers or

weight measurements. Now "carbon" and fuel usage is not so easy. First despite what all the political type researchers say we cannot demonstrate a measurable cost to carbon release. There are all sorts of "projections" but it is not as clear as a dead horse or a big gut! So the one to one allocation between users and costs does not exist.

3. Replacement for a user is available for the obese, they can live longer and better if they cut back, and from the horse, it really smells less. But gasoline usage is inelastic the more one goes down the economic ladder. Our Harvard professor may take his blue limo or his black limo. He can choose the Mercedes or the BMW. But the poor Harvard floor cleaner has a twenty year old junker he drives in from the south shore everyday and that is all. He may have a day job at McDonald's that requiring the car as well. He most likely has no discretionary travel.

Thus as I have argued so many times, the Pigou Tax, Fee, Charge, works if and only if we can identify a negative externality, place a price on it to society, can then lay upon it a fee and collect it, and to use the fee to pay for the cost! That just does not work with Pigou Taxes on gasoline. You see, from my simple minded MIT engineer mentality, you know, facts and all that stuff, we have no idea what the cost is, and secondly and most importantly we all know that the Government will not and cannot use the funds collected for the purpose intended. Just look at Social Security!

So this Harvard professor want me to believe that he has a better idea. I really do not think so. Unless we abandon all logic. And yes, the facts as well.
Labels: Economics

SATURDAY, JANUARY 26, 2013

WEALTH TRANSFER OR CONFISCATION

We all bemoan the tax changes and we complain endlessly about Government waste. But the true robber in the process is Professional Sports. I have noted this for years. Now the NY Times has an interesting piece detailing but a small portion of it. The way the Sports folks rip off we poor folks is via charging for sports channels especially with exceptionally high rates and especially by charging everyone.

Simply put this highway robbery works as follows. We all end up with some dozen or more sports channels, and we pay several dollars for each channel whether we watch it or not. Now I have never seen a football game, and frankly I have no interest in watching some group of morbidly obese males dressed in bright and tight fitting costumes, wander around some large field patting each other on the butt. I assume that there must be some logic there somewhere but I fail to grasp it. I have seen one basketball game, I had to since it was a client, and my wife is an avid Red Sox fan so well you see where that goes. But I pay most likely almost 50% of my cable bill for channels I never watch and never will.

So let us assume that we have 120 million cable HH, a good number, and we pay at least $250 per HH per year. That is $$20 billion to the cable companies, then to the teams and then to the players. Do players generate jobs, no, do they add to out net wealth, no, do they do anything beneficial? No. So why are we forced to do this? The FCC is one example. It could stop this in a

heart beat by mandating individual cable line ups. Namely you and I get to choose, and then pay, for what we want. Simple, yes? Yes? But has any FCC Chairman had the courage to implement this? No way, too much money going to Congress etc.

The Times states:

Per-subscriber fees for sports networks keep going up: ESPN, the granddaddy of them all, passed the $5-a-month mark last year.

The eye-popping price tags have restarted debate about a topic near and dear to sports fans, fairness: many TV customers never watch the mightily expensive channels at all, yet almost all must pay. There was a shudder in the industry when John Malone, the business tycoon who helped create the modern-day cable system, said in November that "runaway sports rights" costs amounted to "a high tax on a lot of households that don't have a lot of interest in sports." The only short-term fix, he said, was government intervention.

The price increases reflect the leverage big sports leagues have as distributors like Time Warner Cable and programmers like ESPN desperately try to hang onto live programming in the age of the digital video recorder and the Internet.

Now they continue to reinforce my prior complaints:

"The cable industry has done everything it can to bundle programming and force consumers to buy things they don't want," said Gene Kimmelman, a former Justice Department antitrust lawyer. "Finally, one piece of their bundle has become so expensive that it may finally force the cable industry to shift gears and split the bundle out of fear of pricing its own customers out of the market."

But this is also an antitrust issue. It is called a tying agreement. It is illegal to force me to buy something else that a seller has just to get some other product. You cannot legally tie these two items together. So where is the Antitrust Division of Justice, it appears to have been asleep for at least 30+ years! There has not been a real antitrust action since AT&T and IBM in the 70s! And from this Administration one would expect some respect for "fairness". Don't hold your breath. Cable companies are merely facilitators of this near extortion. You want cable, especially since you really can't get off the air anymore, then you must buy this junk at the high price whether you ever watch it or not.

Now in the same article we have the arrogance of one who is quoted as:

Chris Bevilacqua, an investor and consultant who has spearheaded the creation of several college networks, said, "If consumers were that upset by the costs, they'd be dropping their cable subscriptions in droves."

So what alternative is there? None, If you want say PBS, go pound sand! CNN same answer. Try real time downloading and the Cable guys slam you on usage. The FCC and/or Justice could have done something, anything. But alas these do gooders for the common man have done nothing for decades. The prices keep increasing and there is no end in sight. We have

reassembled the duopoly of wireless and wireline and we have an effective monopoly of cable. We all agree that if there is no competition we need a regulator. So where is the regulator, asleep at the switch, as usual!
Labels: CATV

WEDNESDAY, JANUARY 23, 2013

PSA AND ITS MISUNDERSTANDING

We have examined the use of PSA over the past four plus years in some detail including it extensively in our Draft book on Prostate Cancer Genomics. Simply our conclusions are:

Past analyses of PSA effectiveness fail for several reasons.

First the ask the wrong question. The real question is what temporal PSA data and what threshold provide what level of mortality reduction from PCa.

Second the tested the wrong thing. For example the now classic European study used 4.0 but sampled every few years and not annually.

Third, temporal data of PSA, %Free PSA, and PSA velocity should be used with data taken annually over a minimum of ten years.

Fourth, there are great differences in PSA assays. I have seen variations as great as 25-30% from assay to assay at the same time. It is argued that this is not true but anecdotally I have seen this too many times to believe the research.

Now the Mayo has published a piece decrying the use of PSA. It seems to be in line with the Task Force Recommendations, which we vehemently disagree with. The Mayo paper states:

The contrasting view, perhaps espoused most visibly by the US Preventive Services Task Force (USPSTF) is as follows:

There is no randomized clinical trial that has reported overall lives being saved by PSA or equivalent screening programs.

Some of the published randomized trials have actually reported a deficit in survival among some of the screened populations (eg, older-aged cohorts)

Most published data have not found a real population benefit from current prostate screening algorithms.

As a result, the USPSTF has recommended against routine prostate screening strategies that are based on the currently available tools.

As we have demonstrated several times before, the USPSTF results are in error. The reasons we have summarized above. They conclude:

The important message of this study is that we should be focusing on the genesis of this cancer because it has become an important demographic and epidemiologic challenge. Toward this goal, these types of large and expensive surveys should be used more efficiently to cover a broad range of targets.

We also need to apply PSA in its full context, moving rhetoric to the side, and attempt to implement thoughtfully designed and well structured, hypothesis-driven studies to reveal ways to diagnose the more dangerous prostate cancer variants earlier, or prevent them from occurring, and to develop better management paradigms for those who present with advanced disease.

International data suggest that there is a new epidemic of prostate cancer among urban Chinese, Koreans, and Japanese, domiciled in their homelands or in Western nations,16 and this may present an opportunity for further field testing of some of the strategies enumerated in this editorial at a sufficiently early time to have a real population-based effect.

The author bases the result on such comments as:

Prostate cancer is a remarkably heterogeneous disease, and there clearly is a subtype that will coexist in elderly men for many years, which poses no threat to their longevity or lifestyles unless disrupted by the consequences of aggressive post screening treatment algorithms.

We need to educate men about the existence of prostate cancer, its symptoms and presentations, the availability of treatment, and key facts relating to the debate about screening.

Yes, PCa is complex, and as we have demonstrated in our Draft book the genetic pathways are one of those complexities. However there are both indolent and aggressive forms and at present we do not understand the difference. Stopping the gathering of data will not assist in that differentiation, gathering more data will. To the extent possible, we should also be genetically profiling every tumor, and with as many cells as is possible. Denigrating the few tests we have really does little.
Labels: Cancer

WEDNESDAY, JANUARY 23, 2013

EHR AND THEIR COLLAPSE

The Electronic Health Record has been an oft praised tool and was incented by the Stimulus bubble of 2009. It was to have changed the practice of Medicine and saved billions. We have had serious concerns from several perspectives. First it detracts from "listening" to the patient, second it does not allow even minimal temporal record analysis, and third it was mandated by the Government.

Now comes a report by RAND, who had initially promoted the concept, which in amednews states:

Researchers at the RAND Corp. say their 2005 prediction that health information technology could save the U.S. more than $81 billion annually has not come to pass. But the organization isn't placing the blame on itself for its inaccurate prognostication.

Instead, in a report in the January Health Affairs, researchers from the policy think tank placed the blame on "shortcomings in the design and implementation of health IT systems"

Instead of saving $81 billion I would argue it costing that on top of everything. It was not the shortcomings of the design, it was the demands of HHS and the meaningful use standard process. Physicians have added new staff, the avoid contact with patients, the systems cannot communicate, and the systems failed to allow simple correlations over time, such as weight and HbA1c.

The article continues:

They blamed vendors for creating systems that are difficult to use and can't connect with other electronic health records, echoing physician complaints about them. However, the researchers also said doctors and hospitals have not invested the "considerable" time and effort necessary to learn how to use the systems, and adapt their work flow to ensure that technology is smoothing processes, not hindering them.

In reality the blame should be placed upon the current Administration and its process of Government mandated rules.
Labels: Electronic Medical Records, Health Care

TUESDAY, JANUARY 22, 2013

A NEW HEAD FOR HHS?

Every once and a while we get a politician saying what they really think. In the Guardian a new Japanese Minister is recorded saying he wants the d folks to hu.

The Guardian states:

Japan's new government is barely a month old, and already one of its most senior members has insulted tens of millions of voters by suggesting that the elderly are an unnecessary drain on the country's finances.

Taro Aso, the finance minister, said on Monday that the elderly should be allowed to "hurry up and die" to relieve pressure on the state to pay for their medical care.

"Heaven forbid if you are forced to live on when you want to die. I would wake up feeling increasingly bad knowing that [treatment] was all being paid for by the government," he said during a meeting of the national council on social security reforms. "The problem won't be solved unless you let them hurry up and die."

Aso's comments are likely to cause offence in Japan, where almost a quarter of the 128 million

population is aged over 60. The proportion is forecast to rise to 40% over the next 50 years.

He may have a chance as the new head of HHS. Why not, he has an answer to the Medicare bubble as well as Socia Security. Just a bad joke folks!
Labels: Health Care

HIPPA, THE EVER GROWING SET OF RULES

HIPPA is the health care privacy act, passed in the mid 1990s, when the Internet was real, mandated fax transmissions and prohibited email and other Internet services. It froze Health Care technologically in the 80s at best. Why not mandate telegraph and hand delivered paper telegraph letters as well.

Now the HHS has issued a 563 page set of rules "updating" HIPPA. Try reading through this Administrative Law piece. The FCC documents are elegant compared to this.

As Medpage states:

The long-awaited rules enhance the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which governs health records and patient information.

HHS is expanding the government's scope over healthcare providers, health plans, and other entities that process health insurance claims to include their contractors and subcontractors -- "business associates" -- with whom they share protected health information.

Some of the larger breaches in patient privacy have involved business associates, HHS noted in a press release announcing the rules.

"Much has changed in healthcare since HIPAA was enacted over 15 years ago," HHS Secretary Kathleen Sebelius said in the release. "The new rule will help protect patient privacy and safeguard patients' health information in an ever expanding digital age."

The new rules increase penalties for noncompliance to a maximum of $1.5 million per violation.
The changes also strengthen the Health Information Technology for Economic and Clinical Health (HITECH) breach notification requirements by making clear when breaches must be reported to HHS.

Also, the new rules allow that, when a patient is required by a provider to request records or documents in writing, the request may be made electronically.

This is based upon old law, namely HIPPA, so we await what can come from the new law. One must be careful of what is a medical record, who is a business associate, and that $1.5 million fine is per incident. That may be one way to fund ACA.
Labels: Health Care

MONDAY, JANUARY 21, 2013

IS PIGOU THE ECONOMIC ZOMBIE?

As my readers know I am not a fan of the Pigou tax. Namely if some human action has an externality effect whose cost is not paid by the person acting, then the Government should tax this act and recoup the cost of the negative externality.

For example, if a railroad uses coal steam engines to pull its commuter cars and the cars spew coal ash across some residential area then the Government should have the right to tax the railroad to recoup the social costs. Do you see the fallacy here? Simple, it is a cost to the residents and not the Government and the Government is not an effective re-distributor to the harmed entities. It tends to spend money to maximize the chance of the politicians in office to stay there.

Now consider my favorite example, obesity. We know just how much it costs, on average, for every point above 25.0 of BMI, body mass index. The costs are not linear but quite nonlinear so that the costs of a 30.0 are not 4 time the costs of say a 26.0. In fact a 30.0 may be exponentially greater. But we can calculate the, I have. Thus we know costs and then we could tax the offenders and collect the money to be dispensed to health care providers caring for these people. In this case the negative externality is weight and subsequent disease and its costs.

Now a week ago the NY Times had a piece on Pigou taxes in the context of social annoyances. It has been gnawing at me ever since. Why, because it makes little if any sense as I have explained Pigous taxes.

The article states:

Republican economists, like Mankiw, normally oppose tax increases, but many support Pigovian taxes because, in some sense, we are already paying them. We pay the tax in the form of the overcrowded roads, higher insurance premiums, smog and global warming. Adding an extra fee at the pump simply makes the cost explicit. Pigou's approach, Mankiw argues, also converts a burden into a benefit. Imposing taxes on income and capital gains, he notes, punishes the work and investment that improve society; taxing negative externalities allows the government to make money while discouraging activity that hurts the overall economy.

It continues:

Economics offers no objective criteria for deciding what to tax or by how much. That's one reason many libertarians, like Russ Roberts, a George Mason University economist, will never join the Pigou Club. Sure, he says, externalities exist, but that doesn't mean the government needs to tax them. Yet in the past few weeks, there has been intense discussion among some economists about one particular externality: the social cost of gun ownership. A National Bureau of Economic Research study by Philip Cook and Jens Ludwig determined that guns cost society, on average, a minimum of $100 each and as much as $1,800. Some economists say that a Pigovian tax on weapons, rather than strict regulation, could break the political impasse on gun control.

Now I am not a gun fan, although I do own a Daisy BB rifle in New Hampshire to chase the deer away from my chipmunk farm, but that is a tale for another day. Both of these tales fail to tell the correct economic story.

Pigou taxes are very complex.

First, if we want to reduce the use of something, then taxing it may be a way to do it. Say auto emissions. But for the poor folks who drive long distances to work, since they cannot afford to live closer, it is just another tax. The Harvard Professors may not realize that, but it is a true fact.

Second, if we are trying to recover a cost, we better know what the cost is. In obesity we can and do. In emissions we really do not.

Third if we want to compensate for the cost of the negative externality than in obesity we can. We collect on a BMI basis and then repay back to the health care providers the amount collected. Government gets to keep nothing. If you think that will work then I have a bridge to sell you.

Fourth, objective criteria exist for obesity, cost per person per BMI unit. We have it, we can index it, it is real. So the argument is not correct. As for gun ownership it really is uncertain. For there the solution may be simple; ban certain weapons, be more aggressive with mental illness issues, and give and enforce stiff sentences for law breakers who do so with guns, any lawbreaker. But that has nothing to do with Pigou, unless you tax guns to pay for incarceration, but that really is not Pigou, it is a penalty at best.

So is Pigou reasonable anywhere? Possibly, but it really assumes that it does good and not harm, and that is taxes the users where they have a clear alternative to select a non taxable choice. Fuel is not one of them no matter what they say at Harvard Obesity is!
Labels: Economics

A NEW WORLD WAR

Factor	WW I	WW II	Korea	Vietnam	Cold War	Fundamental Islamic War (FIW)
Cause	Political Agreements	Attack, unilateral	Attack, unilateral	Progressive bad moves by all parties. Enduring colonial attitudes.	Belief set of Communism.	September 11, 2001 Belief set of Islamic Fundamentalism against Western beliefs.
Allies	English, French	English, French, Poles, Russians	UN Nations	South Korea, Australia	US, UK	Very mixed depending on who is under attack. Now we see French, we see UK, US, etc.
Enemies	Germany	Germany Japan	North Korea, China, Russia	North Vietnam, Russia	Soviets, and national entities	Diffuse sets of dedicated believers
Locations	Europe, Middle East	Europe, Asia	Korean Peninsula	Vietnam, Cambodia, Laos	Diverse	Diverse and Disperse
Losers	Germany	Germany, Japan	Stalemate, US Lost Economic vitality	North Vietnam	Not really Russia, just old Guard	TBD Less by the West, broadly speaking, would destroy society as we know it.
Winners	France, England, US	England, US	Stalemate	North Vietnam	US Poland, Czech, Others including Russia	Winners are TBD, if there is no true end then no true winners.
Ultimate Means	Attrition	Nuclear Bomb	Attrition	Attrition, Popular Displrit	Economic	Most likely a silent war. Of attrition
Victory	Negotiated Surrender	Unconditional National Surrender	None	Withdrawal	USSR disintegrates and Russia re-emerges	TBD The only possible victory would be total liquidation and attrition

War occurs when two or more parties have taken steps that result in one or both of the parties to inflict damage upon the other party. Japan's attack upon Pearl Harbor is a clear example of how such an event starts with certainty, the attack on Pearl Harbor, a result of years of threats between the parties. In the case of Japan, both sides were identifiable by nationality and extent and the enemy, Japan, was clearly identifiable within the context of its uniformed armed forces and national identity. In contrast Vietnam was much less clear. The precipitating event was diffuse at best and the "enemy's" forces were diffuse as well, including civilians and hundreds of thousands of non-uniformed adversaries. Korea had a precipitating event, the crossing of the North into the South. The enemy was uniformed and the territory defined. In all three cases the outcomes were different. In WW II there was a clear victory, in Korea an endless stalemate and in Vietnam, a clear loss.

So with September 11, 2001, we have a clear precipitating event. Yet, we have a diffuse adversary. Furthermore, unlike Vietnam, we have a geographically and even ethnically diffuse adversary, non-uniformed and spread across areas where boundaries and territories are ill defined at best. This is not a war for some form of national sovereignty or territorial gain. It is a war for global influence; it is a war for an idea, a religious belief. It is a war of Fundamental Islamic Terrorists, FIT. The adversary is not in a uniform, not confined to a geographical limit, yet whose objective is global conversion or submission to their form of belief. In a sense, this is fundamentally different than many previous wars. There may be a few prior exceptions. For example, starting in the mid seventh century the ancestors of the current adversaries set out in a similar belief set to capture territory. In a somewhat similar vein, one could see the Spanish invaders of South America, in a similar mix of belief and gold, to have been to the indigenous people similar to the FIT.

In WW II, the desire of Germany and Japan was regional dominance and control, by physical and political means. The tactic was expansion and occupation. There was no desire, by either country, to "convert" the captives to their belief. Nor were the attacks driven by a hatred of the "beliefs" of the attacked party; the one clear exception being the anti-Semitism of the Germans. It was purely a territorial grab. In Korea, the issue was the dominance of the North over the South and the same applied for Vietnam. For the current conflict, however, it is clearly and solely the dominance of one belief set over those not believing.

Thus, what does a nation or set of nations need to effectively fight such a diffuse non-nation based religious adversary? How does one fight and overcome, for unless total and complete victory is attained, it will never end.

We believe that there are three simple elements or strategies to achieve success;

1. ***Intelligence must be at the ground level***. As we had imbedded intelligence agents, spies, in the 40s through 60s embedded with the enemy, we need the same here. We need to have dedicated and trusted agents who can inform us of the enemy's moves, actions, intents, strengths and weaknesses. Instead of the person at the Bar in Istanbul or Lisbon, or Berlin, we need some at the stalls in Cairo, Islamabad, Damascus, Tehran, and yes even Mumbai, to understand the traffic of communications. We also need the same human presence at the camps in the deserts

and hinter lands. This takes time and dedication, it takes sophisticated training and competence, and it takes what we had just after WW II when the CIA first started. Namely it requires the very best and a dedicated team of the most competent. It also requires an intelligence capability provided by technical means, such as covert over-flight capabilities. It also requires broad Signal-Intel. Cyber-Intel, broadly speaking, will be at the leading edge as well.

2. ***Utilize primarily covert Forces and technical means to pre-emptively liquidate threats before they become real***. Is this a classic US Military role? I do not think so. In fact, there may not be a role for the US Army as we understand it today anywhere here. There is no uniformed armed national aggressor. The Marines, yes, they are tactical, surgical, do a specific task in coordination with the Navy, and then redeploy to the next task. The Army is just too big, slow and fat to act in this new theatre of war. The Air Force, yes if we mean using their resources for technical means of intelligence gathering, siting and locating, and remote liquidation. Yet in saying all of this, one may envision a totally new "Defense" organization. China has an Army of millions, to protect the country from invasion and to secure domestic tranquility. It works; no one in their right mind would invade China. But that very same army may not be able to protect it against the same enemy we face.

3. ***Maintain a highly competent means for rapid deployment and redeployment of the Covert Forces anywhere we would need them to achieve the desired effect***. This means a Navy, a flexible and new Navy of mobile platforms for deployment and resources to support the deployment and neutralize threats. But what kind of Navy does this require? Clearly a carrier force is essential, one with multiple carrier groups as platforms for rapid and somewhat secure deployment. Second, it may require a littoral fleet of close in vessels, especially for those areas where such are essential like the South East Asia and African coast areas.

What tactics should we deploy under such circumstances? What do we tell the Covert Forces to do? Clearly there are several key points:

1. ***Do not make things worse***. Since this is a war of belief, we must not take actions that reinforce the belief. Large forces deployed to change "minds and Hearts" or to restructure governments may not work, are costly in dollars and lives, and often result in making things work. Focus on the problem, eradicate it, and let things alone. This is not a war where Nation Building has any role. One may have to return again and again to neutralize threats. There may not be any singular victories, just ongoing cleaning up. This is a chronic threat that can only be made worse if not handled in a delicate and surgical manner.

2. ***Do not tell anyone what has been done***. Let them find out for themselves. This is not a War for a vainglorious politician. It is a War for a cold tactician who does not seek self-pride and self-aggrandizement. That of course is a tough thing to expect in any politician. Yet, take the liquidation of the 911 mastermind, that should have been done without a word, let the adversary yell it out, the failure to self-promote will all too often make the adversary make false moves, often out of frustration. Bottom line, it is always better just to keep your mouth shut, it adds to the intensity.

3. ***Reward friends and punish enemies***. Yes, most likely one hopefully can identify a "friend" and yes it may require some "reward". After all, heads of investment banks get large rewards for their "value added" and the same for "friends". Also one punishes enemies, yes that means liquidation. I remember the Church Commission in the 70s which was aghast at the liquidation of enemies. Perhaps all of those actions were not really that a bad, if the targets neutralized were truly threats to our very existence then they should have been liquidated. Augustine and Aquinas were fans of "just war" and this element of a goal and strategy is totally consistent if properly managed.

What is victory in such a War? That is the most critical question, namely how does one know when success is achieved.

1. ***There may never be an end, at least in the short term.*** It may become a process, a chronic and ongoing process. The Cold War only had an end when the other side got old and tired. When young and enthusiastic there could never be an end. The end occurs when the enemy just gives up and goes away. Regrettably, it may take generations.

2. ***Identify the enemy, who is really a threat in this war?*** Thus, is North Korea an enemy? That is doubtful, a supplier of weapons perhaps, but just a poor country taking risky actions which may explode in their face. Thus, who is really the enemy? That will be the most critical question that must be asked and answered. It clearly is Fundamental Islamist Terrorists, but of no specific nationality. They can be profiled based upon a belief set, not necessarily demographics, it is a psychographic profile. To some degree we had a complex set of profiling criteria in the Cold War. Demographically in the Cold War we had a well-defined set of Soviet nationals and psychographically we had the fellow travelers and spies. Profiling works if done properly.

Thus what does this brief analysis tell one? Simply:

1. ***One must identify, understand, and target the enemy***. One must understand why they have become and remain an enemy but "solving" the problem of the cause may not be an effective act. There are just some people who hate others, especially for religious reasons. To paraphrase Voltaire, he saw the benefit in England of having many religions and supporting none. At least if they were Protestant; but alas, Voltaire frequently let his ego get in the way of facts. In understanding an enemy, one must not let one's politically correctness get in the way of the facts, for there are some truly evil people. We have to assure ourselves that we go after enemies because they represent a clear and present danger to out very existence, and that is clear to our current post 911 enemy base.

2. ***One must reduce the number of enemies rather than create new ones.*** That is often best done by not advertising victories. Further it is also best done by not making neutral parties into enemies by the actions taken. Enemies, all too often if left to their own accord, tend to take actions which make them clear and present dangers to themselves as well.

3. ***Liquidating the enemy must be targeted, quick, and effective***. Collateral damage is always a concern because it creates new enemies. Thus highly effective human intelligences as well as technical intelligence are both essential.

4. ***Liquidating the enemy must be done in quiet***. Both the public recognition of the enemy as well as taking credit for the liquidation of the enemy has significant negative effects. Silence is a keyword of the process. Silence about achievements also has the added effect of terrifying the enemy and making the non-combatants recognize the power of the opposing force.

There is the question of; how well we have progressed thus far? The Afghanistan invasion was a sledge hammer approach rather than that of a scalpel. It was politically motivated to show that the Government was responding but in many ways it may just has made things worse by establishing corrupt entities which will ultimately be unstable. Iraq was just an unnecessary exercise. It eliminated a nuisance but distracted many from the true enemy as well as massively undermining the economy of the United States. However, it did provide fine tuning to the military, yet it was fine tuning for perhaps the wrong war.

5. ***Nation building is all too often a fruitless process***. Cultures clash and those involved in effecting the process of Nation Building are all too often incompetent to do so. Secondly, there may just not be a basis for any Nation to be built around the efforts. The best thing to do is not to Nation Build. Focus on the specific and limited goal which is total neutralization and elimination of the adversary. Nation Building presents the opportunity for significant collateral damage. It further presents the opportunity to install local leaders who may, in the minds of the local residents, be worse than what was there before.

The current actions against the FIT, Fundamentalist Islamic Terrorists, is somewhat mixed. On the one hand we seem to be deploying many more “black ops” which is essential, and we may very well be slowly expanding our human intelligence, but not at the rate we truly should be doing so. We are, however, taking public adulation for accomplishments, which all too often have negative effects. The negative effects are that we telegraph much too much intelligence to the adversary. In fact, if we were not to take any public adulation we would create uncertainty, confusion, and potential paranoia in the adversary. Those weapons of psychological uncertainty in an adversary are often more powerful than a million troops deployed in the open.

Thus we know we are at war, we understand the enemy in the most broad of terms, and we know that winning is essential, costly, and of long duration. It may be even longer than the Cold War. It also is a war like no other we have been involved in in the course of our brief history as a nation. Yet historically it is a war we have seen before. In the mid-7th century and for a few centuries thereafter a similar war of ideas took place, and with many of the same cast of characters. The movement of the Arab followers made its way across North Africa and up halfway through Spain as we know it today.

It was not truly reversed until 1492, after almost 800 years of give and take. That period was also a war of ideas, of ideas much more than territory. But it was also a war of large armies, one against the other. Yet in today’s world, much smaller forces can affect the same or possible greater damage using weapons not available 1400 years or so ago.

Another question in this construct of a new battlefront is; who else is involved and what side are they on? Clearly the Russians have had their concerns with the FIT for a couple of decades now,

with the same class of adversaries. How well they have managed this is still an open question but it is clear that they have had their losses as well. The next country facing the threat is India, and the raid on the Mumbai hotels was just one of many acts that have dragged them as well into this global engagement as in a great degree an engagement that they have been in for decades.

Then there is China, one wonders just how they will progress in this threat environment, some mild strains have been observed but, as of yet, no significant front appears there. Thus we have a global front of concern. There are pockets of response, from the shotgun start and stop response of the US, namely the blatant denial by the US Administration that the Ft Hood attack was not just another battle in this conflict but some form of "work place violence", to the immediate and aggressive response of the French to the attempted overthrow of Mali.

The current Administration tried to classify Ft Hood as anything but what it was. They called it another internal "work place violence" incident. The failure of the U.S. to recognize what the existential nature of this conflict truly is must change. The sine qua non step in addressing its solution is recognition that it is existential, global, and enduring. The FIT have not been suppressed. To the contrary, the FIT is spreading and metastasizing into a globally disperse movement threatening those parts of civilization which surrounds all of us.

The French seem to have finally and aggressively awakened to the threat. Algeria and Mali were their backdoor. The English are more than highly cognizant having suffered several assaults. At what point does a single and united force deal with the adversary? How do they define the adversary, those a direct threat to them, a true global mesh of loosely connected enemies to their very existence.
Labels: Commentary

FRIDAY, JANUARY 18, 2013

A GOOD STEP FORWARD

It appears that the TSA has ended the acquisition of the X Ray scanners. From Bloomberg we have:

The U.S. Transportation Security Administration will remove airport body scanners that privacy advocates likened to strip searches after OSI Systems Inc. (OSIS) couldn't write software to make passenger images less revealing. ...

TSA has contracted with L-3, Smiths Group Plc (SMIN) and American Science & Engineering Inc. (ASEI) for new body-image scanners, all of which must have privacy software. L-3 and Smiths used millimeter-wave technology. American Science uses backscatter.

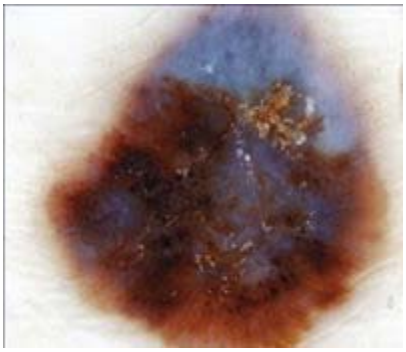
The agency's strategy for handling passenger traffic relies on the capability of L-3's millimeter-wave machines to process passengers in about half the time for Rapiscan machines, Sanders said. TSA will be getting about 60 more L-3 scanners in January and February, he said.

Hopefully the last of the X Ray systems will be removed. As we had analyzed a couple of years ago the X Ray systems present in our opinion a potential clear and present danger.

Labels: Cancer

FRIDAY, JANUARY 18, 2013

MOBILE MEDICAL APPS



I have been looking at mobile apps for several years, even pre i-Phone. The initial focus was on Obesity control and Type 2 Diabetes management. It just never seemed to have gotten where it can truly work, and oftentimes this is proven by the explosion of such apps which purport to do something but don't quite. (Note: Image from ***Dermoscopy*** by Soyer et al, Elsevier Ltd, 2012)

In JAMA Dermatology there was a recent analysis of a few apps applied to identifying melanomas, a highly aggressive malignancy of the skin. Now back in the early 1960s when I first was introduced to this as a student one all too often saw a patient with a Stage IV melanoma, large, bleeding, and most likely terminal. Also most physicians would be conservative and not do a referral until till often too late. I saw patients whose legs were amputated in attempts to stop the ravages of the disease.

Patients and general physicians, even dermatologists, were not attuned to treating any suspicious pigmented lesion carefully and quickly.This has changed for the better and dermoscopes have helped, magnifying devices which allow for better examination of the pigmented lesions. From my perspective, if one had even a hint, better to carefully excise and biopsy by a highly competent dermatopathologist.

Now there are quite a few apps which use a smart phone to take a picture of a lesion and analyze it. However the results were far from positive. They state:

The performance of smartphone applications in assessing melanoma risk is highly variable, and 3 of 4 smartphone applications incorrectly classified 30% or more of melanomas as unconcerning. Reliance on these applications, which are not subject to regulatory oversight, in lieu of medical consultation can delay the diagnosis of melanoma and harm users. As smartphones use increases, these devices are applied to functions beyond communication and entertainment and often become tools that are involved intimately in many aspects of daily life through the use of specialized applications. Several applications in the field of health care, marketed directly to the public, are readily available. Some examples include applications that

are intended to aid users in learning about adverse effects of medications, to track their caloric intake and expenditure to manage weight loss, and to log their menstrual cycles to monitor fertility. Although such applications have the potential to improve patient awareness and physician-patient communication, applications that provide any type of medical advice might result in harm to the patient if that advice is incorrect or misleading.

Patient self-diagnosis is always a double edged sword. On the one hand one gets the hypochondriac patient who has some strange and rare disorder and needs extensive treatment. I often think of the Lyme Disease culture who ascribe every human ache and pain to some prior infection, not that there are no such cases, but most likely not as many as are presented.
The article concludes:

Technologies that improve the rate of melanoma self-detection have potential to improve mortality due to melanoma and would be welcome additions to our efforts to decrease mortality through early detection. However, extreme care must be taken to avoid harming patients in the process. Despite disclaimers presented by each of these applications that they were designed for educational purposes rather than actual diagnosis and that they should not substitute for standard medical care, releasing a tool to the public requires some thought as to how it could be misused. ***This potential is of particular concern in times of economic hardship, when uninsured and even insured patients, deterred by the cost of copayments for medical visits, may turn to these applications as alternatives to physician evaluation. Physicians must be aware of these applications because the use of medical applications seems to be increasing over time; whether such applications may be subject to regulatory oversight, whether oversight is appropriate, and when oversight might be applied remain unclear.*** *However, given the recent media and legislative interest in such applications, the dermatologist should be aware of those relevant to our field to aid us in protecting and educating our patients.*

The highlighted portion is of special concern. In a piece from the Wall Street Journal on the JAMA article the writer indicates that reimbursement for reading a smart phone image is $5 per image. From what I also know that is the benchmark for teleradiology readings of chest X Rays. On the one hand we have explosive Health Care costs and on the other we have a pittance for what is a life saving procedure. It will be interesting to see if this field evolves.
Labels: Health Care

WHO AM I?

In a recent article in Science the investigators demonstrated an uncanny ability to identify family trees by using Y chromosome STR, short tandem repeats, and integrating that with open source data. The use such sites as Y Search which focuses on agglomerating such Y chromosome data with family trees.

As the authors state:

Sharing sequencing data sets without identifiers has become a common practice in genomics. Here, we report that surnames can be recovered from personal genomes by profiling short tandem repeats on the Y chromosome (Y-STRs) and querying recreational genetic genealogy

databases. We show that a combination of a surname with other types of metadata, such as age and state, can be used to triangulate the identity of the target. A key feature of this technique is that it entirely relies on free, publicly accessible Internet resources. We quantitatively analyze the probability of identification for U.S. males. We further demonstrate the feasibility of this technique by tracing back with high probability the identities of multiple participants in public sequencing projects.

So the concern about genetic privacy is not a concern, there is none. The interesting observation is how quickly these things are created and become public and free. This is indeed worth following.
Labels: Genetics

WEDNESDAY, JANUARY 16, 2013

STAR TREK OR HARRY POTTER

There is an interesting paper in the journal Light concerning invisibility cloaking. Yes, making things invisible. Just like Harry Potter or some of the episodes of Star Trek.

The authors state:

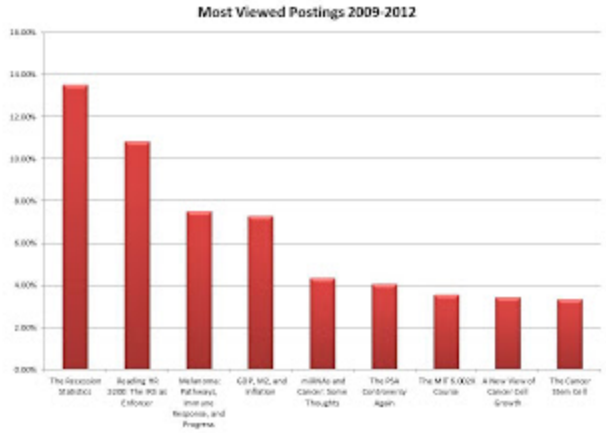
In this review, we will specifically focus on the electrodynamics of transformation-based invisibility cloaking, and we will attempt to provide some hindsight regarding several electromagnetic problems on this topic with the author's own research experiences. As an alternative approach to invisibility cloaking, the recent exciting development of plasmonic cloaking which is based on scattering cancellation, deserves another special review, and thus, is not covered here. The recent, ingenious proposal of 'cloaking at a distance utilizing media with a negative refractive index has been reviewed in detail from the perspective of folded geometrical properties; therefore, this topic is not repeated here.

One finds this most interesting, it was done in Singapore and the analysis is quite compelling as well. Needless to say the applications could be mixed at best. It will be interesting to follow this work.
Labels: Commentary

SATURDAY, JANUARY 5, 2013

MOST POPULAR POSTINGS

Thought it would be of interest to see the most popular postings over the past 4 years. There were about 75,000 visitors and here is the ranking:

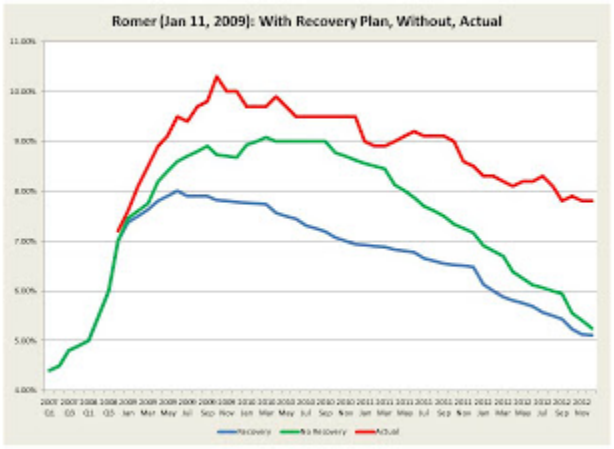


Interesting to see the mix.
Labels: Commentary

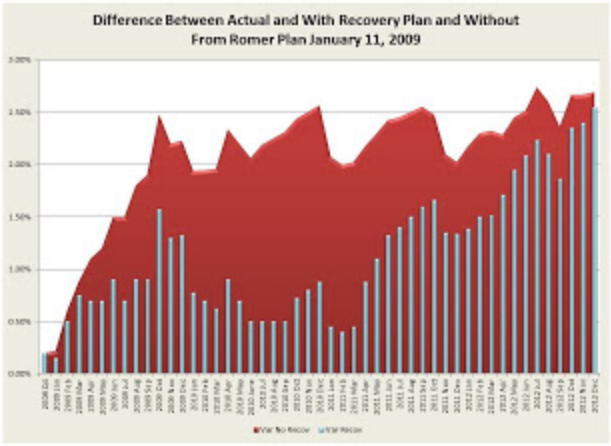
FRIDAY, JANUARY 4, 2013

EMPLOYMENT JANUARY 2013

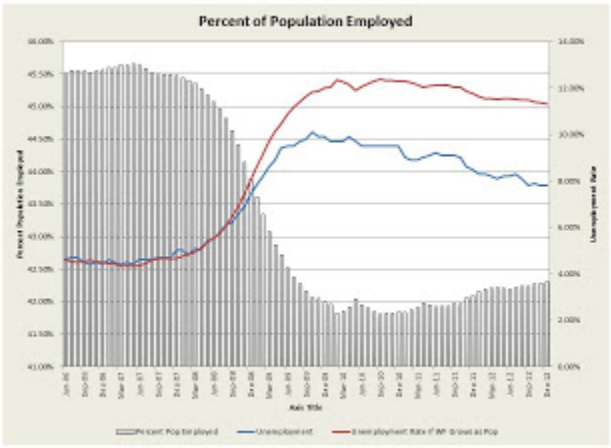
We begin as usual with the Romer Curve. It shows what she predicted now four years ago.



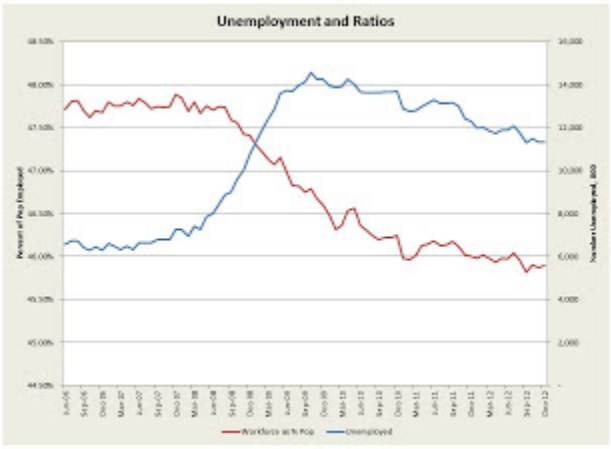
Above we have the prediction and reality. As we have noted for the past 4 years reality and the economists prediction never even come close.



The above is the errors of the Romer curve. Note they just seem to get bigger.

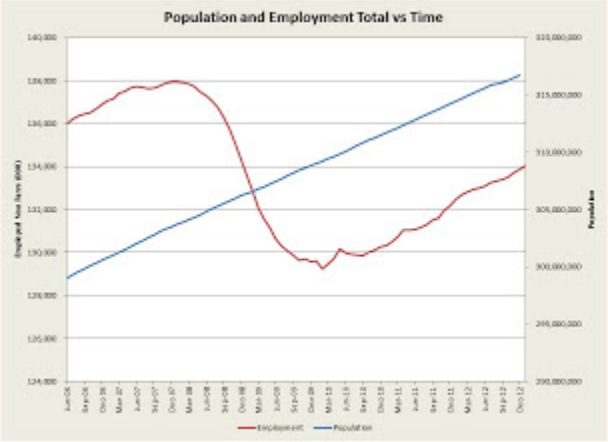


This is unemployment based on DoL data on the reality of what was in the work force as of 2008, percent wise of population. We are still above 11% unemployment, or another way of saying we have a structural unemployment.



The above is the workforce as a percent of the population and the unemployed. We still have a substantial amount unemployed as of DoL but worse we have lost 2% of the population to

systemic unemployment. That is growing and it is 2%+ of the total population. That is a main driver to the loss in tax revenues as well.



The above demonstrates that structural change. As the population grows we see the drop never closing.

CBO'S OBSERVATIONS

The CBO reports:

Like all of CBO's cost estimates, our estimate for this legislation shows the effects of the legislation relative to current law at the time we did the estimate. Relative to the laws in place at the end of 2012, we estimate that this legislation will reduce revenues and increase spending by a total of nearly $4.0 trillion over the 2013-2022 period. ...

From that perspective, why will the legislation increase deficits?

Mostly because, under the laws previously in place, numerous tax provisions originally enacted in 2001, 2003, and 2009 would have expired.

As a result, in 2013 personal income tax rates would have gone up for people at all income levels, the alternative minimum tax (AMT) would have applied to many more people, estate and gift taxes would have risen, and a number of other revenue-increasing changes in tax law would have taken effect.

This legislation will prevent those changes in law from occurring or reduce their scope; hence, relative to what would have happened without the legislation, it embodies substantial tax cuts.

The legislation also will boost deficits by increasing spending, mostly for refundable tax credits and unemployment compensation.

We have argued this in previous analyses. The big issue is the expenditures and certain tax cuts. Unemployment and food stamps are a big driver and the becalmed labor force is a principal driver. Nothing seems to correct this.

Labels: Economy

WEDNESDAY, JANUARY 2, 2013

WHAT IS $60 BILLION FOR?

Now I was born and raised on Staten Island and I spend many wonderful hours at the Jersey Shore, but $60 Billion is real money. One should have an accounting, one thinks. What is $60 Billion to be spent on, is it to assist the truly needy, or as one may suspect is it packed with pork, gifts to constituents, near and far, and creating just a greater burden on those for whom the support may be truly needed.

Indeed, some of the areas of the Jersey Shore and Staten Island may best be left for mother Nature to settle, one really cannot stop the Ocean. But what are those areas, and do we know so much so quickly that $60 Billion is the correct number. Four years ago we heard of and spent the Stimulus, and as I have been tracking it monthly it had done not one bit of good.

In the Guardian there is a piece on the New Jersey Governor's diatribe against the House asking for some details before agreeing to hand out $60 Billion. It states:

Christie, speaking at a 40-minute long press conference before that announcement, reflected widespread criticism, mainly on the left but also among independents and many Republicans, that the Tea Party-backed Republicans in the House are a disruptive influence, creating chaos in Washington.

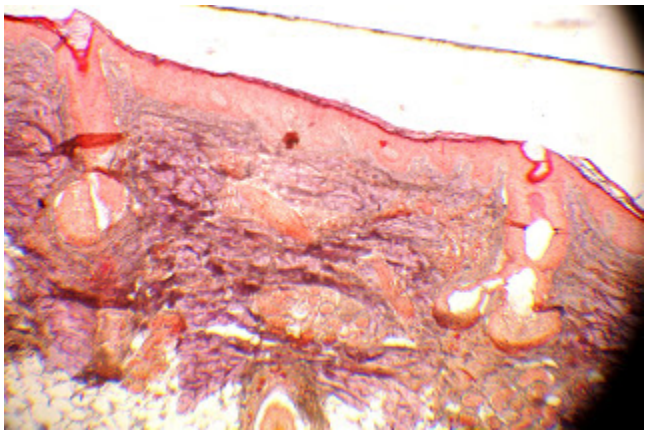
"Americans are tired of the palace intrigue and political partisanship of this Congress, which places one-upmanship ahead of the lives of the citizens who sent these people to Washington DC in the first place," Christie said.

Now slinging mud is perhaps not the benefit that we seek. Leadership seems to be lacking in being able to communicate. It may be fun to listen to the new guy on the street shouting out their complaints, but leadership at times requires tempered communications, explaining what needs to be done, why we should add more on our burden, nit just whipping the mule, until perhaps the poor animal just collapses under the burden.

Regrettably, in my opinion, we seem to be lacking in true political leadership, lacking in that tempered ability to lead by communicating, lead by example, lead by bringing the masses along in a rational manner.

One of the most critical elements I see not being anywhere is that very simple ability to lead by example, to show others that we too can carry the load. One of the best CEOs I have ever seen would take the subway, sit in coach, and buy his own lunch. The arrogance of leadership leaves the leader without followers. Marcus Aurelius was as a Stoic also a great leader. Reading his works may sometime help those who are in positions of leadership learn the art of leading. We seem to lack a great deal of leadership talent in our current politicians.
Labels: Politics

CHANGES TO PATHOLOGY



In the recent JAMA there is an interesting discussion regarding the treatment of biopsy samples. The issue is simple and critical. Typically the pathologist examines the tissue sample using a variety of techniques and reaches a conclusion. However with the advances in genomics one would like to examine the gene and pathway micro structure of the sample. They state:

Genomics is poised to revolutionize cancer treatment. Whole genome sequencing is becoming more rapid, accurate, and affordable, and the ability to use genomic data to match biologically based therapy to an individual is becoming a reality. As the sequencing endeavor transitions from a heroic effort performed by a dedicated team for a particular patient to a routine component of most, if not all, cancer diagnoses, standards for acquiring appropriate tissue samples also must evolve. This is necessary because an individual's native (germline) genome must be compared with the genome of the tumor.

They then continue:

Gerlinger et al reported an analysis of whole exome sequencing of frozen tissue from multiple regions of tumors among patients with metastatic renal cell carcinoma. The most salient finding was intratumor diversity, whereby driver mutations in the mTOR gene were found only in some regions of the tumors. The authors concluded that single tumor biopsies may "underestimate the tumor genomics landscape" and "may present major challenges to personalized medicine and biomarker development." Here, the implication is particularly striking because many needle biopsies and aspirations performed routinely today have barely adequate tissue to be regarded as fulfilling an ideal "single" sample, let alone enough to detect intratumor heterogeneity.

The issue is significant for many reasons. Having the germline and the somatic profiles we can start to see where changes go. But I believe that there are more issues:

1. Stem cell: If indeed we have stem cells and they are somewhat rare then we need a large selection of cells to compare.

2. Metastasis: If we have mets then we need to compare the in situ cells to the mets, and perhaps across many such mets to see what changes where. This may be especially true for such things as the miR-26a microRNA local environment discussion made recently.

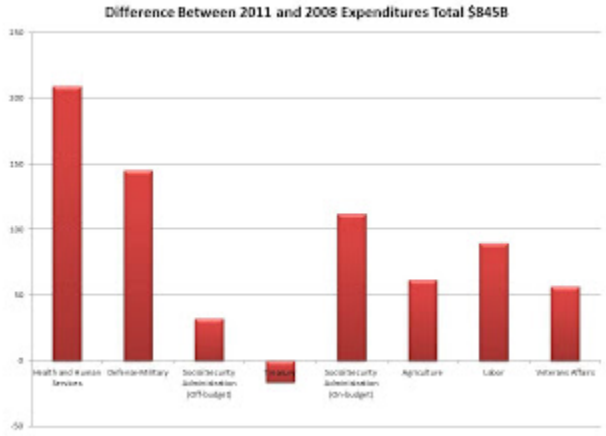
3. miRNA: What about the miRNAs, these must also be tracked.

This opens a set of truly critical issues. Collecting cells is important, enough cells is critical, and establishing a data base and access to it is essential. Clearly a new set of tools will be needed but this open a vast array of new data usages which we need.
Labels: Cancer, Genetics

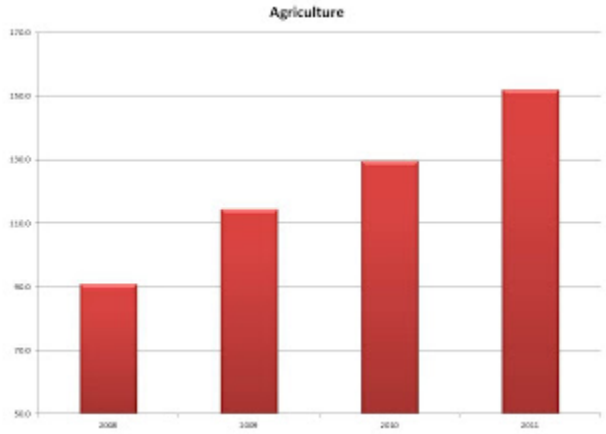
THOUGHTS ON THE DEFICIT

The deficit is a problem but why? We are still looking at $1T and the folks in DC seem clueless. Well let's look at a back of the envelope analysis. I use some recent but not great data. It seems it is tough to get the latest from the Feds, although the FRB in St Louis does a great job.

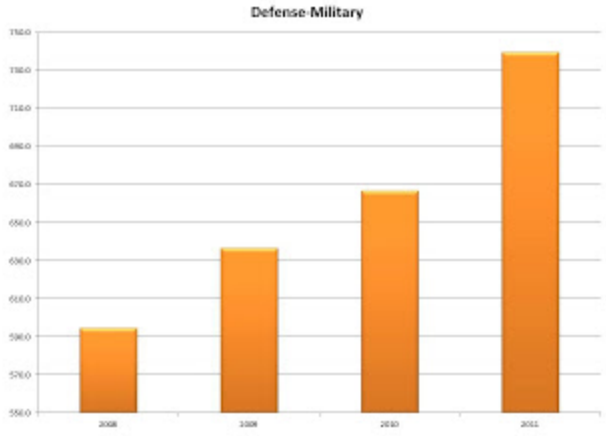
Now here are some thoughts:



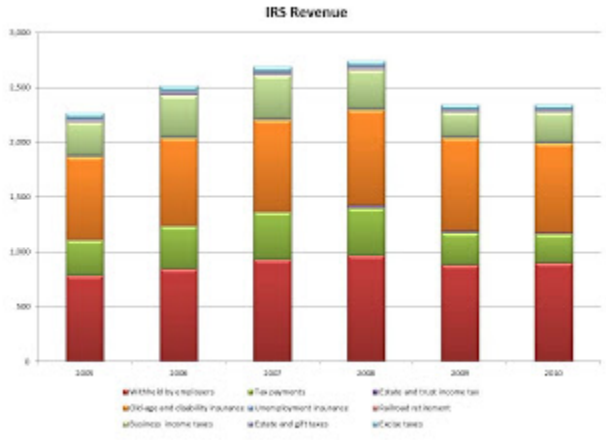
First, above is the change in expenditures by Agency from 2008 to 2011. It is a $400B increase. Nothing much has happened, just an increase. Why?



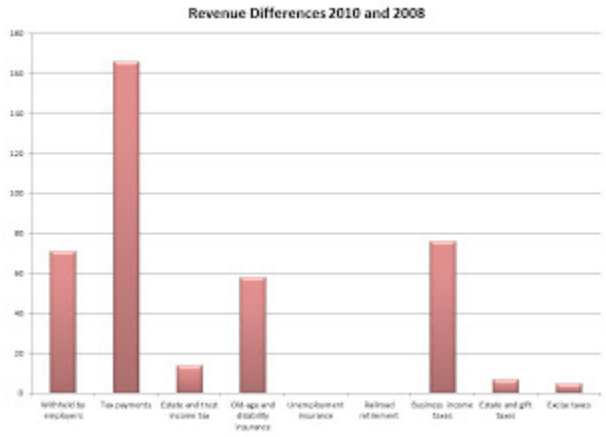
First Agriculture increased because of Food Stamps and the Broadband Stimulus etc. For a nation which is bordering on the morbidly obese why the food stamp excess?



Now for one of the big ones, Defense, a $150B increase. We were getting out of 2 wars so why the increase? Never really gets explained. Frankly $500B is not a bad number, $750B is insane. So here is a great place to start.



Now the revenue is a problem. Here we have a $400 drop. Taxes are just not there; fewer people working and lower business taxes. Simple. Get people back to work. Easier said than done.



But easier said than done. Yet we are not collecting SSI from those employed, part of the Tax Break.That is significant and it frankly is a large part of the drop.

So we have here $800B of the$1T. This can be solved by (1) cutting expenses, and we know where, (2) hopefully getting more back to work, simply by demonstrating an understanding of the problem and showing that it is being fixed.

But wait, now we have the ACA, and if you thought the above was a mess just wait till we finish 2013! Happy New Year.

TCP/IP AT 30

I read a piece today in Le Monde describing this as the 30th anniversary of TCP/IP,the Internet protocol. From an IEEE paper in May 1974, by Kahn and Cerf, entitled A Protocol For Packet Network Intercommunication, there evolved this simple method of communicating over a computer network. As they stated then:

A protocol that supports the sharing of resources that exist in different packet switching networks is presented. The protocol provides for variation in individual network packet sizes, transmission failures, sequencing flow control, end-to-end error checking, and the creation and destruction of logical process-to-process connections. Some implementation issues are considered, and problems such as internetwork routing, accounting, and timeouts are exposed.

Le Monde states:

Internet, 30 ans déjà ? En écrivant cela, on imagine déjà les commentateurs de ce post s'étriper sur la "vraie" date de naissance du Réseau. Alors précisons tout de suite : il y a trente ans (et un jour), le protocole TCP/IP voyait le jour, rappelle l'un de ses pères fondateurs, Vint Cerf, sur le blog des équipes de Google....

C'est pour palier ce problème que Vint Cerf et Robert Kahn ont développé un nouveau protocole TCP/IP, afin que tous les réseaux, et les ordinateurs parlent le même langage. Le 1er janvier 1983 avait été fixé comme dead-line pour migrer tous les serveurs du réseau Arpanet vers le nouveau protocole. "Quand ce jour-là est arrivé, l'émotion était palpable (...) Il n'y eut pas de grande célébration – je ne trouve pas même une seule photo – indique Vint Cerf. Le seul souvenir que l'on a gardé ce sont les badges 'j'ai survécu au passage au TCP/IP' que portaient fièrement ceux qui avaient surmonté cette épreuve !"

Thus as Vint states on his Google posting:

It's been almost 40 years since Bob and I wrote our paper, and I can assure you while we had high hopes, we did not dare to assume that the Internet would turn into the worldwide platform it's become. I feel immensely privileged to have played a part and, like any proud parent, have delighted in watching it grow. I continue to do what I can to protect its future. I hope you'll join

me today in raising a toast to the Internet—may it continue to connect us for years to come.

I remember coming from MIT to Comsat in 1975 and being told that one task was to try this protocol out on our satellite links. Harry Van Trees headed the Department and Estil Hoversten and BobKahn, forever tennis partners, tried this out, and I managed to get the links in place, oftentimes going around corners and dealing with "friends" to help out. In it went to Goonhilly (England) and Trondheim (Norway) and I even got a few to other strange places as we tested variants.

So Happy 30th birthday.
Labels: Internet

TUESDAY, JANUARY 1, 2013

UNDERSTANDING CANCER RISKS

Now in today's NY Times[85][1] there is an article by some woman who is concerned about here genes. As the writer states:

I jogged into the Stanford Cancer Clinic with my boyfriend, the youngest people there by two decades. We stood there sweating and holding hands, a jarring sight in the sickly light.

"You are 18, right?" the receptionist asked. Behind me, a woman so gaunt that her cheekbones protruded rolled by in a wheelchair. The oncologist called me alone to the exam room, and I told her the story I had revealed to more doctors than friends: I carry the BRCA1 mutation, which gives you a 98 percent chance of developing cancer.

Somatic versus germline, this is somatic. Namely the presence of this gene mutation in a Bayesian sense yields a high probability of incidence. So what does one do? Remove the offending organs, watch and wait, forget about it? All of these are options, and options that have costs and consequences. Remember the aphorism, "prior planning prevents poor performance".

Now what can one do when one may be faced with such a dilemma? Let us consider several examples. They may all be primarily somatic and they are all Bayesian. There are two questions; what to do when and why to do what? Let us consider the first question; what to do when?

1. Colon Cancer: Assume there are three family members who have had colon cancer, two first degree, mother and sister, and a second degree, an aunt. What should one do? This tells one almost as much as BRCA status. Clearly if one has this family history one should have frequent colonoscopies. Finding an adenoma early means it is excised before becoming malignant. It reduces the risk of a malignancy.

[85][1] http://well.blogs.nytimes.com/2012/12/31/carrying-a-cancer-gene-unsure-i-want-to-know/?ref=health?src=dayp

2. Melanoma: Assume that one has two first degree relatives with melanoma and that you have had four atypical or dysplastic nevi. Now what should one do? Clearly one has a significantly elevated risk of melanoma. Melanoma for the most part is on the surface skin, it can also be in the eye, colon, mouth, or other epithelium. So how best to handle it? Periodic skin examination and excision of lesions as early as possible, seems at present to be the best. Are there any gene tests? Not really, not yet. But one must euphemistically just keep ahead of the bow wave.

3. Prostate Cancer: This gets tricky and political. Assume you have one first degree relative who dies of a highly aggressive form of prostate cancer; PSA of 4-40 in two years and 40-dead in another two. You have annual PSA tests, best we can do, excluding PCA3, and you find a velocity of 0.8 pa. Namely there is a sudden spike. What to do? Here is where its gets political. Akin to the BRCA issue, kind of, you get a prostate biopsy. It is negative. Does that tell you something? Yes but not all, a second one in 912 months is essential, especially if PSA still rising. What you see is a complex process, with risks, costs, and uncertain outcomes.

4. BRCA Breast Cancer Presence: Now look at the case in the paper. You have relatives with BRCA mutation positive and you wonder what to do. Now that depends. In this case your test if also showing a mutation means you have a very elevated risk of breast and ovarian cancer. Do you get a mastectomy and the ovaries removed? It is costly and yet the risk if substantial. It is disfiguring and possibly even more. Is the cost worth it, is the discomfort, physical and mental worth it, possibly. It is a personal decision. For society is it worth it, yes, having a productive member may very well be more important than having a deceased one.

Now the author continues:

So was I wrong to unwind my double helix?

My risks of getting cancer at 21 are too low for me to do anything differently to better my odds. The knowledge is both irrelevant and painful; it's obsessed me and made me behave irrationally. I wake from nightmares in which I am dying from cancer. I reread the memoirs of patients with metastatic disease until I can't see the text through my tears. In my supposedly rational pursuit of knowledge, I've gone a little mad.

Despite an excess of information, I pursued more, enrolling in Stanford's cancer biology class. The professor filled his slides with dark oncological puns, lecturing with the almost robotic detachment I sometimes see in those who work closely with cancer. Maybe I, too, am becoming robotic. I can laugh at the puns, calmly press lecturers on survival rates for breast cancer, marvel at the elegant molecular mechanisms by which it eats us alive. Just as tumors eventually swell too large for their hosts to endure, will all this knowledge grow past what I can handle?

Now let us consider the second question, why to do what? This is the tough question. This is the self-searching, soul searching, process. Each person in a way answers it differently. I have seen the following types of people:

1. Pragmatics: These people just do not want to leave a mess around, and they believe that if they get ill they create a mess for themselves and others and then why not just take preventive measures now and get the risk reduced if possible. The go for colonoscopies, skin exams, and yes eve gene testing, if the result has a positive mitigating factor. If the gene test, however, shows a deadly disease potential for which there is no cure, then let fate take its toll. On a cost benefit analysis basis these are not the cheapest overall for society, but are cheap.

2. Hypochondriacs: Yes they exists, they want every test no matter how costly and how ineffective. On a cost benefit basis, this cost a fortune.

3. Deniers: These people would not get tested for any reason until the end is near. The old man who has not had a bowel movement for eight weeks, has lost 20% body weight and has sever back pain. They he finally is dragged in and we see metastasized pancreatic cancer, and he has a best a week to live. On the cost basis, they are the lowest. In this case they go from diagnosis to a hospice for a very short while.

4. The Terrified: This is a mix between the hypochondriac and the denier. They have a real basis for concern, yet they do not outright deny it. They vacillate between considering and effecting preventive care and then falling back into nothing for fear of the result.
These four groups are just a few of the generalizations that one sees. But one of the most important questions that a physician can ask themselves is what type of patient am I seeing, how will they react, what motivates them to do the right thing, assuming we know what that even is. Thus how does a physician motivate a smoker to stop, a diabetic, Type 2, to shed weight, and a drug abuser to quit? What of the mammogram for a woman, do we harass her to have one? Evan if there is no family history. All too often we have the one test fits all, yet with genomic tests we do have much better tools. How will a patient react?

In ten years of less, along with the CBC, done by a simple machine, we will have a full gene profile of somatic genes. What do we do with it? Knowledge will change each year as we understand more and more. Yet the full gene profile may not change. What does the patient want to know, need to know, and what does the patient not really have to know? These will be the driving questions.

But in a way this article is akin to the first and second year Med students, who often come down with diseases they are studying, at least a few come down with certainty with Dengue Fever, despite the fact that they never left Massachusetts. Then it slowly disappears. The more one knows the more one understands the disease and the person often separate, but always in the same package.

Labels: Cancer, Government, Health Care

MORE ON MIRNAS

Muller Fabbri reports in Cancer Research[86[1]]:

MicroRNAs (miRNA) are small noncoding RNAs with gene regulatory functions. Their expression is frequently dysregulated in almost all human tumors and they can be found circulating within exosomes secreted by cancer cells.

In addition to being promising cancer biomarkers with diagnostic, prognostic, and theranostic implications, circulating miRNAs have also important biologic functions: they can be engulfed by immune cells surrounding cancer cells within the tumor microenvironment and bind to toll-like receptors (TLR7 in mice and TLR8 in human) expressed by the immune cells.

*As a result, the binding miRNAs function as agonists of these single-stranded RNA-binding TLRs**, leading to NF-κB signaling activation and secretion of interleukin (IL)-6 and TNF-α, which promote cancer cell growth and metastasization.***

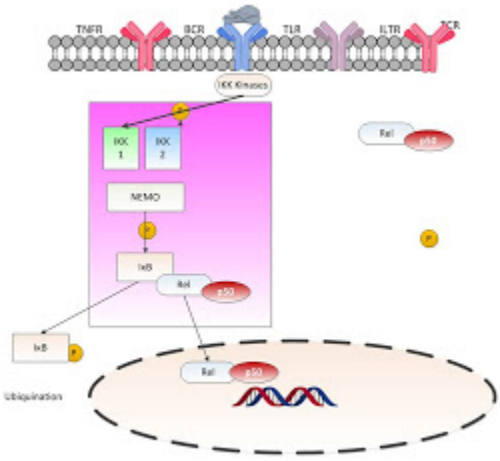
This novel miRNA mechanism of action suggests that these small noncoding RNAs can act as hormones (we call these miRNAs hormone miRNAs or H-miRNAs).

The discovery that miRNAs released by cancer cells can bind to a receptor in a surrounding immune cell is completely novel. Other receptors (in addition to TLR7 and TLR8) are likely to be found, but this is the first identified miRNA receptor and it is relevant to cancer. This review discusses the meaning of this discovery and comments on the exciting future implications of these findings in the context of tumor microenvironment biology as well as of other human diseases.

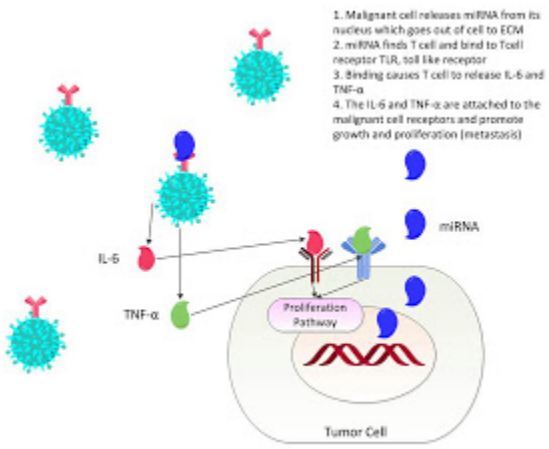
Recall that NF-κB is a protein complex which has the ability to control transcription. This means that activation of this protein and its related pathways can result on growth and proliferation and if done in a malignant cell can result in metastasis. Simply it senses from the kinase receptors and then if activated sends out transcription factors to start the process. We show this below.

[86[1]] Fabbri, M., TLRs and miRNA Receptors, Cancer Research December 2012, http://cancerres.aacrjournals.org/content/72/24/6333.abstract

Now the specifics are detailed below. We need an activator and when the activator ligand is attached to a receptor the process begins, allowing the Rel and p50 to move to the nucleus and start transcription.



Here is what the author argues happens. The Figure below depicts it in some detail:



Specifically the steps are as follows:

1. Malignant cell releases miRNA from its nucleus which goes out of cell to ECM

2. miRNA finds T cell and bind to Tcell receptor TLR, toll like receptor

3. Binding causes T cell to release IL-6 and TNF-α

4. The IL-6 and TNF-α are attached to the malignant cell receptors and promote growth and proliferation (metastasis)

Namely the malignant cell can by emitting miRNAs get the surrounding cells to assist it in proliferating. This is an observation consistent with some we commented on a few months ago, namely that cancer cells have the ability to enlist the neighboring benign cells to assist it in spreading. The difference here is the use of miRNAs to do that.

This is a positive feedback loop, an unstable process, one where the cancer cell has enlisted the benign cells which should be doing a different task to seed the malignant cell with metastatic strength. This is a wonderful example of how the small miRNAs can act in a multiple set of ways.

We find this most interesting not only from its prognostic ability but also from its ability to target and suppress the miRNAs.

On the other hand our simple models just keep getting more complex.

Labels: Cancer