1/31/2013

The Squirrel's Nest 2012

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THE SQUIRREL'S NEST

MONDAY, DECEMBER 31, 2012

GETTING RESPECT

Lebanon created Sanjoub the Squirrel, a mascot who teaches children and villagers about preventing forest fires.

Thus states the Voice Of America. OK, it is the end of the year and the only other news is that stuff about some cliff, or as the French call it the mur or wall. But a squirrel being a national symbol, how great can it get!

Happy New Year to all you Cliff watchers.
Labels: Commentary, Squirrels

SATURDAY, DECEMBER 29, 2012

WHAT IS RETAIL?

Retail is selling to people, you, me, other people. Starbucks is in retail, Dunkin Doughnuts is in retail, LL Bean is in retail, and yes Amazon is in retail. Retail means having the customer come back again and spend more money, and having the customer tell their friends how great the stuff was. Retail is a happy customer.

What else characterizes retail? First, if all else fails, listen to the customer. And who is the customer? The person buying your stuff, simple. Now take Amazon, if I buy something and I don't like it, for any reason, I get to send it back, free, no questions asked, almost. It works, it is simple, and I feel comfortable buying from Amazon. Bezos gets it, he knows retail. That is why Amazon gets so many customers. Now Apple is retail, they make a product, the design it well, they stand behind it, and they demonstrate their love of their customer. It is a religion, it works.

Now for Google. Google is NOT in retail. It seems to see its only customer those who pay them, namely advertisers. And for a long while that is exactly what they were. Then someone thought of selling the Nexus. Well, now the customer was you and me, dear readers, and Google was clueless. The Nexus has it appears a fantastic failure rate, by that I mean it appears to be quite high, and I can personally attest to it.

Now try and go back and remedy it with Google, I did, no luck. I even sent it with a nice note to Eric Schmidt, the Chairman, who I worked with on a Presidential Commission a decade ago, so I was not some schlub from the street, and any luck, no way. Had I written say Ivan Seidenberg at Verizon, in hours there would have been a response, and for years there was. Verizon is in retail, Google seems clueless.

So what is Retail, at its core it is keeping your customer happy, secure in knowing if its broke you will fix it, one way or the other. For Google in my opinion and in my experience, we the customer are a dumb annoyance. So what did I do at Christmas, got the team Kindles, yes, Kindles, not Nexus, would never go there. And oh by the way, I try and tell this tale to everyone. If I buy a Nexus from Google, I am terrified if it is defective, no warranty helps, the characters on their customer service just want to tell me they feel my pain, they really do. But fixing anything, are you nuts, they are Google.

Now one final note, I also have seen that somehow the Googleniks have in my opinion seemed to get to slam bad reviews on Amazon, perhaps Amazon would want to investigate, just a thought. Will Google ever understand Retail, after all Apple did, but then Jobs had his walk in the Desert, Google has not had that, yet.
Labels: Google

FRIDAY, DECEMBER 28, 2012

USDA: AN EXAMPLE OF WASTE

Now the USDA is one of the largest branches of the Executive. It controls much of our life. For example, I have a small, 0.25 A, daylily hybridizing business, not really big, I generate and sell, a few, daylilies. Now I am not big Agribusiness. I have been doing this for 27 years and it is a nice small sum from time to time, not going to be Hedge Fund level stuff. It also has helped our work in genomics, as some of you may have seen on our other Blog entries.

So today I got my annual 50 page USDA National Agricultural Statistics Service Questionnaire. By Law I must fill it out and send it in. Yes, if I fail to do this I guess the USDA cops will be at my door. I have about 550 daylily hybrids, on small plots and some 4,000 seeds! But I had to tell them how many people are caring for my goats, how many peas I grew, my race, my income, my prperty value, how much water I used, how many immigrants I hired, and the list went on for hours!

This is an example of Government waste.The last question was what type of Internet connection I had. One would have thought that I could have answered the whole thing on line. But no, this is USDA, caught somewhere in 1921 to 1922!

The USDA building in DC is massive, halls upon halls of workers who in turn contract out to other workers, who in turn ... you get the point. Why in the good Lord's name do I have to tell them, under penalty of law, what I did with my 0.25 A of daylilies! I get inspected, I pay my fees, and then I have to, under penalty of law, make a report on nothing, really, it is almost nothing. But someone will read the data, enter it, put it in a data base and make monumental decisions.

Well I followed the law, filled out the form in complete, and then signed it and sent it back. I could have been making some money, but alas, with taxes going where they are why work. I will have too many forms to fill out under penalty of law. Kafka, where are you when we really need you?

Labels: Government

MEDICARE CUTS

As of next Tuesday Medicare payments will be cut 28.5% from where they are now. What will that mean?

Medpage states:

It's looking less and less likely that Congress and the White House will strike a deal to keep the country from falling over the "fiscal cliff" next week, so physicians are preparing for a 28.5% cut in Medicare payments that will take effect on Jan. 1.

That figure includes a 26.5% cut under Medicare's sustainable growth rate (SGR) reimbursement formula and a 2% cut mandated by the Budget Control Act, the piece of legislation that outlined the tax increases and spending cuts that define the fiscal cliff.

"Given the current progress with the legislation, CMS [the Centers for Medicare and Medicaid Services] must take steps to implement the negative update," the agency said in a Dec. 19 notice on its website.

CMS states:

The negative update of 27% under current law for the 2013 Medicare Physician Fee Schedule is scheduled to take effect on January 1, 2013.

Medicare Physician Fee Schedule claims for services rendered on or before December 31, 2012, are unaffected by the 2013 payment cut and will be processed and paid under normal procedures and time frames.

The Administration is disappointed that Congress has failed to pass a solution to eliminate the sustainable growth rate (SGR) formula-driven cuts, and has put payments for health care for Medicare beneficiaries at risk. We continue to urge Congress to take action to ensure these cuts do not take effect. Given the current progress with the legislation, CMS must take steps to implement the negative update.

Under current law, clean electronic claims are not paid sooner than 14 calendar days (29 days for paper claims) after the date of receipt. CMS will notify you on or before January 11, 2013, with more information about the status of Congressional action to avert the negative update and next steps.

So what might that mean for those 55 million on Medicare:

1. Generally according to Medical Ethics if you have a physician they must see you if you are returning or being treated. Perhaps you may pushed to the end of the line but you will get an appointment, sometime.

2. If you are seeking a new physician, good luck, many will no longer take Medicare. You will be providing reimbursement lower than Medicaid. If for example you have a cancer and need special treatment and it is discovered January 1, 2013 or later, you may very well not find a physician available where the best ones are.

3. The level and quality of care may actually suffer, in small ways. You may find you are treated akin to food stamp holders at a candy store, with scorn.

So will the Fiscal Cliff cause harm? We don't really know, it does solve some problems but it creates many more. Add the ACA to the mix and one sees an explosive disruption in Health Care, a disaster which will soon expand on all fronts. Welcome to 2013.
Labels: Health Care

THURSDAY, DECEMBER 27, 2012

MICRO RNAS AND MELANOMA

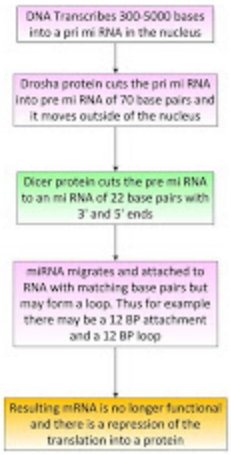
We have previously examined the impact of miRNAs in the development of cancers from several perspectives. In this new White Paper we take a recent finding regarding melanoma and a specific miRNA and then use it as a baseline to examine miRNAs in a broader context, focusing specifically on melanoma. The interest here is twofold; first, as a potential therapeutic target and second as a potential prognostic marker.

miRNAs have been examined for the past twenty years but just the last decade have they been understood specifically as elements in cancer control. Even more so, only in the past five years has their full impact been understood and the ability to manipulate certain miRNA paths controlled.

This section details many of the elements of miRNA as regards to cancer and metastatic control as well as the therapeutic control via miRNAs. What is of most significant interest is that miRNAs have such a pervasive set of control paths via activating oncogenes and suppressing genes which control metastatic growth. The miRNAs are not just control elements in select paths but appear to be control elements in the day to day paths of cellular homeostasis. This makes modeling of pathways significantly more complex.

It is critical to understand that as we have seen genomic models built around proteins, genes and pathways, we have also not seen the clear presence of miRNAs as integral parts of this process. One need just look at the many papers on pathway dynamics and almost to each one there is a total absence of miRNAs. We had proposed about five years ago that we look at miRNAs as noise, as at best epigenetic accidents which result in loss of expression. Now however it may be argued that they play as significant a role as the well-known pathways, albeit not yet fully understood.

Let us recall that the miRNA functions in a manner shown below:



We shall detail this process later in the document. However it is good to understand the nature of the miRNA. One key factor is that reproducing and introducing miRNAs appears to be rather straightforward. This perhaps they represent a powerful tool in the therapeutic arsenal.

The specific focus here is on miRNA-26a[1[1]]. There are many databases now with a great deal of information regarding the miRNAs and we refer to them as in course.

Recent Observations

We begin by examining a recent paper regarding miR-26a. As we shall discuss later this miRNA is found to be aberrant in multiple cancers and in the case of melanoma the disruption associated with several pathways is somewhat clearly understood. In a recent paper by Reuland et al the authors make the following observations[2[2]]:

Melanoma is an aggressive cancer that metastasizes rapidly and is refractory to conventional chemotherapies. Identifying microRNAs (miRNAs) that are responsible for this pathogenesis is therefore a promising means of developing new therapies. We identified miR-26a through microarray and quantitative reverse-transcription–PCR (qRT-PCR) experiments as a miRNA that is strongly downregulated in melanoma cell lines as compared with primary melanocytes. Treatment of cell lines with miR-26a mimic caused significant and rapid cell death compared with a negative control in most melanoma cell lines tested.

In surveying targets of miR-26a, we found that protein levels of SMAD1 (mothers against decapentaplegic homolog 1) and BAG-4/SODD were strongly decreased in sensitive cells treated with miR-26a mimic as compared with the control.

The luciferase reporter assays further demonstrated that miR-26a can repress gene expression

[1[1]] http://www.mirbase.org/cgi-bin/mirna_entry.pl?acc=MI0000083

[2[2]] http://www.nature.com/jid/journal/vaop/ncurrent/full/jid2012400a.html

through the binding site in the 3' untranslated region (3'UTR) of SODD (silencer of death domains). Knockdown of these proteins with small interfering RNA (siRNA) showed that SODD has an important role in protecting melanoma cells from apoptosis in most cell lines sensitive to miR-26a, whereas SMAD1 may have a minor role. Furthermore, transfecting cells with a miR-26a inhibitor increased SODD expression. Our findings indicate that miR-26a replacement is a potential therapeutic strategy for metastatic melanoma, and that SODD, in particular, is a potentially useful therapeutic target.

The observations focus on several key areas:

1. The impact of miRNAs on melanoma metastasis. As we will discuss there have been many previous studies implicating many miRNAs in this area. Thus seems to expand the results.

2. There appears to be a therapeutic approach to the issue by increasing the miRNA26a to further reduce by binding to the SODD facilitator product. There again have been several studies along this line recently. SODD is an interesting controlling gene/protein complex and the control via miR-26a is of significance.

3. There may be a prognostic indicator here as well. Again there has been a great deal of work in this field.

First we examine both the miRNA26a and SODD respectively and then we examine the issues discussed above in some detail. This represents just another of many studies regarding the use of miRNAs for the potential control of melanoma.

Before continuing it is useful to examine some of the additional comments the authors of the referred to article have made to the trade press relating to the release of the paper. Now one trade press article states[3][3]:

A University of Colorado Cancer Center study in this month's edition of the Journal of Investigative Dermatology describes a new target and potential treatment for melanoma, the most dangerous form of skin cancer. MicroRNA can decide which genes in a cell's DNA are expressed and which stay silent. Melanoma tends to lack microRNA-26a, which makes the gene SODD go silent.

"It's a double negative," says Yiqun Shellman, PhD, investigator at the CU Cancer Center, associate professor at the CU School of Medicine, and the study's co-senior author. "miR-26a works to stop the growth of cancer. You turn off this thing that should stop growth, and you have growth." When Shellman, David Norris and colleagues reintroduced microRNA-26a to melanoma cell lines that lacked it, they saw a marked decrease in cancer cell survival.

[3][3] http://medicalxpress.com/news/2012-12-serendipity-potential-therapy-melanoma.html also http://medicalxpress.com/news/2012-12-serendipity-potential-therapy-melanoma.html#jCp

MicroRNA-26a killed melanoma cells while leaving healthy cells unharmed. In fact, the discovery started back a couple steps. First the group compared microRNA expression in healthy cells to that of microRNA expression in melanoma cells. "We hoped the difference between microRNA expression in healthy and melanoma cells would show which ones were contributing to tumorgenesis," Shellman says. The microRNA most consistently different between healthy and cancerous cells was 26a. The discovery of how it works and what exactly it does was serendipitous. "We started by testing the effect of microRNA-26a on known gene targets to see if it was effecting the expression of logical, cancer-causing pathways, but none of them seemed affected in melanoma," Shellman says. "We were working with the SODD gene in an unrelated project, and SODD has a putative but not high-scored binding site for miR-26a, and thought, why not test it? Sure enough, it turned out to be the target – microRNA-26a downregulates this gene." Shellman hopes this robust finding in cell cultures will help pave the way for future work with microRNA-26a as a therapeutic target in animal models and eventually a human trial. "The first step is to further pinpoint the genetic signatures of the patients likely to benefit from microRNA-26a replacement therapy," Shellman says, noting that only some and not all melanoma cells were killed by miRNA replacement. "Maybe it's simply the downregulation of microRNA-26a itself, or maybe we can use SODD expression as the biomarker," Shellman says. Once Shellman and colleagues discover the characteristics of a melanoma susceptible to microRNA-26a treatment, they hope funding will allow the lab to follow the promising therapy up the evolution from cells to humans.

As can be seen from the conversation above, there still may exist some questions of the details of the process. What is critical, however, is the fact that the miRNA plays such a prominent role, that one may target the miRNA, and that a pathway is a fundamental part of the development of a putative therapeutic. But fundamentally the last sentence above does diminish the ultimate enthusiasm.

The critical observations made here is the relationship between the controlling proteins, their related mRNA and the interference coming from miRNA. This has not been explored in significant detail until of late.

Another trade press review states as follows[4[4]]:

Researchers from the University of Colorado Cancer Center say that they have discovered a new, more targeted way of treating melanoma, the most deadly form of skin cancer
The findings, described in a recent edition of the Journal of Investigative Dermatology, describe how small pieces of genetic material known as MicroRNA can choose the genes in a DNA cell that are either expressed or kept silent. With melanoma in particular, the researchers discovered a deficiency of microRNA-26a that usually silences the gene SODD. "It's a double negative," explained the study's co-senior author Yiqun Shellman, an investigator at the University of Colorado Cancer Center and associate professor at the University of Colorado School of Medicine, in a prepared statement. "MiR-26a works to stop the growth of cancer. You turn off

[4[4]] http://www.redorbit.com/news/health/1112752907/genetic-culprit-for-melanoma-found-122112/

[4[5]] http://www.molecular-cancer.com/content/11/1/44

this thing that should stop growth, and you have growth."

In the study, melanoma cell lines that lacked microRNA-26a were reintroduced to the cell in a lab. As a result, there was a reduction in cancer cell survival and the microRNA-26a eliminated melanoma cells while leaving healthy cells alive. The team of investigators was able to compare the expression of microRNA in healthy cells to the expression of microRNA in melanoma cells. "We hoped the difference between microRNA expression in healthy and melanoma cells would show which ones were contributing to tumorgenesis," continued Shellman in the statement. The researchers saw that the expression of micro-RNA-26 was consistently different between healthy and cancerous cells. Some, but not all, of the melanoma cells were eliminated by the replacement introduction of mRNA. "The first step is to further pinpoint the genetic signatures of the patients likely to benefit from microRNA-26a replacement therapy," noted Shellman in the statement. "Maybe it's simply the downregulation of microRNA-26a itself, or maybe we can use SODD expression as the biomarker." Moving forward, Shellman believes that her team's discovery of the role of MicroRNA in the development of carcinoma in cell cultures may eventually help develop new therapeutic techniques that could be used in real cancer patients.

This above statement is a simple reiteration of some of the prior work. Again it is clear that although experimentally observed, one is still quite a way from clinical reality.

Other researchers have examined miRNAs and melanoma as well. For example the work of Segura et al (2012) state:

Melanoma incidence and associated mortality continue to increase worldwide. The lack of treatments with durable responses for stage IV melanoma may be due, at least in part, to an incomplete understanding of the molecular mechanisms that regulate tumor initiation and/or progression to metastasis. Recent evidence supports miRNA dysregulation in melanoma impacting several well-known pathways such as the PI3K/AKT or RAS/MAPK pathways, but also underexplored cellular processes like protein glycosylation and immune modulation. There is also increasing evidence that miRNA can improve patient prognostic classification over the classical staging system and provide new therapeutic opportunities. The integration of this recently acquired knowledge with known molecular alterations in protein coding genes characteristic of these tumors (i.e., BRAF and NRAS mutations, CDKN2A inactivation) is critical for a complete understanding of melanoma pathogenesis. Here, we compile the evidence of the functional roles of miRNAs in melanomagenesis and progression, and of their clinical utility as biomarkers, prognostic tools and potential therapeutic targets. Characterization of miRNA alterations in melanoma may provide new angles for therapeutic intervention, help to decipher mechanisms of drug resistance, and improve patient classification for disease surveillance and clinical benefit.

The above work readily complements the work upon which we have focused this analysis. Additional melanoma analyses has been done by Zehavi et al. Zehavi et al state[5][5]:

We show that the expression of miRNAs from a large cluster on human chromosome 14q32 is significantly down-regulated in melanoma cell lines, benign nevi and melanoma samples relative to normal melanocytes. This miRNA cluster resides within a parentally imprinted chromosomal region known to be important in development and differentiation. In some melanoma cell lines, a chromosomal deletion or loss-of-heterozygosity was observed in the cis-acting regulatory region of this cluster. In several cell lines we were able to re-express two maternally induced genes and several miRNAs from the cluster with a combination of de-methylating agents and histone deacetylase inhibitors, suggesting that epigenetic modifications take part in their silencing. Stable over-expression of mir-376a and mir-376c, two miRNAs from this cluster that could be re-expressed following epigenetic manipulation, led to modest growth retardation and to a significant decrease in migration in-vitro. Bioinformatic analysis predicted that both miRNAs could potentially target the 3'UTR of IGF1R. Indeed, stable expression of mir-376a and mir-376c in melanoma cells led to a decrease in IGF1R mRNA and protein, and a luciferase reporter assay indicated that the 3'UTR of IGF1R is a target of both mir-376a and mir-376c. Our work is the first to show that the large miRNA cluster

Note in the above the selection and determination of other miRNAs as well. It is not expected that any single miRNA will be considered the sole controlling element. In fact one may anticipate a progression as the tumor develops. The setting off of miRNAs as the tumor stage changes would be an interesting by-product of this analysis.

Another quite useful analysis of miRNAs and melanoma has been done by Taveira da Cruz and Jasiulionis. In their work the two authors state:

miRNAs are non-coding RNAs that bind to mRNA targets and disturb their stability and/or translation, thus acting in gene posttranscriptional regulation. It is predicted that over 30% of mRNAs are regulated by miRNAs. Therefore these molecules are considered essential in the processing of many biological responses, such as cell proliferation, apoptosis, and stress responsiveness. As miRNAs participate of virtually all cellular pathways, their deregulation is critical to cancer development. Consequently, loss or gain of miRNAs function may contribute to tumor progression. Little is known about the regulation of miRNAs and understanding the events that lead to changes in their expression may provide new perspectives for cancer treatment. Among distinct types of cancer, melanoma has special implications. It is characterized as a complex disease, originated from a malignant transformation of melanocytes.

Despite being rare, its metastatic form is usually incurable, which makes melanoma the major death cause of all skin cancers. Some molecular pathways are frequently disrupted in melanoma, and miRNAs probably have a decisive role on these alterations. Therefore, this review aims to discuss new findings about miRNAs in melanoma fields, underlying epigenetic processes, and also to argue possibilities of using miRNAs in melanoma diagnosis and therapy.

The conclusions drawn from the above paper are considerable. After just a few years there is now a well-accepted understanding of how miRNAs function and that they play critical roles in pathways. However, and this is a very significant however, we do not understand what precipitates them nor do we fully understand their relationship in pathway analysis. What is clear

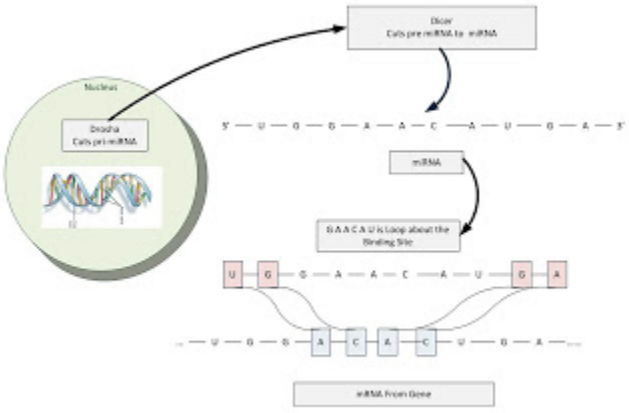
is that they are found in a multiple set of cancers, that that are pathway control elements, but the complex interactions we would anticipate are still unknown.

Micro RNAs

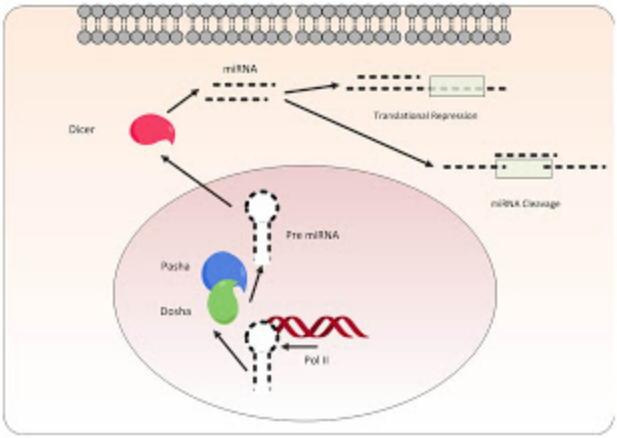
miRNAs are small (19-25 nucleotide single strand RNA) which have been created off intron sections of the DNA of a cell through pol II or pol III. They then operate on mRNA from exons which have escaped from the nucleus and are putatively maturing to proteins in the cytoplasm. Some of the proteins may be beneficial and some may not. The miRNAs seem to be secondary, and in some cases primary, pathway control elements. miRNAs contain RNA nucleotides, U, A, C, G. Thus simply stated if any possible combination is available there could be 4^{22} such miRNAs or about one trillion, equal to the national debt each year! This is a simplistic statement but it does provide a metric. We have discovered just more than a 1,000 miRNAs to data, with variants on some. Therefore a great deal more can be determined.

To demonstrate the recent occurrence of miRNA, it was not until the 6th edition of Watson's Biology of the Gene in 2008 that we see a Chapter on controlling RNAs with miRNA (See Chapter 18). In addition even some of the recent literature lends miRNAs a place as a curiosity. In fact the more they are understood the more powerful they become.

In the classic review paper by Esquela-Kerscher, A. and F, Slack, they present an excellent discussion on miRNAs. First we present the overall construct. miRNAs are produced like all RNA and then pass through the Drosha/Pasha complex and emerge from the nucleus as a double RNA with a loop. Dicer cuts the loop creating single strand short RNAs which are the miRNA.



Now from the paper we have the more detailed description where we show how miRNA can interfere with RNA translation by either inhibiting it or by slicing the RNA and in turn also inhibiting it. We depict that below



We rely upon that here, They state:

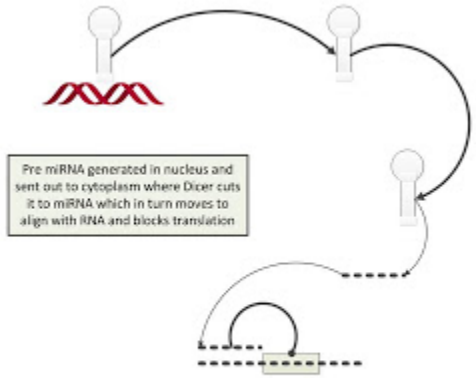
The biogenesis of microRNAs. *MicroRNA (miRNA) genes are generally transcribed by RNA Polymerase II (Pol II) in the nucleus to form large pri-miRNA transcripts, which are capped (7MGpppG) and polyadenylated (AAAAA). These pri-miRNA transcripts are processed by the RNase III enzyme Drosha and its co-factor, Pasha, to release the ~70-nucleotide pre-miRNA precursor product. (Note that the human let-7a-1 miRNA is shown here as an example of a pre-miRNA hairpin sequence. The mature miRNA sequence is shown in red.) RAN–GTP and exportin 5 transport the pre-miRNA into the cytoplasm. Subsequently, another RNase III enzyme, Dicer, processes the pre-miRNA to generate a transient ~22- nucleotide miRNA:miRNA* duplex. This duplex is then loaded into the miRNA-associated multiprotein RNA-induced silencing complex (miRISC) (light blue), which includes the Argonaute proteins, and the mature single-stranded miRNA (red) is preferentially retained in this complex. The mature miRNA then binds to complementary sites in the mRNA target to negatively regulate gene expression in one of two ways that depend on the degree of complementarity between the miRNA and its target. miRNAs that bind to mRNA targets with imperfect complementarity block target gene expression at the level of protein translation owever, recent evidence indicates that miRNAs might also affect mRNA stability (not shown). Complementary sites for miRNAs using this mechanism are generally found in the 32 untranslated regions (3' UTRs) of the target mRNA genes. miRNAs that bind to their mRNA targets with perfect (or nearly perfect) complementarity induce target-mRNA cleavage (lower right). miRNAs using this mechanism bind to miRNA complementary sites that are generally found in the coding sequence or open reading frame (ORF) of the mRNA target.*

They further detail it as follows:

MicroRNAs can function as tumour suppressors and oncogenes. a. In normal tissues, proper microRNA (miRNA) transcription, processing and binding to complementary sequences on the target mRNA results in the repression of target-gene expression through a block in protein translation or altered mRNA stability. The overall result is normal rates of cellular growth, proliferation, differentiation and cell death. b. The reduction or deletion of a miRNA that functions as a tumour suppressor leads to tumour formation. c. A reduction in or elimination of mature miRNA levels can occur because of defects at any stage of miRNA biogenesis (indicated

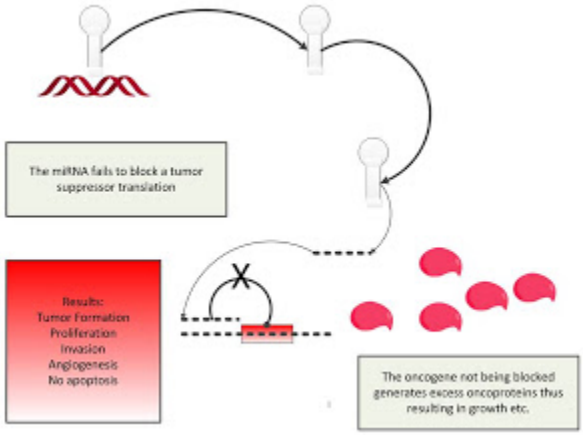
by question marks) and ultimately leads to the inappropriate expression of the miRNA-target oncoprotein (purple squares). The overall outcome might involve increased proliferation, invasiveness or angiogenesis, decreased levels of apoptosis, or undifferentiated or de-differentiated tissue, ultimately leading to tumour formation. The amplification or overexpression of a miRNA that has an oncogenic role would also result in tumour formation. In this situation, increased amounts of a miRNA, which might be produced at inappropriate times or in the wrong tissues, would eliminate the expression of a miRNA-target tumour-suppressor gene (pink) and lead to cancer progression. Increased levels of mature miRNA might occur because of amplification of the miRNA gene, a constitutively active promoter, increased efficiency in miRNA processing or increased stability of the miRNA (indicated by question marks). ORF, open reading frame.

We depict these three cases shown as follows. First, miRNA acting in a normal manner. This is below:

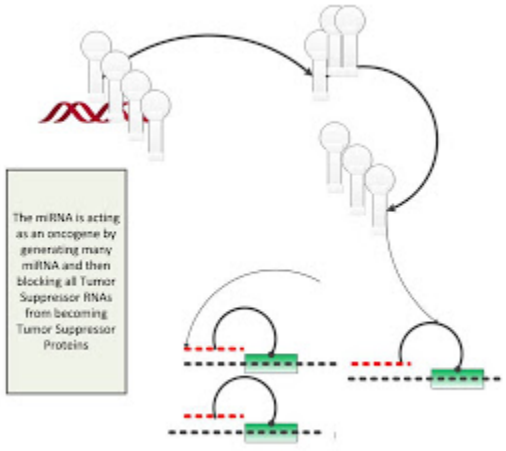


Notice above the miRNA is assumed to be a normal part of the control mechanism of the control of the conversion of the mRNA into a protein. It block the conversion.

Second, we now consider the second case. Here we have an oncogene which is not blocked by the miRNA and it results in many oncoproteins as shown below.



Third and finally in case 2 we have a massive explosion of miRNAs acting as onco activators as shown below.



These methods demonstrate in a somewhat simple manner how the miRNA functions in the case of certain cancers. It also demonstrates how the miRNA can become a target for therapeutics.

Observations

Much of what we know about miRNAs and their functions has evolved in the past five years to a decade at most. In fact in the past decade one has seen a great opening to RNAs in general. Before that it could be said that RNAs were the poor cousin in the process, the glory given the DNA and then the pathway dynamics dominated by proteins. We now appear to have opened a door on control mechanisms at the RNA level, dominated by miRNA and their control of mRNA before it becomes a protein. Thus RNA is somewhat exciting, and the miRNA have presented an added level of complexity to our modeling of complex cellular dynamics.

Based upon the analysis herein:

miRNA present new Paradigms for Cell Signalling

The most significant result from the explosion of miRNA effects is that what we have seen as now classic pathways may have significant undercurrent resulting from the miRNAs. Are miRNAs dominant control elements, is so where do they impact the most. We have seen many of the miRNA discoveries as just incidental to studying pathways. In our prior analysis we assumed them to be just noise. Now we can no longer accept such a proposition. In fact they seem to play significant if not dominant roles.

miRNA provide opportunistic targets for Therapeutics

The use of miRNAs as therapeutic targets is of significant interest. We have discussed some of the results and we have tried to place miRNAs in context of a broad therapeutic approach. The true reason is the simplicity of the miRNA structure. It is not a complex protein of hundreds of

nucleic acids folded in a complex manner. The miRNA is just some 22 nucleotides on a sugar backbone.

miRNA expand the Interest in Introns as Control Elements

We have been trained to ignore the introns. It was the trash heap of evolution, perhaps of some use in the past. However since miRNAs are intro sourced, we now have a new window on the importance of introns.

miRNA may have Broader Roles in Metastatic Growth

We have looked at such proteins as PTEN, p53, and others as the control element. We looked at kinases and receptors and instigating ligands as part of that process. When we examine miRNA we see control coming from within. What instigates the processing and release of miRNAs. What are the feedback loops, if any, between the surface changes on receptors and the activation of miRNAs.

miRNA can be a Significant Target for Diagnostic and Prognostic Analysis

One of the problems we have in many cancers is both diagnosis and prognosis. In melanoma unfortunately prognosis may often be dire, but not always. In addition diagnosis of pigmented lesions is often problematic. Take a simple melanoma in situ, where it is diagnosed based on upward movement of the melanocyte. Are there differences in the MIS? Namely is each MIS identical, just losing its stability, say through loss of E-cadherin, and if not are there simple miRNAs which can be targeted and profiled.

There are many more observations which will evolve as we better understand miRNAs. Since we are at the beginning of understanding them we must keep in mind the ever changing field of play, and thus any analysis must include miRNAs as significant participants.

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Labels: Cancer

WEDNESDAY, DECEMBER 26, 2012

SOCRATES AND THE PRESS

Over the Holidays I reread Gorgias, the debate Socrates had with the Sophists, today we would most likely call them politicians. Anything to get elected. It evoked the logic of the Greeks some two and a half millennia ago.

Then I read the piece in the NY Times about the Gannett paper in Westchester which printed an interactive map of every person with a gun license in Westchester and the surrounding counties. Now I do not know NY Law on the matter but in New Jersey one must have a gun license to have a Daisy BB gun. Not an AK47 or M16, but yes a BB gun. Thus the nexus between abiding by the law and having a firearm does not exist. The nexus between a gun license and the right to then buy a gun may exist but the possession of such gun is not in evidence. Socrates would have a field day with the morons who put this together.

I suspect that most individuals who have a gun license may have a gun but not all. Again in New Jersey they may like me have a single dated Daisy BB rifle in New Hampshire, but no heavy armament of any kind in New Jersey. (Just to let the folks know, the Daisy is to keep the deer from my daylilies, but it seems the newly imported wolves have done a great job). Yet I suspect that in Newark the murders for the most part were committed by unlicensed individuals. One does not go out and get a license for such a purpose, one gets a license to not break the law, or to obey the law, I suspect it is the same thing. I am not a gun fan, never used one other than having been trained, never liked the things, but that is my opinion. Upcountry they actually hunt and eat the result. I will stay with store bought stuff.

I read the comments and surprisingly they were overly negative. What purpose does this serve. Perhaps reckless endangerment by targeting homes a potential sources of weapons. Or homes weaponless. In either case there is no purpose, only the self aggrandizement one finds all too often in the Press. Perhaps it makes someone feel good, why not publish the names of all physicians dispensing oxycodone. None f this makes any logical sense.The consequences may be deadly, the positive effect is zero, and the problem is not avoided. Well it is our Press after all.
Labels: Commentary

TUESDAY, DECEMBER 25, 2012

MERRY CHRISTMAS

1 And it came to pass in those days *that* a decree went out from Caesar Augustus that all the world should be registered.
2 This census first took place while Quirinius was governing Syria.
3 So all went to be registered, everyone to his own city.
4 Joseph also went up from Galilee, out of the city of Nazareth, into Judea, to the city of David, which is called Bethlehem, because he was of the house and lineage of David,
5 to be registered with Mary, his betrothed wife, who was with child.
6 So it was, that while they were there, the days were completed for her to be delivered.

7 And she brought forth her firstborn Son, and wrapped Him in swaddling cloths, and laid Him in a manger, because there was no room for them in the inn.
8 Now there were in the same country shepherds living out in the fields, keeping watch over their flock by night.
9 And behold, an angel of the Lord stood before them, and the glory of the Lord shone around them, and they were greatly afraid.
10 Then the angel said to them, “Do not be afraid, for behold, I bring you good tidings of great joy which will be to all people.
11 For there is born to you this day in the city of David a Savior, who is Christ the Lord.
12 And this *will be* the sign to you: You will find a Babe wrapped in swaddling cloths, lying in a manger.”
13 And suddenly there was with the angel a multitude of the heavenly host praising God and saying:
14 “ Glory to God in the highest, And on earth peace, goodwill toward men!
15 So it was, when the angels had gone away from them into heaven, that the shepherds said to one another, “Let us now go to Bethlehem and see this thing that has come to pass, which the Lord has made known to us.”
16 And they came with haste and found Mary and Joseph, and the Babe lying in a manger.
17 Now when they had seen *Him,* they made widely[d] known the saying which was told them concerning this Child.
18 And all those who heard *it* marveled at those things which were told them by the shepherds.
19 But Mary kept all these things and pondered *them* in her heart.
20 Then the shepherds returned, glorifying and praising God for all the things that they had heard and seen, as it was told them.
Labels: Commentary

THURSDAY, DECEMBER 20, 2012

POOH POOH PIGOU, REDUX

As my readers know I am not a fan of the Pigou Tax despite the many eminent economists who propose it. Now here is a great video from Cafe Hayek discussing the Pigou Tax and why it makes no sense and there is a good reference to the Coase argument.

Now at the heart of the Pigou Tax is two assumptions:

1. That Government knows the right rate. Well have we ever seen Government ever get anything right? No so we dismiss that one.

2. That it solves the externality problem. Well consider the two cases. One, carbon emissions. Now that is not fixed since we cannot move people or have them use alternative means of transportation, at least not in any reasonable time frame. It just becomes another tax on the poor. Second, obesity. Now here we possibly could do something. One need just look at the video, the problem is not the noise it is obesity, the externality is that the third party pays for the obesity related diseases. Thus we could actually get an almost exact tax for obesity. Really, it works and almost real time. Stop those chips and then watch the disease costs decrease.

Now the argument I made above as regards the chips was not part of the video but it should be part of the discussion.
Labels: Economy

4 YEARS OLD!

Today marks the 4th anniversary of this blog. We have had some 134 countries visit, about 50% of the visitors are from outside the US, we have had some 100,000 visitors total, and we have written over a million words. Who would have thought.

The intent then and still is to focus on items of interest, to me, based upon what is currently in the Press, public and professional. I started out with a focus on the economy, and that soon turned to Health Care, a focus based both upon economic size and personal interest and competence. I then followed that as far as worth doing so and started to focus more on areas of personal interest and research in health care.

Hopefully some people have found this of interest from time to time. I want to thank my readers for their continued interest and as always welcome any comments from readers via emails.

So, Happy 4th Birthday!
Labels: Commentary

SUNDAY, DECEMBER 16, 2012

ENGINEERS AND DOCTORS

I re-read the Double Helix again, perhaps for the tenth time, and I came across the following from Watson: *Maurice refused to get excited*.

My repeated refrain that DNA could fall at any moment sounded too suspiciously like Francis in one of his overwrought periods. For years Francis had been trying to tell him what was important, but the more dispassionately he considered his life, the more he knew he had been wise to follow up to own hunches. As the waiter peered over his shoulder, hoping we would finally order, Maurice made sure I understood that if we could all agree where science was going, everything would be solved and we would have no recourse but to be engineers or doctors.

Yes, engineers and doctors, to these mid 20th century "scientists" the truly lowest of those who had a modicum of thinking capacity. I often wondered if he still thought that way and I was told by some of my students a few years ago when he spoke at MIT, that indeed we engineers and doctors are still down the food chain a bit. But the world has changed, we look at DNA in a system manner, a complex dynamic random system, where the tools and ideas of the engineer, along with the talents of those doctors are put to use.Yes, the bench work, the science if you will, is still being followed, but there are times when the engineering work is necessary and the doctoring is required.

Labels: Commentary

SATURDAY, DECEMBER 15, 2012

A GREAT PLACE FOR SPIES

Decades ago when we all worried about Soviet spies, one often was told that New York was a great place for them to hide in the open, and speak Russian. For it was on any corner of New York that one could hear any tongue spoken on the planet and not be surprised. It was here that I learned my Italian, which decades later I tried in Florence to be told rather bluntly that I sounded like some Mafia character from Sicily, yet after all I learned it on Staten Island.

Then my Spanish, from the subway, the signs, the guys I ran with, boxed with, but in Spain they had no idea what I was saying, it was Puerto Rican, yet to me it was just plain Spanish. Then for my Russian, Jimmy Bula, a fellow lifeguard, from Ukraine, we sat and I tried my best to learn the Cyrillic and the words, Jerry helped, then when in Russia they asked where in Ukraine did I come from?

Now the BBC has an interesting piece on New York having some hundreds of languages spoken, and some spoken no where else.

***Home to around 800 different languages**, New York is a delight for linguists, but also provides a rich hunting ground for those trying to document languages threatened with extinction.*

To hear the many languages of New York, just board the subway.

The number 7 line, which leads from Flushing in Queens to Times Square in the heart of Manhattan takes you on a journey which would thrill the heart of a linguistic anthropologist.

Each stop along the line takes you into a different linguistic universe - Korean, Chinese, Spanish, Bengali, Gujarati, Nepali.

And it is not just the language spoken on the streets that changes.

Street signs and business names are also transformed, even those advertising the services of major multinational banks or hotel chains.

In the subway, the information signs warning passengers to avoid the electrified rails are written in seven different languages.

The A train has most signs in Spanish, then go China town and even the street signs are in Chinese. I had a Russian partner who had been stationed in Argentina for a period, and surprisingly in a restaurant he was able to speak fluently with the help, and that made dinner perfect. And of course, any Diner in New York is a Greek Restaurant. Try my Greek there and get a free desert, and a long story about a cousin or two.

As for the Number 7 line, I took it for years, traveling to East 54th St to my swimming or boxing

sessions, and learning a few more words in one language or another. New York allows Spanglish, or any combination of multiple languages. After all, having just 100 words allows one to survive anywhere.

But at the base of it was those years of Latin. One learned that language had structure, present, past, future, and that if one grasped these concepts then one could "communicate" albeit at a rudimentary manner.

Yet strangely the one place where I have always had the mos difficulty was England, the words are often the same but the accents are tonal, not the flat atonal American English, and the accents vary so much that it takes quite a while for many to be comprehensible. Thus in a sense New York can spoil one, you can be a sloppy learner, but you may often learn that dialect then may not travel that well. Then again there is French in Paris, I have learned that no one but a native born Parisian could ever master it, perhaps that is why English, sloppy as it is, survives so well.
Labels: Commentary

MORE ON WHY UNIVERSITIES CHARGE SO MUCH

The NY Times has an interesting piece on the building boom in universities. They state:

A decade-long spending binge to build academic buildings, dormitories and recreational facilities — some of them inordinately lavish to attract students — has left colleges and universities saddled with large amounts of debt. Oftentimes, students are stuck picking up the bill.

They then go on in an anecdotal manner describing examples. Schools with hundreds of millions to almost a billion dollars in new debt for buildings which frankly are questionable.

The best one is as follows:

Administrators at Ramapo College of New Jersey, a public institution founded in 1969, have harbored a dream of making it the premier public liberal arts college in the New York metropolitan area.

But one big obstacle has been the state of New Jersey, which has provided little money for capital projects on state colleges and universities in the last two decades.

So Ramapo borrowed, and it borrowed some more, building a new business school, dormitories and a recreational facility that includes a 2,200-seat arena. A new wing that will house the nursing program is under construction.

Ramapo now has $281 million in debt, and its debt payments account for 13 percent of its budget, high compared with most colleges rated by Moody's.

You cannot make this up. "premier public liberal arts college", yes we need more useless English majors from New Jersey. What are they going to do? Jersey Shore II? Then also who is guaranteeing the debt, are we the taxpayers left holding the bag, and never given a voice in the

process. What justification is there for such a program? I suspect that the Trustees enjoy their paid positions and frankly do not want to rock the boat.

But alas this is just one example. As I have argued before this is one of the many examples of what is driving up costs. A new cancer center at MIT, the Koch building, paid for by Koch gifts but it will have a life time costs many times its construction costs. Who pays for that? Well at MIT it would the the research contracts, and not the students, but the students would benefit by having this on campus. But a new recreational facility in norther New Jersey, at a state school, on its way to $300 hundred million in debt, ultimately at the feet of already over taxed taxpayers.
Labels: Academy

FRIDAY, DECEMBER 14, 2012

PCA3, EZH2, THE ANDROGEN RECEPTOR AND CONTROL OF SURVIVAL

Multiple epigenetic markers have been determined as determinants for prognostic values in prostate cancer, PCa. There are two recent papers, one of PCA3 and its pathway control, and on EZH2 and its use as a marker. We briefly summarize these efforts and attempt to place them in a common and ever growing context of both prognostic markers as well as putative pathway control therapeutic targets.

PCA3

PCA3 has received a great deal of attention of late. It is a non-coding RNA and the controlling gene is located at 9q21-q22[6][1]. It is also called prostate cancer antigen 3 (non-protein coding). The presence of PCA3 is generally now believed to be a marker for PCa. Testing is now underway on may patients to determine if they have PCa using the PCA3 assay. Thus there is a great deal of interest in better understanding what the full networks are for PCA3 generation as well as looking at those pathways as a possible means to control PCa. We examine two recent studies in this area.

In the recent paper by Ferreira et al, they state:

Our findings suggest that the ncRNA PCA3 is involved in the control of PCa cell survival, in part through modulating AR signaling, which may raise new possibilities of using PCA3 knockdown as an additional therapeutic strategy for PCa control.

This may be of significant merit as a new potentially useful therapeutic. Now it should be recalled that the AR pathway and the PSA generation is known as shown below[7][2].

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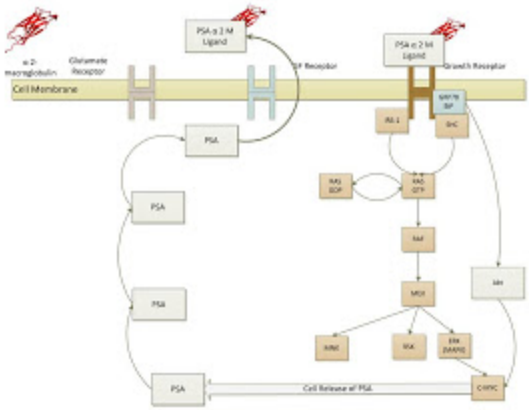
[6][1] http://www.ncbi.nlm.nih.gov/gene/50652

[7][2] Note we use the reference, Prostate Cancer Genomics, McGarty (2012, DRAFT, http://www.telmarc.com/Documents/Books/Prostate%20Cancer%20Systems%20Approach%2003.pdf) as the source for some of this information. From this source one may obtain the initial sources.



Now Ferreira et al continue:

Due to the increased PCA3 expression in androgen-responsive cells compared with androgen-insensitive cells, and because AR signaling is an important pathway controlling PCa survival, we tested whether PCA3 expression was modulated by the androgen-active metabolite DHT and whether this expression pattern involved the activated AR.

Upregulation of PCA3 expression in response to LNCaP stimulation with DHT was significantly counteracted by the AR antagonist flutamide, indicating that PCA3 expression was induced by the activated AR. AR activation was further confirmed by the observation that LNCaP cells stimulated with DHT also showed AR transcriptional activity. Consistently, all of the AR target genes tested that contain canonical AR response elements (AREs) in their promoter sequences, were upregulated upon DHT treatment. Although eight of the genes showed at least a 1.5-fold increase after AR activation, only two of them showed a significant increase in their expression levels. Interestingly, PCA3 upregulation upon DHT treatment has been observed previously, but no study has demonstrated the involvement of activated AR in PCA3 expression by using AR antagonists. Although our data also suggest that PCA3 is an androgen-responsive gene, the precise molecular mechanism by which PCA3 expression responds to this activation is still unknown.

One hypothesis is that activated AR can directly activate the PCA3 promoter, as has been demonstrated for the miR-101 and miR- 21 regulatory regions, which are also modulated by the activated AR. However, no consensus AREs have been identified in the 500-bp PCA3 promoter region. We further screened for consensus ARE elements in the entire PCA3 genomic region at the 5 Kb region upstream from the PCA3 transcription start site, and have so far identified no canonical element (data not shown). Nevertheless, we cannot exclude the possibility that other, noncanonical ARE elements could also promote AR binding and directly activate PCA3 expression, as has been previously described for other genes modulated by the AR activation. PCA3-upregulated expression in response to DHT treatment could also be a result of activated AR binding to the regulatory regions of other AR-responsive genes, which in turn could induce

PCA3 expression. Further experiments should investigate direct AR binding to different PCA3 genomic regions, in order to answer these open questions.

Now they examined genes which are known pathway controllers of PCa. The CDKs especially control cell cycle flow.

As an approach to investigate the signal by which PCA3 controls PCa cell survival, we analyzed the transcript expression of PSA, AR, TMPRSS2, NDRG1, GREB1, FGF8, CDK1, CDK2, and PMEPA1 genes, all of which have key roles in PCa growth and progression, and are classical AR target genes.

Also highly regulated by androgens, fibroblast growth factor 8 (FGF8), cyclin-dependent kinase 1 (CDK1), cyclin-dependent kinase 2 (CDK2), and the gene regulated in breast cancer 1 (GREB1) gene products have classical stimulating roles in prostate growth and proliferation. Conversely, the PMEPA1 gene, although a direct transcriptional target of the AR, has been described as a negative regulator of cell growth in the prostate epithelium, as well as negatively regulating AR protein levels in different cell-culture models. We also observed that the AR transcription level was downregulated after PCA3 knockdown. These results accord with previously published data, which demonstrated that the AR gene is transcriptionally regulated by AR through binding to AR regulatory elements (autoregulation). However, differently from the other AR-responsive genes tested here, the ARE elements required for this process have not been found in the AR promoter or in the 5'-flanking region, but rather in AR coding sequences.

The observation that PCA3 is involved in the control by modulation of the AR target genes is a key observation. As we have shown, based upon various prior works, the change in AR is critical to the loss of any control over the PCa cells. They state:

Here we demonstrate for the first time that PCA3 is involved in the control of PCa cell survival, at least in part by modulating the transcriptional activity of AR target genes. To our knowledge, this is the first characterization of the functional role of PCA3 in PCa cells, and will not only improve the understanding of key roles of this transcript in prostate carcinogenesis, but also suggests an alternative strategy to use PCA3 as a putative specific target for PCa treatment approaches. Because PCA3 seems to be a regulator of the expression of AR target genes and PCa cell survival, treatment options aiming to downregulate PCA3, in combination with other androgen-depletion-based strategies, could potentially circumvent androgen-ablation resistance mechanisms.

In an earlier paper by Ferreira et al, they state:

The prostate cancer antigen 3 (DD3/PCA3) is a non-coding RNA (ncRNA) specifically expressed in prostate tissues and overexpressed in prostate cancer (PCa) tumors. Although widely applied as a diagnostic marker for PCa, to date nothing has described about its role in PCa biology. We used herein small interfering RNA (siRNA) in order to knockdown DD3 mRNA message as an approach to elucidate DD3 functional roles in PCa cells.

LNCaP cell line was been used herein as an in vitro model for DD3 functional assays. siRNA sequences were specifically designed for DD3 exon 4 mRNA sequences (siDD3), as well an scrambled siRNA (siScr), as negative control. LNCaP cells were transiently transfected with siDD3 or siScr and DD3 expression was analysed by real time PCR (qRT-PCR) using DD3 specific oligonucleotides. LNCaP cells transfected with siDD3 demonstrated a marked decrease in cell proliferation and viability, as compared to siScr transfected cells.

Further, LNCaP cells in which DD3 was knocked-down presented a significant increase in proportion of cells in SubG0/G1 phase of cell cycle and presenting pyknotic nuclei, indicative of cells undergoing apoptosis. In order to investigate the putative mechanisms underlying the decrease of LNCaP cell survival as a result of DD3 knockdown, we then evaluated the involvement of DD3 on androgen receptor (AR) pro-survival signaling. DD3 expression was significantly uregulated as a result of LNCaP treatment with dihydrotestosterone (DHT), the active androgen metabolite. This effect was reverted by the addition of the AR antagonist, flutamide.

Consistent to an AR activation by DHT treatment, LNCaP cells presented a significant upregulation of AR target genes. Notably, siDD3/LNCaP transfected cells significantly inhibited the expression of tested AR responsive genes. Besides, DD3 knockdown was able to counteract DHT stimulatory effects over AR target gene expression. Despite negatively modulating the transcription of AR target genes, DD3 knockdown did not alter Akt and ERK phosphorylation, suggesting that DD3 is mainly controlling the expression of signaling pathways downstream to AR activation.

In summary, our findings indicate that DD3 is a ncRNA whose expression is AR regulated and is involved on the control of PCa cell survival and proliferation, in part by modulating the AR signaling pathway and its target genes.

These findings correspond to the first description of DD3 roles on PCa cells and could provide new insights into understanding prostate carcinogenesis, besides opening new prospects to use DD3 not only as a biomarker for PCa, but also as an specific target for therapeutic approaches aiming to inhibit PCa growth by negatively modulating AR pro-survival signal and their target genes.

In this slightly earlier paper the authors focus on the PCA3 as a target and examine its pathway significance.

Other researchers have examined PCA3 as well as other markers. It is well known that the TMPRSS2:ERG fusion is often seen in PCA. As Salagierski and Schalken conclude:

In recent years advances in genetics and biotechnology have stimulated the development of noninvasive tests to detect prostate cancer. Serum and urine molecular biomarkers have been identified, of which PCA3 has already been introduced clinically.

The identification of prostate cancer specific genomic aberrations, ie TMPRSS2:ERG gene fusion, might improve diagnosis and affect prostate cancer treatment. Although several recently

developed markers are promising, often showing increased specificity for prostate cancer detection compared to that of prostate specific antigen, their clinical application is limited. The only 2 true prostate cancer specific biomarkers identified to date remain PCA3 and TMPRSS2:ERG gene fusion.

Let us briefly summarize these two genes and their fusion.

TMPRSS2:ERG

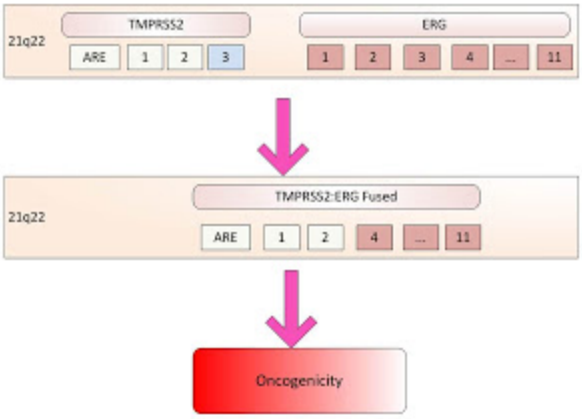
The TMPRSS2-ERG fusion is the single most seen molecular lesion in prostate cancer. (see Taylor et al 2010) TMPRSS2 is on 21q22.3 and ERG is on 21q22.3. Both are dominant. Unlike the pathway disturbances, this is a fusion, translocation on the same gene, and the resultant is expressive of ERG and not of TMPRSS2.

Transcriptional regulator ERG is a protein that in humans is encoded by the *ERG* gene (**E**ts **R**elated **G**ene, Chromosome 21). ERG is a member of the ETS family of transcription factors. Transcriptional regulator ERG is a nuclear protein that binds purine-rich sequences. ERG can fuse with TMPRSS2 protein to form an oncogenic fusion gene that is commonly found in human prostate cancer, especially in hormone-refractory prostate cancer. This suggests that ERG **overexpression** may contribute to development of androgen-independence in prostate cancer through disruption of androgen receptor signaling.

Transmembrane protease, serine 2 is an enzyme that in humans is encoded by the *TMPRSS2* gene. This gene encodes a protein that belongs to the serine protease family. The encoded protein contains a type II transmembrane domain, a receptor class A domain, a scavenger receptor cysteine-rich domain and a protease domain. Serine proteases are known to be involved in many physiological and pathological processes. This gene was demonstrated to be up-regulated by androgenic hormones in prostate cancer cells and down-regulated in androgen-independent prostate cancer tissue. The protease domain of this protein is thought to be cleaved and secreted into cell media after autocleavage. The biological function of this gene is unknown. TMPRSS2 protein's function in prostate carcinogenesis relies on overexpression of ETS transcription factors, such as ERG and ETV1 through gene fusion. TMPRSS2-ERG fusion gene is the most frequent, present in 40% - 80% of prostate cancers in humans.

As Weinberg notes:

In the case of the TMPRSS-ERG fusion, both genes are located on 21q22, and the fusion frequently occurs because of an interstitial deletion . The resultant fusion transcripts are androgen responsive and usually encode an ETS gene (ERG) truncated at its N terminus without any coding elements from TMPRSS2. It is unknown if the biologic consequences of misexpression of the truncated ETS family protein are different from expression of the full length protein and whether truncation contributes to oncogenicity. (Ref Weinberg)



There has been a significant amout of research as to the overexpression of PCA3 and why specifically this may be the case. As Auprich et al stat

The PCA3 gene is highly overexpressed in specific PCa cell lines and prostatic tumours. In 2006, a simple and robust urine test (Progensa) became commercially available. Despite its costs, prostate cancer antigen 3 (PCA3) is superior to prostate-specific antigen (PSA) and percent free PSA in the early detection of PCa. PCA3 improves the diagnostic accuracy of externally validated nomograms among men with an elevated PSA undergoing biopsy.

PCA3 independently predicts low-volume disease and pathologically insignificant PCa but is not associated with locally advanced disease and is limited in the prediction of aggressive cancer. Preliminary data demonstrate that combining PCA3 with other new biomarkers further improves diagnostic and prognostic accuracy.

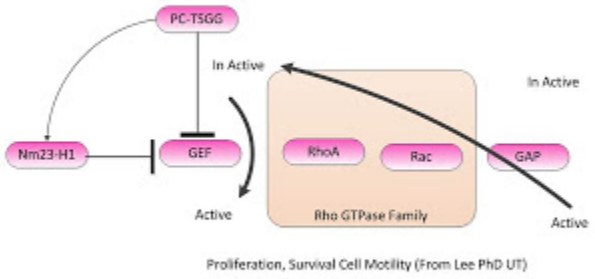
Finally, findings of the first PCA3-Gene-ViroTherapy study suggest therapeutic potential by exploiting PCA3 overexpression. PCA3, integrated in novel biopsy nomograms or risk stratification tools, can be used to counsel or confirm biopsy indications. If confirmed in further studies, using PCA3 together with established staging risk factors could assist clinicians in specific pretreatment decision making. So far no evidence for the usefulness of PCA3 in active surveillance programs has been presented.

The above seems to indicate that although PCA3 is indicative of PCa in low volume states but they state that it is not a metric for high volume states. Other work appears to provide added light of PCA3 and may change this observation.

We look at a recent thesis presented by Lee specifically on a more detailed analysis of PCA3. From Lee we have:

Proposed mechanism of action of PC-TSGC toward the downregulation of signal transduction of Rho GTPase family members. PC-TSGC inhibits the binding of RhoA to its activator Lbc-RhoGEF by direct interaction with RhoA through the BCH domain, and recruits nm23- H1

which in turn inhibits Tiam1, a specific Rac activator. GEF: Guanine nucleotide Exchange Factor; GAP: GTPase Activating Protein.

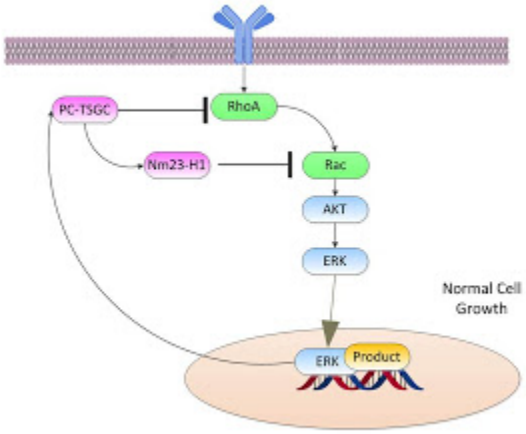


From Lee p 89 we have:

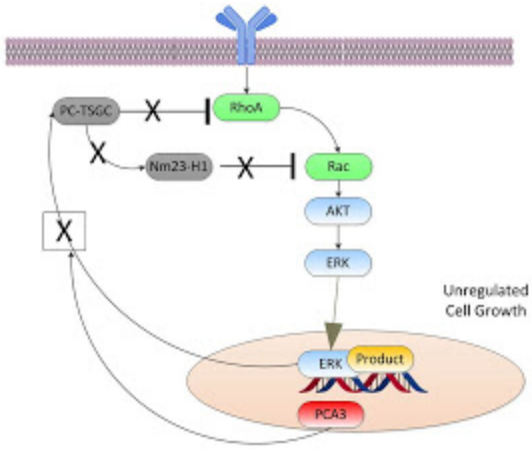
Proposed biological roles of PCA3 and PC-TSGC in prostate cancer.

(A) Normal cell: growth stimuli are signaled to the nucleus through multiple pathways that include activation of RhoA and Rac and subsequent phosphorylation of AKT and ERK1/2. The signal transduction cascade stimulates gene expression in order to initiate cellular replication and inhibit apoptosis. Simultaneously, the same signals elicit the expression of PC-TSGC which in turn inhibits RhoA and Rac (through nm23-H1), thereby resulting in a negative-feedback loop on the activity of cell growth signaling pathways.

(B) Cancer cell: in a malignant cell, the same mechanism is altered by the abnormal expression of PCA3, which opposes the expression of PC-TSGC. As a result, the control over the RhoA and Rac signaling pathways is lost, and the cell engages an unregulated cell growth that potentially leads to oncogenic transformation.



Now for abnormal cell growth we have:



EZH2

We now examine another recent marker which also acts in an epigenetic manner, specifically EZH2. EZH2 (located at 7q35-q36) is a member of the Polycomb group, members of which are often associated with the silencing of genes. The epigenetic capabilities allow it to block the expression of multiple genes which are useful in normal cell homeostasis.

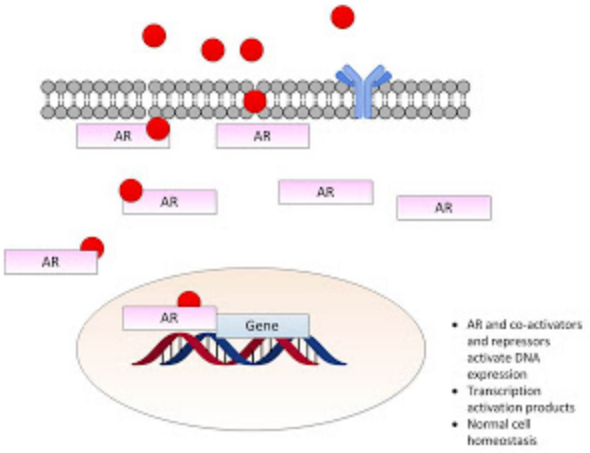
As NCBI states[8][3]:

This gene encodes a member of the Polycomb-group (PcG) family. PcG family members form multimeric protein complexes, which are involved in maintaining the transcriptional repressive state of genes over successive cell generations. This protein associates with the embryonic ectoderm development protein, the VAV1 oncoprotein, and the X-linked nuclear protein. This protein may play a role in the hematopoietic and central nervous systems. Multiple alternatively splcied transcript variants encoding distinct isoforms have been identified for this gene.

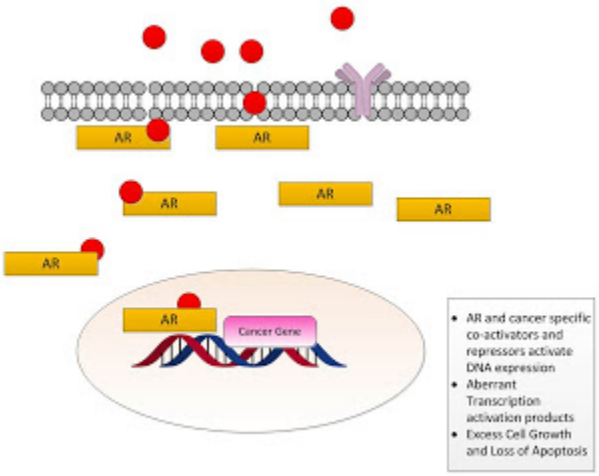
PCa can move from Androgen responsive to Androgen resistant by the blocking of certain genetic controls and also the activation of others. Simply we see the three step process as follows:

First the normal cell operation is as shown below:

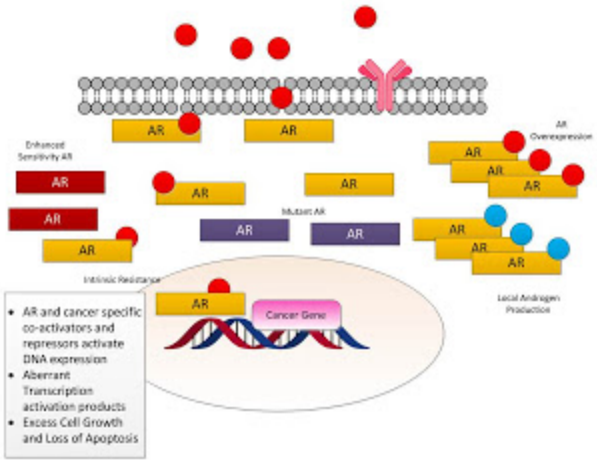
[8][3] http://www.ncbi.nlm.nih.gov/gene/2146



Then when the cell becomes cancerous, we see the expression of the cancerous genes but they are supported by activated AR products. Often in this stage we still have a localized stage and by depriving the androgen the AR are suppressed in their activation.



Finally we can get to the androgen resistant state as we show below. Several things happen here. First, androgen is actually produced to self-sustain the malignant cell. Second, mutant AR cells can activate independent of the presence of androgens. Third AR proteins can become enhanced with specific sensitivity. The cell then becomes resistant to any reduction of cell exogenous androgen availability. This stage of PCa then becomes the most aggressive.



As is reported in Science, EZH2 has been seen to have special significance in AR resistant PCa. They state:

Epigenetic regulators are implicated in cancer progression and proposed as therapeutic targets. Xu et al. report that EZH2 (Enhancer of zeste homolog 2), a factor previously thought to exert its oncogenic function primarily as part of the polycomb repressive complex, acts through a distinct mechanism in cells of castration-resistant prostate cancer. Rather than exclusively silencing gene expression through histone methylation, EZH2 acts as a transcriptional coactivator. The activation function of EZH2 plays a critical role in the growth of castration-resistant prostate cancer cells, which could be relevant in future drug development.

Xu and the authors state:

Epigenetic regulators represent a promising new class of therapeutic targets for cancer. Enhancer of zeste homolog 2 (EZH2), a subunit of Polycomb repressive complex 2 (PRC2), silences gene expression via its histone methyltransferase activity. We found that the oncogenic function of EZH2 in cells of castration-resistant prostate cancer is independent of its role as a transcriptional repressor. Instead, it involves the ability of EZH2 to act as a coactivator for critical transcription factors including the androgen receptor. This functional switch is dependent on phosphorylation of EZH2 and requires an intact methyltransferase domain. Hence, targeting the non-PRC2 function of EZH2 may have therapeutic efficacy for treating metastatic, hormone-refractory prostate cancer.

Again a targeting of the AR resistant form of PCa has a potential target in this protein. They conclude:

This study demonstrates that phosphorylation of EZH2 at Ser_{21}, mediated directly or indirectly by the PI3K-Akt pathway, can switch its function from a Polycomb repressor to a transcriptional coactivator of AR (and potentially other factors). Rescue experiments and the lack of correlation with H3K27me3 levels support a role for EZH2-directed methylation of substrates other than H3K27, including potential nonhistone proteins. The current rationale for EZH2 inhibitor design

is based primarily on targeting its Polycomb-repressive activity and uses H3K27me3 as the pharmacodynamic readout.

However, the observed loss-of-function mutations of EZH2 inmyelodysplastic syndrome and acute leukemia raise concerns that such inhibitors might exhibit important hematologic side effects.

Our finding of an altered function for EZH2 in CRPC cells raises the potential to develop inhibitors that specifically target the EZH2 activation function while sparing its PRC2-repressive function. In addition, our finding that EZH2 cooperates with AR-associated complexes and requires phosphorylation to support CRPC growth suggests novel combination therapies for the treatment of metastatic, hormonerefractory prostate cancer.

Thus they contend that developing a therapeutic for this specific product could address the AR instabilities.

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Labels: Cancer

WEDNESDAY, DECEMBER 12, 2012

WATCH THE FED BALANCE SHEET

At some time, after it explodes its Balance Sheet, the FED will unload the junk and it will result in most likely massive inflation. One way to drive down debt. Today the FED said:

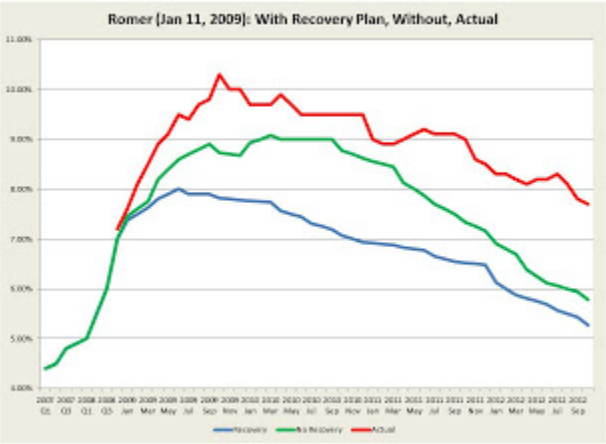
To support a stronger economic recovery and to help ensure that inflation, over time, is at the rate most consistent with its dual mandate, the Committee will continue purchasing additional agency mortgage-backed securities at a pace of $40 billion per month. The Committee also will purchase longer-term Treasury securities after its program to extend the average maturity of its holdings of Treasury securities is completed at the end of the year, initially at a pace of $45 billion per month. The Committee is maintaining its existing policy of reinvesting principal payments from its holdings of agency debt and agency mortgage-backed securities in agency mortgage-backed securities and, in January, will resume rolling over maturing Treasury securities at auction. Taken together, these actions should maintain downward pressure on longer-term interest rates, support mortgage markets, and help to make broader financial conditions more accommodative.

Reading between the lines it will accepts tons more junk.But as we noted a brief while ago the FEDs BS is already over bloated and yet the banks have kept stuff still on the books.

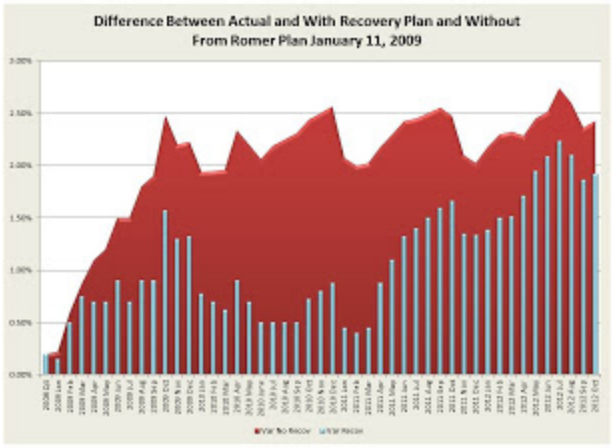
So what to do? Good question. It starts to feel like 1920s Germany all the time. Did we lose the War, what War?

Oh and yes, the leftists have praised this move. Just remember the systemic loss of some 20+ million employed.
Labels: Economy

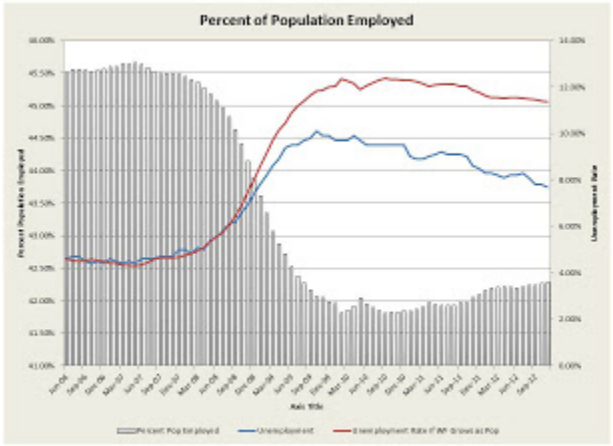
THE EMPOYMENT PROBLEM: IT HAS A REAL SERIOUS ISSUE



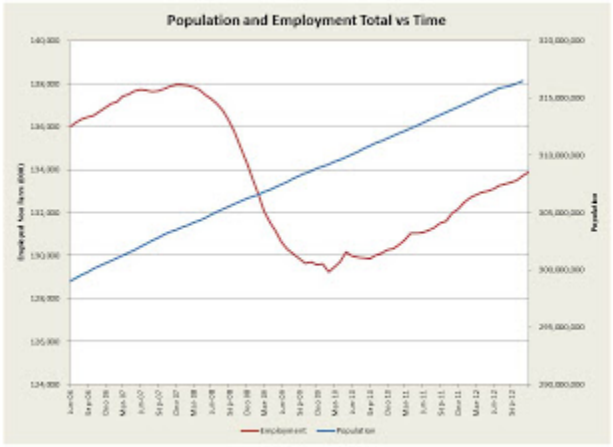
Each month for for years we have examined the employment report especially after the predictions of Romer and her ilk as to what the Stimulus would do. First Romer's curve as above. Note that we have her predictions which said by now we would have an economy on fire, NOT.



Above are her errors. Still hanging embarrassingly high.

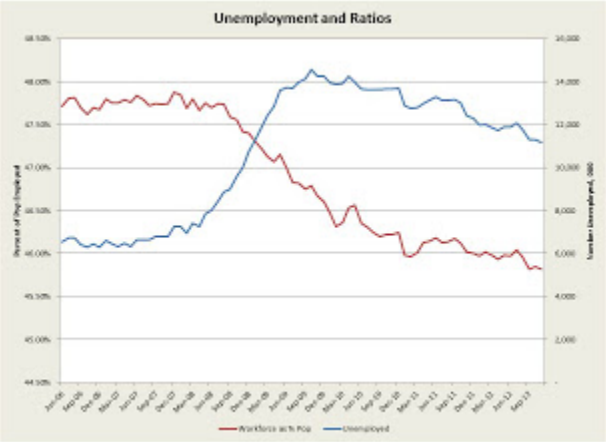


Now above we have unemployment based upon the current Administration's calculations, at 7.7% and the number if we were to assume the employment base as per the previous Administration, a whopping 11.5% unemployed.



The above is telling. We have a systemic loss of tens of millions from the employment base. That is the problem with the economy. We are paying them and they are not generating GDP or

tax revenue. It does not appear to show any improvement. I have been pointing this out for a while. It is a real problem.



Finally we show the employment base. This is the problem which we will have for decades going forward. These people are just out of the economy. Where are they, what are they doing. That should be the first question. The second is how do we put them to work. The third is why are we paying for them.

Labels: Economy

FRIDAY, DECEMBER 7, 2012

DECEMBER 7, JUST REMEMBERING

Just a reminder every year. The above is the crew of the DD 649 after the battle at Leyte in October 1944.

Labels: Commentary

THURSDAY, DECEMBER 6, 2012

GREAT INTRO TO CANCER GENOMICS

The introductory book by Pecorino, Molecular Biology of Cancer, is a superb introduction to the molecular issue related to cancer. The book presents a highly readable and enlightening summary of many of the key issues of pathways and cancer. It can be used as a first step in this exciting field.

The style is straightforward and all encompassing. It can be used by any student who is approaching the field for the first time and it can be an update refresher for those who may have been exposed in the past. It is not of the level of Weinberg but it does address all of the salient issues in a level of depth that allows for a ready follow on using the more in depth texts.

I have used the second edition in the past as a guide to writing materials and obtaining a grasp of broad concepts and issues. The third edition is a superb follow on to the last one.

Chapter 2 is a brief summary of DNA and its interaction in carcinogenesis. Chapter 3 is gene expression. I especially liked the discussion on epigenetic regulation which is a simple and direct coverage of this increasingly important area. Section 3.4 discusses epigenetics and cancer which is current and a critical topic.

Chapter 4 is on growth factor signalling. I typically like to look at the process as a complete system, starting with a statement and model of ligands, receptors, cytoplasmic pathways and then transcription. Although this is done in parts the presentation as an integrated whole is important. The kinase cascades are discussed. One of the general weaknesses of many presentations is the discussion of just how do these proteins interact, at binding sites, and then whether or now one should use kinetic models applicable more appropriately to higher concentrations. Perhaps that goes into more depth than would be necessary but I find it useful for students who have the chemistry background to grasp the concepts. The diagrams are useful and provide constructural understanding.

Chapter 5 discusses the cell cycle. The CDKs are the heart of much of this portion of mitotic growth and the author covers them in adequate detail.

Chapter 6 discusses growth inhibition and tumor suppressor genes. The heart of this is the discussion of p53 the classic control gene. I would have liked a more detailed discussion of ubiquitin and also of the MDM proteins but again for the level of the text's audience the introduction is more than adequate.

Chapter 9 on metastasis is simply stated and gives the reader a somewhat detailed overview. My only critique is that it would have been useful to have a bit more detailed discussion of the ECM, extracellular membrane, its structure, elements, and functions, with a separate subsection. The author does refer to it and provides

The author blends therapeutics very well across the presentations showing how progress is made. I would have like some discussion of pathway dynamics. There are many books which detail these approaches but perhaps again this is a bit too much. One final nit is that the experimental basis of the results would be useful to have been added, for example by an Appendix.

Overall the book is a superb addition to anyone's library on molecular cancer genomics.
Labels: Books, Cancer

TUESDAY, DECEMBER 4, 2012

PET SCANS, A GREAT INTRO

PET scans are highly useful in multiple areas of imaging. They have the unique capability of providing information on the activity of cells in certain areas, not just the density. The short book by Phelps, PET: Physics, Instrumentation, and Scanners,provides a hand reference to understanding some of the principles of PET. It is a simple and direct overview of the underlying physics and of the means of capturing and creating the images.

The first chapter reviews the physics in simple to understand terms while keeping close to the underlying physics. To anyone with a reasonable college level exposure the details fill in the principles with adequate details to understand how PET functions. This first Chapter is well written, easy to understand, reasonably comprehensive and sets the stage for the other issues.

The Chapters on image construction are rudimentary and as with the introduction provide the necessary insight for a visceral understanding. I found the discussions on pp 44-45 very straightforward and spot on in terms of getting the principle across. What I found missing was the details on image reconstruction especially as applied to 3D images. However such depth would have made the book much longer and may have been a bit too complex for the intended audience.

The later chapters discuss applications and these were quite readable and useful. Integrated CT and PET have become useful in tracking certain malignancies and the authors provide a good overview. Again I would have liked more detail and discussion especially for multiple malignancies but as with the prior comment it would have substantially lengthened the text and set it at a much higher level.

Overall this is a superb overview with depth adequate to allow an educated reader to have all the key gaps filled as well as laying out a path for more in depth reading and examination. I would strongly recommend this work for anyone seeking a refresher or a first start on PET.
Labels: Books, Commentary

GERMANS, OPERA, AND HOW TO WIN

Now over the past centuries Germany has been know for its military might, and has been seen to be the nasty neighbor in Europe. Wars have been costly, deadly, and had left Germany seen as the less than friendly neighbor on the Continent.

But as noted in the Guardian perhaps there is a new tactic now that Germany has money, an efficient economy, and a culture that can be re-invigorated in a more civilized manner.

I speak of the Guardian's comments on the opening night at La Scala. La Scala is the premier center of opera in Europe, especially Italian Opera. But this year opening night is Wagner! Yes Wagner, not Verdi or some other famous Italian composer. Wagner, in the midst of the European meltdown.

As the Guardian notes:

The theatre's decision to opt for Wagner, whose pounding operas were the soundtrack for German unification, over Verdi, whose uplifting works inspired Italy's own Risorgimento, comes as Italians feel the bite of austerity policies they see as dictated by Berlin, a humiliation lightened only by Italy's beating of Germany in the European championships this summer.

"This choice is a smack for Italian art, a blow for national pride in a moment of crisis," Milan's daily newspaper, Corriere della Sera, declared, claiming there was disquiet in the orchestra at La Scala, where Verdi made his professional debut. "Would the Germans have inaugurated a Wagnerian year with a work by Verdi?" asked the paper.

It seems that Germany is taking premier place in Europe; banking, production, intellectual work, and the arts. Italy is financially falling apart so they choose Wagner! I look forward to what happens on opening night. Not a single gun is fired, just Wagner.

The final comment is compelling:

Come Friday, fighting in the audience may not be on the cards when Lohengrin returns to Milan, but Conrad said the night would be more than just about opera: "This row is about the continuing balance of power in Europe – there is always a nationalist edge when we talk about Verdi and Wagner."

Nice to see we have come a long way, I think.
Labels: Commentary

TUESDAY, DECEMBER 4, 2012

AMAZON AND REVIEWS

The NY Times has just printed some comments on the review process. Specifically what they contend are positive reviews from friends or the like.

They state:

Beneath the placid surface of Amazon, authors and reviewers have been in a ferment this fall. After several well-publicized episodes involving writers soliciting or paying for reviews, the

retailer seems to be cracking down on log-rolling. Thousands, perhaps tens of thousands, of book reviews have been killed. Amazon has not explained exactly why.

One possible target: authors who have sent gift certificates to reviewers to buy their books. While it's easy to see the potential for abuse here — "Here's a $100 gift certificate. Buy a copy of my novel for 99 cents and keep the change" — some writers argue it is no different than sending a physical copy of a book to someone, which is what publishers do in the offline world and therefore is allowed by Amazon. At least, the line between the two is blurry.

The problem I have seen is somewhat the opposite. Namely the cramming down of negative reviews. For example there were many negative reviews of Google products, namely what appears to be the technical defects of the Google Nexus, and bad reviews of Microsoft products. No sooner are they posted than the are crammed down by "Not Helpful" comments. These Not Helpful drive the review to a last place. Thus if a reviewer determines the product, take the Nexus 7, is in their opinion defective, and more so, that Google Customer Service is useless, then there seems to be some "machine" which recognizes the negative review and then automatically crams it down so no one can see it.

Thus there are ways that people and machines can manipulate the reviews.

For example the article states:

Some critics noted that some of Mr. Ferriss' fans had written no other reviews — usually a tip-off that the reviewer has been paid or was a friend of the author.

My suggestion is, now this has nothing to do with the person in question since I have no opinion having seen none of his works, but in general:

1. Always look for the one star review.

2. Look to see if the reviewer uses their real name.

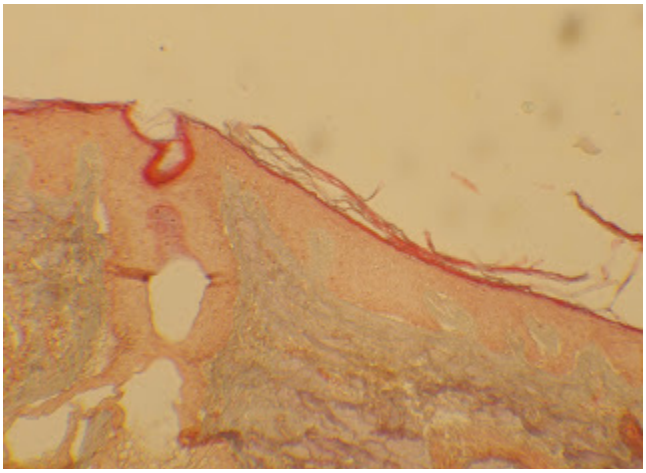
3. Look to see that the reviewer has done a reasonable number of real reviews before.

4. Then look at those reviews especially if they have been crammed down.

The system is being manipulated but following a few reasonable rules one can determine who is real and who is not.

Labels: Books, Commentary

THE ECM AND A GREAT BOOK



The extracellular matrix, ECM, is that soup which flows between cells and in which various proteins and other factors provide for cell strength, stability, nutrition, growth and control. Many who study cancer look inward towards the cell pathways often limiting understanding of the external portion to ligands and perhaps receptors. There has been recent expanded interest in understanding the ECM as an entity of some import and in fact as a parallel key element in cancer progression and control.

The text, Cell-Extracellular Matrix Interactions in Cancer, by Zent and Pozzi provides an excellent introduction to this area from the perspective of examining recent results and their corresponding literature and placing these overviews in a well structure document.

The book starts with a brief overview of the ECM and its elements. The collagens, fibronectins, integrins and all other elements which make up this soup are simply presented in summary form. As I will comment later it would have been useful to expand this a bit more for the reader aware of but not expert in the ECM.

Chapter 2 begins with integrins, the critical importance of integrins as receptors and interfaces with the ECM. Chapter 4 discusses the basement membrane. This is a critical part of the ECM and the presentation is well done in updating the reader with the literature.

The document follows with laminins, fibronectins, vitronectin, proteoglycans and others and discusses the relationships to various cancers. Chapters 11 and 12 are exceptionally useful for connecting the ECM to internal pathways. Chapter 11 details integrin linked kinases, ILK, and Chapter 12 the focal adhesion kinase, FAK, in pathway control. Recent work has demonstrated FAK centrality in many cancers including melanoma and these kinases also are looked upon as targets for control of these cancers as well.

The positive points of the book as I have tried to explain is the combination of exceptionally good authors and a well detailed examination of the research to date as of the publication. My only criticisms are related to expanding the audience by perhaps making the text more broadly acceptable. Although not clearly the intent of the authors, they accomplished superbly what they set out to do, but from the perspective of the otherwise focused professionals this could be an opportunity to expose the ECM more fully and in an integrated manner with so much of what is being developed in cancer understanding and modeling.

The book is somewhat dated, now 2008-2009, but it does a great job on getting the reader to that point. There are some things which may be useful in later editions; (i) some more pedagogic detail on the ECM, (ii) some possible discussion or targets of specific proteins for therapy, (iii) more detail on pathway dynamics, (iv) some discussion on ECM functions other than just the related research.

Overall this is a superb edition to any library of those doing cancer research, including those looking at spatio-temporal models since the ECM is often a neglected step-child.
Labels: Books, Cancer

MONDAY, DECEMBER 3, 2012

TREE WARDENS

The NY Times has an interesting piece which relates to my problems with the local "tree huggers". Now I am the only registered nursery in my town, I hybridize hemerocallis and have the only registered AHS Display Garden in the state. I have dozens of specimen trees which are rare and unique including a collection, some call it a small forest of Ginkgo and Metasequoia trees in the US. But for maples, ash, and Norway spruce, well you might just as well tear them out. They have surface roots and are weak and destructive and when it blows up a storm down they come.

As the Times states:

Many New England towns authorize local tree wardens to determine the health of shade trees and ban their removal unless they pose a hazard.

Springfield has a "significant tree ordinance" under which a homeowner needs a permit to trim or cut down any tree that is more than 36 inches in diameter or more than 75 years old, even if it is on private property, Mr. Casey said. If the tree is structurally unsound, he will issue a permit. But if it is healthy, the homeowner must petition the parks commission before trimming or removing it.

Utility companies often bear the brunt of complaints during a storm when homeowners lose power, and utilities blame the trees. "Trees are the No. 1 cause of power outages," said Mike Durand, a spokesman for Nstar, which serves eastern Massachusetts.

Now the same problem exists in New Jersey. You get some uneducated tree wardens who think ash trees and tulip trees are just wonderful, as are the Norway spruce and maples. They are invasive weeds! They have no worthwhile root structure and given the slightest push fall over destroying homes and killing the foolish who go out in the storm.

The electric utilities are forbidden to cut the trees and the net result is weeks of power outage and massive loss or property and economic life. Now metasequoia, ginkgo, and even oaks have deep roots and limb structures which for the most part are strong, flexible and not ready to destroy. But do the tree wardens have a clue, not one.

They are ignorant fools who want native plants. Here where we are it was just a few thousand years ago Lake Passaic, the water hole left over from the Ice Age. The flora is junk, stuff that grew up in the remnants of the detritus left over. I have the distinct disadvantage of both being educated in this area, degrees in Botany and Horticulture, amongst others, and operating a nursery. The bad trees should go! The good ones should come in. Native flora is often not native but just hangers on for a period until better stuff gets here.

Ash, maple, Bartlett Pear and others are just opportunities for destroying homes and power lines. The Tree Wardens should have some modicum of an education and experience. In our town they

are often some of the Garden Club ladies who have no other task other to ensure that every dead log is left to cause insurmountable damage!

So before we have another disaster, get rid of the bad trees, trim them, root them out, replace them with the good trees, there are millions of them, not the swamp squatters we have come to "love".
Labels: Politics

SUNDAY, DECEMBER 2, 2012

MORE ON THE ISSUE OF SCREENING

The problem of cancer screening has been at the forefront for several years. The two most visible are that for prostate and breast cancers. Let me make a few observations and then I want to use the recent NEJMdiscussion on breast cancer as a discussion point[9[1]].

Let us examine a single cancer, be it breast or prostate, or frankly almost any other. Let us look at steps.

1. At some time unbeknownst to the patient and physician some genetic pathway aberration occurs. It may be a transposition such as in CML or BRAF V600 as in melanoma or PTEN as in a prostate cancer. This is time 0. Something happens which sets off a chain of subsequent events.

2. Let us assume that the patient can be doing one of four things:

2.1 The patient is, with his physician's guidance, undergoing genetic surveillance. Namely we assume that there is some genetic marker which has high specificity for detecting the remnants of this genetic change. We do not know what it is yet but it gets the cancer when say there are a few thousand cells. It has a high detection probability and a very low false alarm rate. Namely, it is a good test. It may or may not determine if the cancer is aggressive or indolent. Namely it has undetermined prognostic value. The patient if found to have a positive result will undergo a detailed invasive procedure to affirm the diagnosis and then if that is positive then undergo normally accepted surgical and chemotherapeutic treatment.

2.2 The patient is, with his physician's guidance, undergoing some form of marker testing for cancer surveillance. This may be a PSA or mammogram test. It may have a lower detection probability and a higher false alarm rate. As with the first scenario the patient will undergo further examination. The patient if found to have a positive result will undergo a detailed invasive procedure to affirm the diagnosis and then if that is positive then undergo normally accepted surgical and chemotherapeutic treatment.

2.3 The patient, with his physician's guidance, will from time to time be clinically examined to determine if there is an abnormality. Thus for prostate exams it is a DRE and for breast exams it

9[1] http://www.nejm.org/doi/full/10.1056/NEJMclde1212888?query=featured_home#t=cldeOpt3

is a palpating of the breast. If no palpable lesion is present no other tests will be performed. If a palpable lesion is present then normal next steps performed. The patient if found to have a positive result will undergo a detailed invasive procedure to affirm the diagnosis and then if that is positive then undergo normally accepted surgical and chemotherapeutic treatment.

2.4 The patient will see their physician only after they have determined that a problem exists. Namely, in the case of the prostate, back pain is present along with the inability to urinate. For a skin lesion, the pigmented lesion is raised and bleeding. For the breast, the lump is obvious to sight not just touch. This is the way things were a century ago. The patient will then present to the physician. The patient if found to have a positive result will undergo a detailed invasive procedure to affirm the diagnosis and then if that is positive then undergo normally accepted surgical and chemotherapeutic treatment.

3. Treatment is initiated at the time we have specified above. We know the age dependent incidence for all such cancers so we can determine the incidence readily. Now for the outcomes.

3.1 If a genetic test determines early cancers, then local excision may be effective allowing for low costs removal. Follow up care be accomplished as well with genetic follow up. The death rate therefore should be near zero except for those high degree metastasis cancers such as ovarian, glioma, and certain melanomas, for example.

3.2 If we have intermediate tests whereby we can reduce chances of metastasis and excise in early cases then we can reduce the disease related mortality by a material degree.

3.3 If we wait for clinical presentation albeit with periodic surveillance then we may have a larger degree of metastasis and thus substantially higher mortality.

3.4 If we wait for the patient to inform the physician then most likely we have the highest metastasis and highest mortality.

Data relating to the above specific mortality can be derived based on the number of cancer cells at point of detection. For example for genetic markers of PCa we may be able to accomplish this with a tumor load of 1,000 cells. For PSA we need most likely 100,000 cells and for palpable screening based tumors we need 10,000,000 or more cells[10[2]].

4. What we should measure is death from the specific cancer, not death. But that is also complex. For example if a 75 year old man with congestive heart failure is determined to have PCa, then he most likely will die of the cardiac problem than the PCa. Yet if we have death as the all-encompassing end point the results will not be conclusive.

Let us now examine the NEJM comments.

[10[2]] See Weinberg, Cancer, Garland, 2008. pp 361-364, and the actual number of such cells may vary dramatically by cancer type and the issue of cancer stem cells are critical as well.

1. No Treatment or Screening for Anyone: The respondent argues:

More than 600,000 women were enrolled in several randomized trials of mammography screening more than 30 years ago. The trials showed a reduction in breast-cancer mortality but no effect on all-cause mortality. In recent decades, breast-cancer treatment has improved greatly, resulting in reduced mortality even among women with advanced disease. Thus, the reduction in mortality from mammography screening may be significantly smaller today than when the trials were performed.

The statement is somewhat conflicting in my opinion. If a reduction in mortality from breast cancer was observed then that is good. Even if we have improved treatment on later stage disease that is in my opinion no reason to delay early treatment.

The conclusion is:

The decision regarding screening mammography depends on the balance of benefits and harms and the way in which a woman and her physician weigh these competing factors. In my view, the benefits do not exceed the harms. Thus, given the data currently available, I do not recommend mammography screening for average-risk women of any age. I would ask the woman in the vignette to come back when she is 50 years of age. In 10 years, we might have more data to provide a different recommendation for her.

Here we have in my opinion a conflict and an observation. Bayesian analysis always comes to bear. If we have a family history then we had better look more closely. We know that such a history raises risks. But the problem often is uncertain family history as well. How do we handle that/

2. Treatment and Screening at 40

At the extreme the respondent argues:

Screening can be thought of as a kind of insurance. As with all insurance, there are costs for protection against adverse events that have a low probability of occurrence but could be catastrophic if they occurred without the insurance. In that context, given the evidence, there are good reasons to begin screening at the age of 40.

I would agree with this argument. It does save lives, albeit less than economically worthwhile to some, and yet it provides a data base for further analysis as well. The morbidity from false positives is always a concern but frankly that is a patient's choice as it always should be.

Thus for a conclusion, in my opinion it is clear that the logic for no screening hsa little if any merit, that for early and continual screening with informed consent, and even with an added payment, should be the norm.

Labels: Cancer, Health Care

SATURDAY, DECEMBER 1, 2012

MITF AND MELANOMA; TARGETING SPECIFIC PATHWAY ELEMENTS

MITF is a transcription factor which has been linked to melanoma. It can be activated in the RAF/BRAF pathway and thus when activated results in the loss of apoptosis and the migration of cells.

What is MITF?

As noted by Carreira et al[11][1]:

It is widely held that cells with metastatic properties such as invasiveness and expression of matrix metalloproteinases arise through the stepwise accumulation of genetic lesions arising from genetic instability and "clonal evolution."

By contrast, we show here that in melanomas invasiveness can be regulated epigenetically by the microphthalmia-associated transcription factor, Mitf, via regulation of the DIAPH1 gene encoding the diaphanous-related formin Dia1 that promotes actin polymerization and coordinates the actin cytoskeleton and microtubule networks at the cell periphery.

Low Mitf levels lead to down-regulation of Dia1, reorganization of the actin cytoskeleton, and increased ROCK-dependent invasiveness, whereas increased Mitf expression leads to decreased invasiveness.

Significantly the regulation of Dia1 by Mitf also controls $p27_{Kip1}$-degradation such that reduced Mitf levels lead to a $p27_{Kip1}$-dependent G1 arrest. Thus Mitf, via regulation of Dia1, can both inhibit invasiveness and promote proliferation.

The results imply variations in the repertoire of environmental cues that determine Mitf activity will dictate the differentiation, proliferative, and invasive/migratory potential of melanoma cells through a dynamic epigenetic mechanism.

Note that the discussion above shows that overexpression of MITF leads to less invasiveness. We show the details of the pathway dynamics below.

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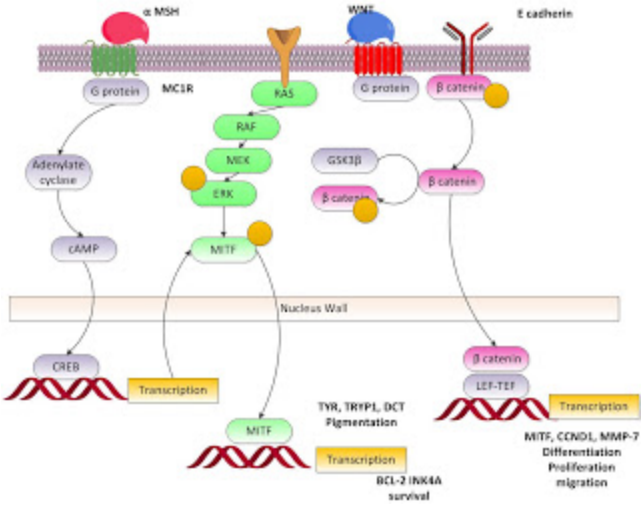
[11][1] Carreira, S., et al, Mitf regulation of Dia1 controls melanoma proliferation and invasiveness, Genes Dev. 2006 20: 3426-3439.



They continue:

Although Mitf is clearly required for melanoma proliferation, why it is necessary has not been previously established. To understand how Mitf depletion led to a block in G1/S transition, we examined a number of known markers of proliferation and the cell cycle. Western blotting of cells transfected with control or Mitfspecific siRNA revealed that depletion of Mitf led, as expected from our previous work, to decreased expression of $p21_{Cip1}$, but intriguingly also induced expression of the $p27_{Kip1}$ cyclin-dependent kinase inhibitor. Note that similar results were obtained using a second Mitf siRNA directed against a different region of Mitf. We also observed reduced expression of cyclin E, and PCNA, most likely as an indirect effect of the cell cycle arrest, but no change in cyclin D1 or Cdk2 levels. Tubulin and lamin B were used as loading controls.

Finally they note:

In summary, Mitf appears to lie right at the heart of the melanocyte, coordinating survival, cell cycle entry and exit, cytoskeletal organization, melanosome assembly and transport, differentiation and migration/metastasis. As such, understanding Mitf regulation and function may well be the key to achieving one of the major aims of cancer research, an effective melanoma therapy.

Thus the MITF function, in their view, is critical.

MITF Targeting and Control

From a current Eureka posting, Zoufal writes of work recently reported in Genes & Development by Pogenberg[12][2] et al[13][3] focused upon targeting and thus controlling MITF:

[12][2] See Pogenberg in http://genesdev.cshlp.org/

[13][3] Zoufal, T., X-ray analysis deciphers master regulator important for skin cancer, http://www.eurekalert.org/pub_releases/2012-12/ded-xad113012.php

The results, published in the scientific journal "Genes & Development", throw new light on the workings of the so-called Microphthalmia-associated Transcription Factor MITF, that is not only connected to skin cancer, but also to a variety of hereditary diseases where the production of the skin pigment melanin is disturbed, and to certain aspects of ageing. "Our data could provide a rational basis for the development of tailor-made drugs targeting MITF", explains first author Vivian Pogenberg from the Hamburg branch of the European Molecular Biology Laboratory

But MITF also makes stem cells turn into melanocytes in the first place and controls cell proliferation and death in these cells. That's why MITF is called a master regulator. In fact, it also has functions in other cell types like mast cells of the immune system and bone eating osteoclasts...

Mutations in MITF not only play a role in the development of skin cancer, but also cause severe genetic diseases like the Tietz and Waardenburg syndromes that lead to deafness, skin and hair pigmentation defects, abnormal eye anatomy and altered vision. The transcription factor also plays a role in our hair turning grey with age and other age-related pigmentation alterations…

Crystals scatter X-rays in characteristic ways and produce diffraction patterns from which the structure of the crystal - and here MITF - can be reconstructed. The analysis revealed unexpected molecular insertions that give MITF a unique kink. MITF forms a dimer with a long coiled-coil protein "zipper", and the kink in this zipper limits MITF's ability to bind to other transcription factors.

This paper thus appears to provide a targeted means to control MITF and then perhaps melanoma metastasis. Identification of binding sites is essential to control.

More on MITF

We can provide a bit more history on MITF and its functions. As NCBI states[14][4], MITF, microphthalmia-associated transcription factor (3p14.2-p14.1):

This gene encodes a transcription factor that contains both basic helix-loop-helix and leucine zipper structural features. It regulates the differentiation and development of melanocytes retinal pigment epithelium and is also responsible for pigment cell-specific transcription of the melanogenesis enzyme genes. Heterozygous mutations in the this gene cause auditory-pigmentary syndromes, such as Waardenburg syndrome type 2 and Tietz syndrome

MITF has been known to be a key player in melanoma metastasis. As Chin et al state in their review paper[15][5]:

[14][4] http://www.ncbi.nlm.nih.gov/gene/4286

[15][5] Chin et al, Malignant melanoma: genetics and therapeutics in the genomic era, Genes Dev. 2006 20: 2149-2182

MITF, a melanoma oncogene targeted by amplification

The promise of DNA-based structural alterations as the entry point for gene discovery has been illustrated by the recent identification of MITF as a melanoma oncogene. The discovery of MITF amplification in melanoma derived from an integrated analysis of genomic copy gains and losses, together with sample-matched mRNA expression data.

When clustering algorithms were applied to SNP array-derived chromosomal copy number data generated for the NCI-60 cancer cell line collection, some of these cell lines aggregated according to tissue of origin, including several melanoma cell lines. The bidimensionality of the hierarchical algorithm also enabled the identification of chromosomal alterations driving these lineage-restricted clustering patterns, and suggested that lineage-specific cancer genes might reside within the genomic regions implicated.

For the melanoma cell lines, the common genomic alteration was a region of copy gain at chromosome 3p14-3p13. To facilitate the identification of an oncogene targeted by this amplification event, the NCI- 60 collection was partitioned based on the presence or absence of copy gain at the relevant chromosome 3p locus. This partitioning served as a two-class distinction that drove a supervised analysis of sample-matched gene expression data. Although the gene expression signature that emerged was dominated by melanocyte lineage genes (as expected given that only melanoma cell lines comprised the 3p-amplified class), MITF was the only gene showing significantly increased expression in association with the 3p-amplified melanoma cell lines that also mapped to the common region of 3p copy gain.

MITF amplification was subsequently detected in 10% of primary cutaneous and 15%–20% of metastatic melanomas.

Although the majority of amplifications were low level (e.g., four to six copies per cell), high-level amplicons were also observed, including one sample that exhibited >100 copies per diploid genome. A Kaplan- Meier analysis performed on metastatic melanomas suggested that MITF amplification in this setting correlated with adverse 5-yr patient survival.

Finally, ectopic MITF overexpression complemented $BRAF_{V600E}$ in conferring soft agar colony growth to immortalized melanocytes engineered to express TERT, and to lack the pRB and p53 pathways. These functional studies thereby suggested a genetic context that might characterize a subset of human melanomas whose survival is dependent on MITF.

MITF also exemplifies a newly recognized "lineage survival" oncogenic mechanism, wherein tumor genetic alterations may target survival functions also operant in the relevant cellular lineages during development and differentiation.

Thus, while the discovery of MITF amplification began as a systematic genomics-based survey of many human cancer types, it provides a striking convergence of melanoma oncogene discovery and melanocyte development.

Next, as Genovese et al state[16][6]:

Histidine triad nucleotide-binding protein 1 (HINT1) is a haploinsufficient tumor suppressor gene that inhibits the Wnt/β-catenin pathway in colon cancer cells and Microphthalmia-associated transcription factor (MITF) activity in human mast cells. MITF and β-catenin play a central role in melanocyte and melanoma cell survival, and this study aimed to investigate the effects of HINT1 on the MITF and β-catenin pathways in malignant melanoma cells.

We found that HINT1 inhibits MITF and β-catenin transcriptional activity, and both proteins can be co-immunoprecipitated with an anti-HINT1-specific antibody in melanoma cell lines. Stable, constitutive overexpression of the HINT1 protein in human melanoma cells significantly impaired cell proliferation in vitro and tumorigenesis in vivo.

These effects were associated with a decreased expression of cyclin D1 and BCL2, well known MITF and β-catenin transcription targets, respectively. We also demonstrated that BCL2 and cyclin D1 can partially rescue the HINT1-driven phenotype. Moreover, we found in ChIP assays that HINT1 binds the chromatin at MITF and β-catenin sites in BCL2 and cyclin D1 promoters, respectively, and that mSIN3a and HDAC1, well known transcriptional repressors, can be co-immunoprecipitated with an anti-HINT1-specific antibody. These findings support the tumor suppressor activity of HINT1 gene in melanoma cells by promoting the formation of non-functional complexes with oncogenic transcription factors like MITF and β-catenin.

Finally as Larribere et al state[17][7]:

Microphthalmia-associated transcription factor (MITF) M-form is a melanocyte-specific transcription factor that plays a key role in melanocyte development, survival, and differentiation. Here, we identified MITF as a new substrate of caspases and we characterized the cleavage site after Asp 345 in the C-terminal domain.

We show that expression of a non-cleavable form of MITF renders melanoma cells resistant to apoptotic stimuli, and we found that the C-terminal fragment generated upon caspase cleavage is endowed with a proapoptotic activity that sensitizes melanoma cells to death signals. The proapoptotic function gained by MITF following its processing by caspases provides a tissue-restricted means to modulate death in melanocyte and melanoma cells.

Their observation does show the impact of MITF in the control of melanoma.

Observations

[16][6] Genovese G, et al, The tumor suppressor HINT1 regulates MITF and β-catenin transcriptional activity in melanoma cells, Cell Cycle. 2012 Jun 1; 11(11):2206-15.

[17][7] Larribere, et al, The cleavage of microphthalmia-associated transcription factor, MITF, by caspases plays an essential role in melanocyte and melanoma cell apoptosis, Genes Dev. 2005 19: 1980-1985.

The recent work demonstrates that we can through an understanding of the pathways then target specific pathway control proteins by understanding their structure. We can already control B RAF in certain circumstances by targeting its specificity and that controlling the path but allowing MITF control in a broad sense may actually be much more powerful if the results hold for clinical applications.

The ability to find, characterize, and design binding site specific blocking agents is an essential step in a broader control of multiple cancers.

Labels: Cancer

FRIDAY, NOVEMBER 30, 2012

THE ACA MONSTER: THE ACO

As we have discussed over the past four years, the emergence of the ACO, mega-hospital consolidation with private practice absorption, will create monsters. The NY Times speaks of one such out in the middle of nowhere.

As the article states:

"But probably the driving reason was the changing landscape of health care delivery and the uncertainty around that," Dr. Johnson said. "The thought was that we were going to be in a safer position if we were aligned and affiliated with a network."

But as St. Luke's moved forward with its plans to acquire most of the Saltzer Medical Group — a practice of about 50 physicians in Nampa, Idaho, about 20 miles west of Boise — St. Alphonsus filed an injunction to block the purchase.

St. Alphonsus argues that St. Luke's dominance is hurting its business because it has experienced steep declines in hospital admissions and referrals from physicians acquired by St. Luke's.

St. Luke's argues that it is positioning itself to compete better by improving its ability to coordinate patient care. In September, it filed an application with Medicare officials to become a so-called accountable care organization. Hospitals designated as A.C.O.'s can typically keep a portion of any savings they generate. The hospitals reduce health care costs by avoiding unnecessary tests and procedures or by keeping patients out of the hospital, while still meeting quality targets.

First, who do you think is paying for the law suits, we are. Second, what is happening to care as these law suits fly back and forth. We are getting poorer care. The ACOs, will merger, then merge, then merge again, into massive regional conglomerates. Independent physicians will disappear becoming employees of the mega institutions.

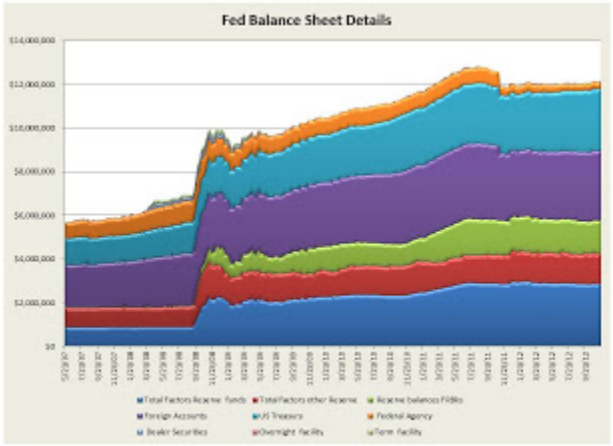
One should remember that we have almost 20% of the economy in this one sector, and that one must look at what catalysts will cause massive consolidation. The ACOs may beat out anything that the HMOs tried to do. The are becoming natural monopolies, they get to hide everything, and the natural tension that in the HMO days between patients, physicians, and hospitals, that is now gone. In fact the ACO will also become the insurer.

One could have envisioned a massive plan for the ACA to create the ACO as insurer, provider, etc. They will be able to get so big that even the Government will be limited. Just my nightmare of the day.

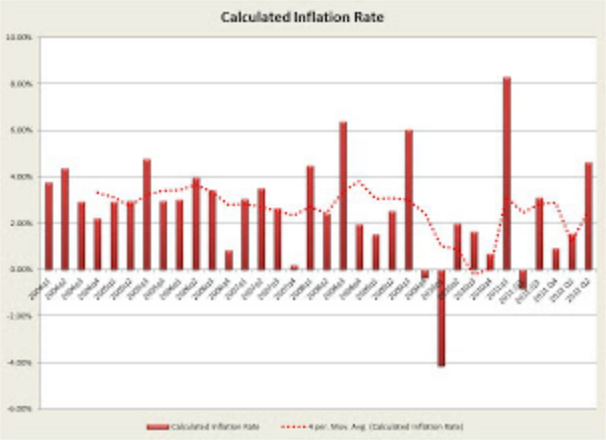
Labels: Health Care

FRIDAY, NOVEMBER 30, 2012

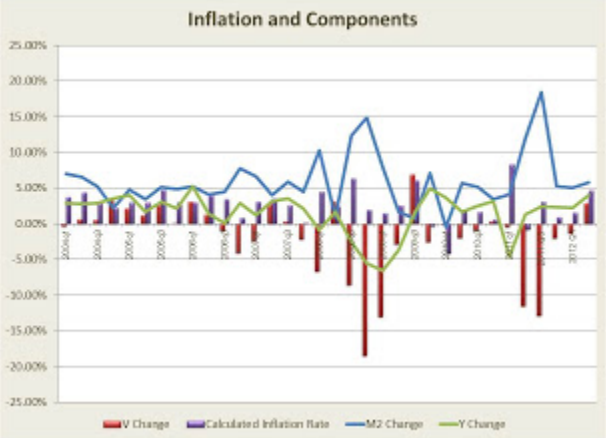
UPDATED MONETARY STATS



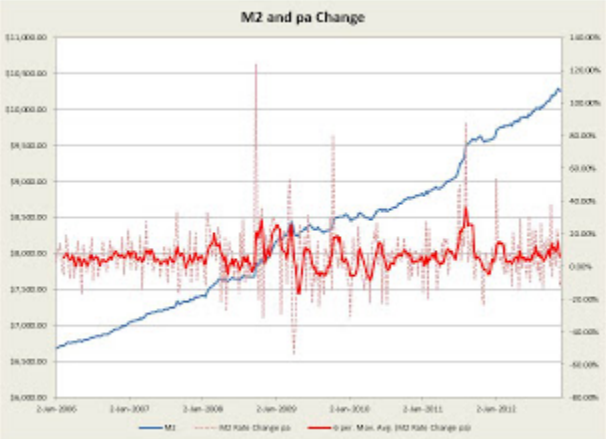
The above is the current status of the FEDs total Balance Sheet. Since the run up from 2008 through the middle of last year we saw the rise but for the past year it has remained stable. One must remember that at some time they will begin unloading this mess. That is when we will see inflation.



The above is the calculated inflation rate annualized by quarter. We see some small amount.



The elements of inflation are shown above/ No significant trends as of yet.



M2 continues to grow. The rate of growth seems to be fluctuating in normal bounds with no early signs of inflation yet.

Finally the Monetary Base is fixed as well. This means that money is still tight but not tightening.

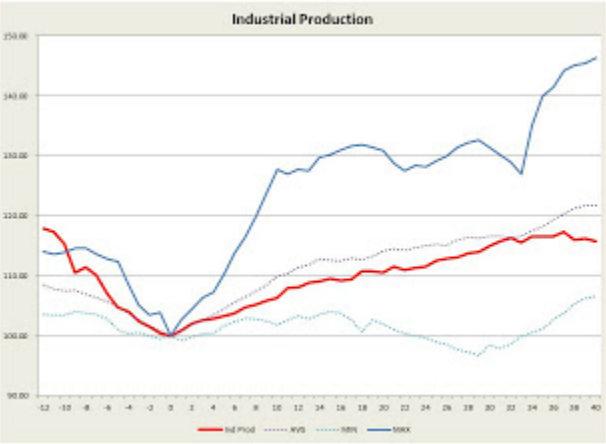
In summary we are in a strong monetary control period. If the FED Chair is changed we may see almost anything.

Labels: Economy

RECESSION STATISTICS, NOVEMBER 2012

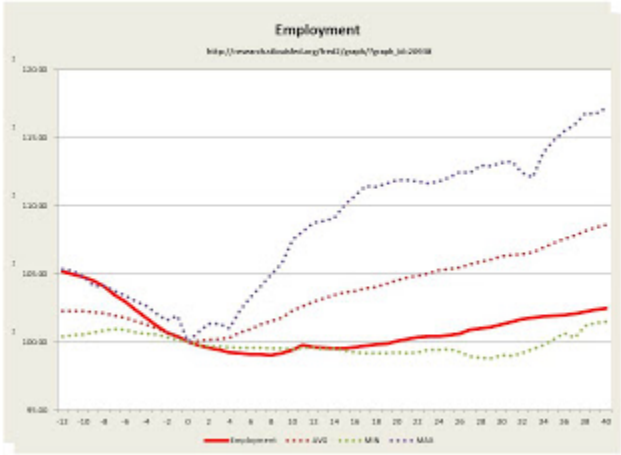
Now that we are four years in to a new economic paradigm perhaps it is worth again looking at how well it is working. Again we rely upon the St Louis FED data and present its latest update.

First is Industrial Production. The problem here is that it is falling again, and frankly this is a serious concern since it appears to be a trend.



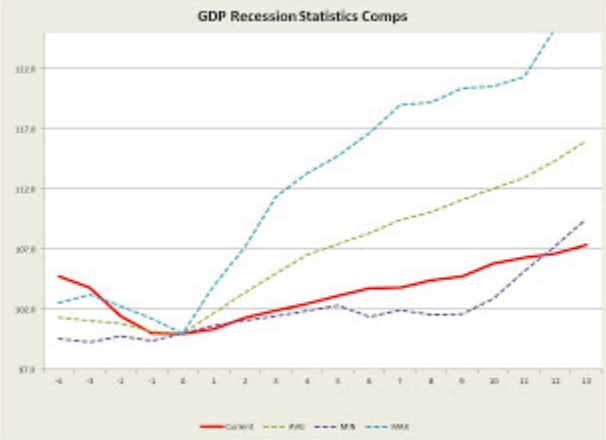
Below we depict Income. This is the most worrisome. We see Income at the lowest in any recession, it is jut not recovering.

The one below is Employment. As with Income it is low and close to the lowest in terms of recovery. This clearly is an employment driven downturn. I suspect as do many that we are seeing a structural shift. Manufacturing is not just going off-shore but is computerized and thus any such jobs just no longer exist. What is required is not allowed under union controlled immigration. We allow low skilled workers but prohibit high skilled technical people thus creating a future competitive country to arise.

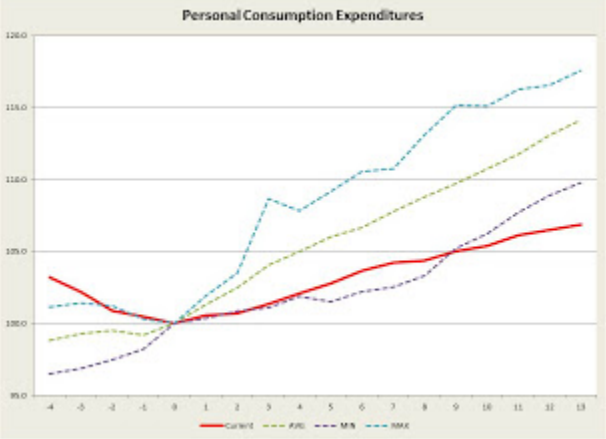


Strangely Retail Sales have been recovering but this along with the employment data is actually concerning. People with lower paying jobs seem to be spending more.

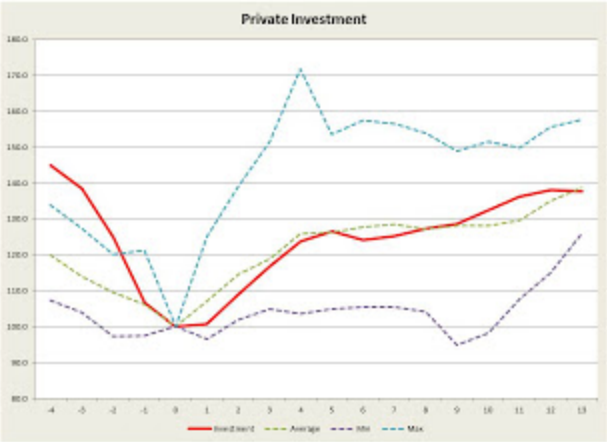
The GDP comps are shown below. Again we seem to be falling off the cliff in terms of any recovery. In fact we are quite close to a second recession and given what DC is doing I suspect we shall see just that in Q1 2013.



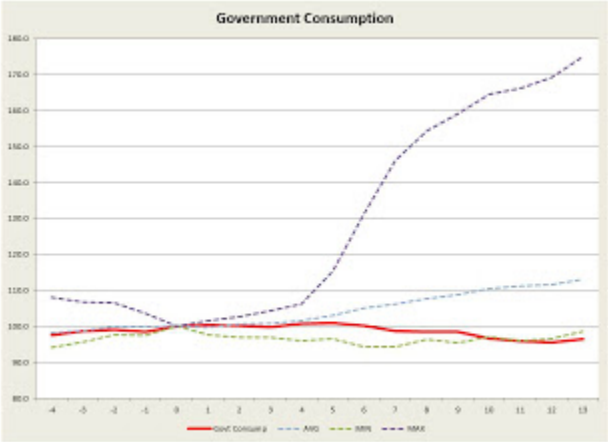
Personal Income is falling consistent with previous discussions. This is a true concern.



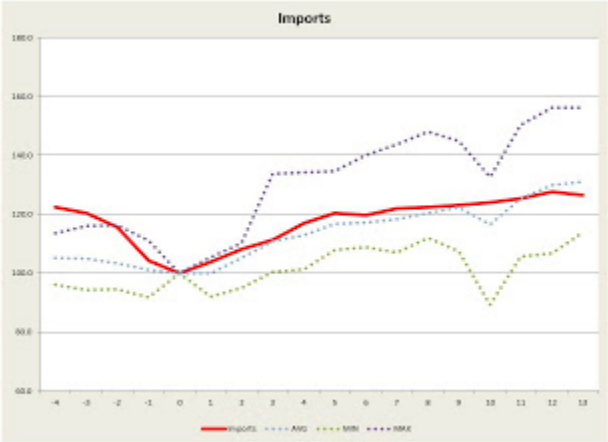
Private Investment is on the norm but again this is a driver for increased productivity and lower work for pay and participation.



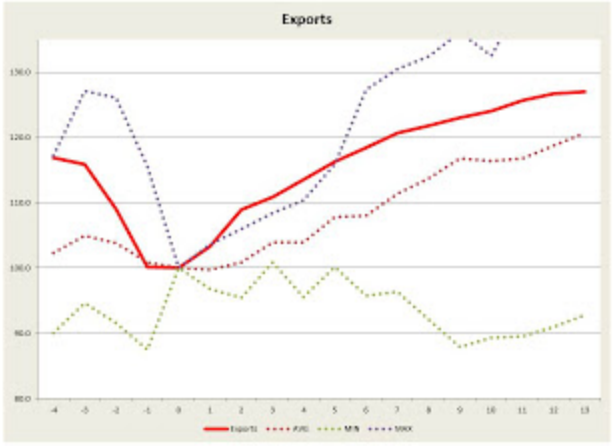
Government Consumption is lower than other recoveries which is a surprise given the various stimulus programs.



Now for Imports we have the chart below. As we shall see with exports, they are stable.



Exports are on par.



In summary we are looking at a weak at best recovery and more than likely a new recession. Four years have not done a great deal, if any deal at all.

Labels: Economy

THURSDAY, NOVEMBER 29, 2012

SCREENING, CANCER AND THE RIGHT QUESTIONS

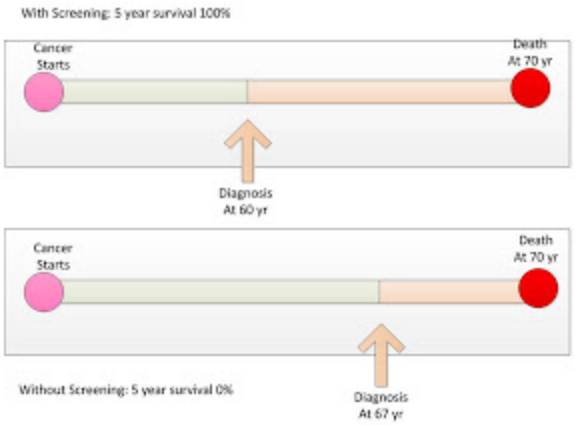
In a recent piece in the NCI Cancer Bulletin they discuss what appears to be the ineffectiveness of cancer screening. Now upon closer examination there are clearly many epistemological issues. The author commences her presentation by stating:

Much of the confusion surrounding the benefits of screening comes from interpreting the statistics that are often used to describe the results of screening studies. An improvement in survival—how long a person lives after a cancer diagnosis—among people who have undergone a cancer screening test is often taken to imply that the test saves lives.

Indeed the interpretation is critical but even more importantly is the question for which the statistics reflect an answer. Let me address this in two ways; first by examining her diagrams and second by examining some cancer specifics.

First, her examples. She provides two cases.

The first case is a demonstration that by diagnosing the cancer early one obtains an improved 5 year survival but no change in time of death. Consider the case shown below where she assumes the following. A patient has lung cancer and it commences at some unspecified time and the patient dies at 70. Now assume that by some unspecified but reliable test we can identify it at say 60 years of age and act in some manner but that despite the actions and early diagnosis the patient dies at 70. She contends we see a 100% 5 year survival. True, but. Then assume we never did anything until some massive event occurred at 67 and we then diagnosis the cancer and take some unspecified actions. Then we would have a 0% 5 year survival.

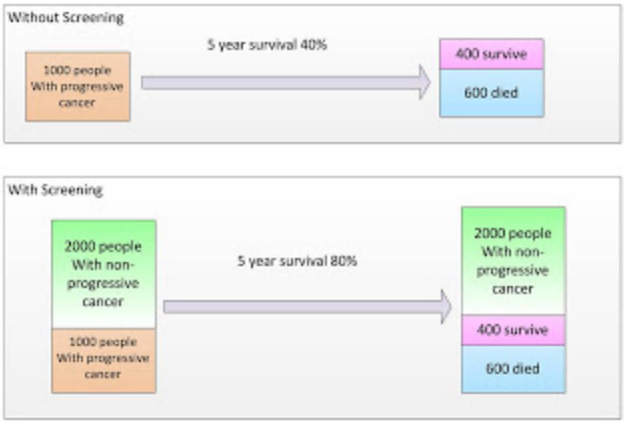


Now what is wrong here? First, lung cancer is generally very aggressive so that any chance of even a three year survival is low. Indeed if there were a 10 year survival then that itself would have been a success. In fact if diagnosed at 60, by whatever means, and treated by whatever means, more than likely if untreated the patient would have died of lung cancer much earlier.

The fault here is that there is an assumption that the two cases are pari passu, equal in all ways but the early diagnosis. In fact I would argue we are comparing apples and oranges.

Now for the second case. Here she assumes that we have a progressive and a non-progressive form of some cancer. The usual victim chose especially by women is prostate cancer. So let us assume that. We then look at two cases. First with no screening. Somehow there is no treatment and the result is 400 dead and 600 alive. The protocol of diagnosis and treatment is left unstated but one can assume that the patient presents say with an inability to urinate or sever bone pain. Namely with no screening the patient waits until the symptoms are obvious and compelling.

Now the second case she uses to demonstrate bias is that if we screen, and that for every 3000 people screened who have the disease as a result of screening, 2000 have an indolent form, which we cannot ascertain at time of diagnosis, and 1000 still have the progressive form. Now she argues that using this erroneous method we have a false survival rate of 80% rather than the “true” rate of 40%.



Let me quote from the Bulletin:

"I had a brilliant oncologist say to me, 'Don, you have to understand: 20 years ago, before mammography, I'd see a patient with breast cancer, and 5 years later she was dead. Now, I see breast cancer patients, and 15 years later they're still coming back, they haven't recurred; it's obvious that screening has done wonders,'" he recounted. "And I had to say no—that biases could completely explain the difference between the two [groups of patients]."

There is a problem here. If the oncologist still sees patients after 15 years then somehow we have managed to accomplish something. After all in prior days the patient was seen at the point of massive tumor load and significant metastasis. We again are comparing apples to oranges.

Now let us step aside and consider three cancers and the screening issues.

1. Melanoma: Anyone familiar with melanoma knows that screening does work. If we waited for the patients to come with a bleeding lesion then most likely we would have a greater mortality rate. There is the question of increased incidence and its relationship to increased screening, but melanoma is one of those cancers that just have no indolent form. It is plain and simple a killer and one can deduce that the increased incidence is due to increased exogenous factors such as sun exposure, just look at Australia. Now if we were to screen, especially those of increased risk (family history, number nevi, sun exposure etc) using dermoscopy, and remove promptly and effectively all suspect lesions, then it can be argued that we can reduce the mortality substantially. Not just 5 year survival, but actual mortality due to that specific melanoma.

2. Prostate: This is often the hot potato of screening. The reason is, the opposition argues, that if biopsy is required, that it is uncomfortable and there may be some limited morbidity.

The author states:

The extreme example of length bias is overdiagnosis, where a slow-growing cancer found by screening never would have caused harm or required treatment during a patient's lifetime.

Because of overdiagnosis, the number of cancers found at an earlier stage is also an inaccurate measure of whether a screening test can save lives. (See the graphic on the left for further explanation.)

The effects of overdiagnosis are usually not as extreme in real life as in the worst-case scenario shown in the graphic; many cancers detected by screening tests do need to be treated. But some do not. For example, recent studies have estimated that 15 to 25 percent of screen-detected breast cancers and 20 to 70 percent of screen-detected prostate cancers are overdiagnosed.

The problem, however, is that we do not know the slow growing from the virulent forms. We do not have genetic markers that tell is that a Gleason 6 will become metastatic in 6 weeks while the Gleason 8 is going nowhere. This is the fatal flaw in her second analysis. It assumes we know indolent from aggressive, we just do not, until after the fact. Thus we treat all as aggressive, which albeit costly may be in the end efficacious to saving lives. Yet again we let the decision be an informed patient decision.

3. Colon: The question here is; what of colonoscopies? Clearly here we have often slowly growing tumors, starting with adenomas and slowly developing into invasive cancers. Removal of adenomas is an almost certain guarantee of non-progression to a cancer. The data seem to demonstrate a saving of lives. The procedure is invasive, and at times costly, with small but existing morbidity factors. Should we ban this also?

Now the issue is; what should be the proper questions? Namely, should we continue to do 5 year survival? More importantly should we even start down the road of denying efficacy if we do not have enough information? Again consider prostate cancer. We do not know how to tell aggressive from indolent, so should we just stop PSA testing? PSA testing helps for the aggressive group, albeit a small but unidentifiable sample.

I suggest stepping back and looking at the questions. The author in her presentation I believe makes a strong argument for it, not by what she understood and said, but what was clearly not understood and left unsaid.
Labels: Cancer, Health Care

WEDNESDAY, NOVEMBER 28, 2012

EXTRACELLULAR MATRIX VS INTRACELLULAR PATHWAY

The focus on intracellular pathways has been a prime direction of research in the development of cancers. However there has from time to time been some focus on the extracellular matrix, the "ECM", which relates in many ways to the stability of the cell, its localization. Cancer cells lose this sense of localization and begin to move. We have written a White Paper which details much of this insight and we summarize it here.

The processes at play in the ECM have a significant impact on the processes that occur within a cell. Thus it is essential to have an understanding of the ECM. Recent work by Fisher and his people on MDA-9, a controller of certain ECM elements, demonstrates a control path that

influences the internal pathways. We discuss the ECM in the context of the MDA-9 developments.

In this section we use a recent development in understanding the impact of Mda-9 and the nexus with the extra cellular matrix, ECM, and the control of metastatic melanoma.

We first review the Fisher Team efforts as recently presented and then we examine the standard intracellular pathways that have been examined and from that we provide an overview of the extra cellular matrix, ECM, which is the "glue" binding together cells and facilitating cell to cell communications.

We find this an interesting focus or research for several reasons:

1. It examines the ECM which has received limited focus.

2. It focuses on pathways as we have been also doing and specifically an interesting adjunct to the current B-RAF approach.

3. It establishes a clear path forward which is logically and experimentally based and verifiable.

There has been limited prior research on these issues. In Hearing and Leong, 380-386, there is a limited discussion regarding the ECM and melanoma with references. The work by Zent and Pozzi provides a broad and detailed perspective of the ECM with many cancers. However their work is not specific to melanoma. In Weinberg there are references but there does not appear to be any singular focus on the ECM as a standalone system element.

In the recent paper by Das et al, the authors (from Fisher's Lab at Virginia Commonwealth) state[18[1]]:

Melanoma differentiation associated gene-9 (MDA-9), also known as syntenin, functions as a positive regulator of melanoma progression and metastasis. In contrast, the Raf kinase inhibitor RKIP, a negative modulator of RAF-stimulated MEKK activation, is strongly downregulated in metastatic melanoma cells. In this study, we explored an hypothesized inverse relationship between MDA-9 and RKIP in melanoma. Tumor array and cell line analyses confirmed an inverse relationship between expression of MDA-9 and RKIP during melanoma progression.

We found that MDA-9 transcriptionally downregulated RKIP in support of a suggested crosstalk between these two proteins. Further, MDA-9 and RKIP physically interacted in a manner that correlated with a suppression of FAK and c-Src phosphorylation, crucial steps necessary for

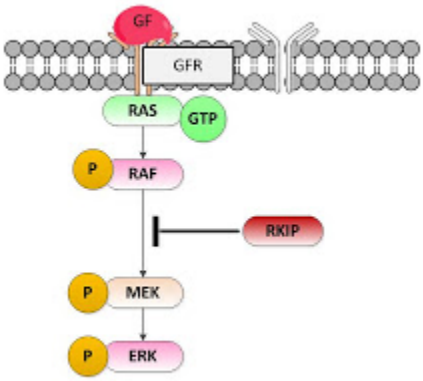
18[1]

http://cancerres.aacrjournals.org/search?author1=Swadesh+K+Das&sortspec=date&submit=Submit ; Therapeutics, Targets, and Chemical Biology Raf Kinase Inhibitor RKIP Inhibits MDA-9/Syntenin-Mediated Metastasis in Melanoma, Das, S., et al, *Cancer Res Published Online First October 11, 2012.*

MDA-9 to promote FAK/c-Src complex formation and initiate signaling cascades that drive the MDA-9-mediated metastatic phenotype.

Lastly, ectopic RKIP expression in melanoma cells overrode MDA-9-mediated signaling, inhibiting cell invasion, anchorage-independent growth and in vivo dissemination of tumor cells. Taken together, these findings establish RKIP as an inhibitor of MDA-9-dependent melanoma metastasis, with potential implications for targeting this process therapeutically.

From the paper by Houben et al we have the RKIP activation as shown below:



As Houben et al state:

The Ras/Raf/MEK/ERK intracellular signalling cascade is a major determinant in the control of cell growth, differentiation, and survival and can be activated in response to a variety of extracellular stimuli. Stimulation of growth factor receptors results in the activation of the small G-protein Ras, which in turn interacts with the protein kinase Raf leading to its activation. MAP kinase kinase kinase (Raf) phosphorylates and activates MAP kinase kinase (MEK), and MEK phosphorylates and activates extracellular signal-regulated kinase (ERK) 1/2 (p42/p44 MAP kinases).

Although Raf and MEK appear largely restricted to only one class of substrates, ERK targets more than 70 substrates including membrane, cytoskeletal, cytoplasmic, nuclear, and even mitochondrial proteins. Recently, a negative regulator of this pathway has been described. The Raf Kinase Inhibitor Protein (RKIP) binds to either Raf or MEK and thereby interferes with the activation of MEK by Raf. The importance of the Ras/Raf/MEK/ERK signalling pathway for carcinogenesis is well established. Indeed, Ras genes (K-ras, H-ras, and N-ras) are the most frequently mutated oncogenes detected in human cancer.

Houben et al further state about RKIP (12q24.23) as a target the following:

To assess the relevance of the Ras/Raf/MEK/MAP kinase pathway, we analyzed for activating B-Raf mutations and we elucidated the presence of the Raf Kinase Inhibitor Protein (RKIP) and extracellular signal-regulated kinase (ERK) as well as the phosphorylation status of ERK. All

MCC samples were negative for the B-Raf$_{V600E}$ mutation. Remarkably, RKIP, which was shown to interfere with the activation of MEK by Raf, was highly expressed in primary as well as in metastatic MCC. … Western blot analysis of three MCC-derived cell lines revealed in one case the pattern present in situ (i.e. high RKIP expression and complete absence of phosphorylated ERK).

Thus the Fisher team seems to seek out a RKIP inhibitor to slow the pathway. This is in addition to the B-RAF inhibitors which are currently in clinical use.

Now in an industry piece on the same article the author Ho states[19[2]]:

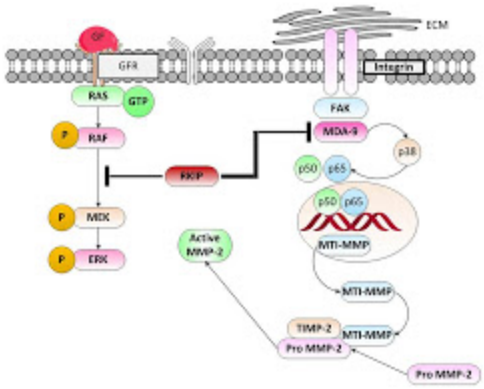
…. the scientist believes that they have the ability to eliminate melanoma differentiation associated gene-9 (mda-9)/syntenin, a specific protein. In the experiment, the researchers discovered that Raf kinase inhibitor protein (RKIP) was able to interact and suppress with mda-9/syntenin. The protein was originally cloned in a laboratory and past studies showed how it interacted with c-Src, another protein, to produce a set of chemical reactions that later boosted metastasis.

"Prior research suggests that RKIP plays a seminal role in inhibiting cancer metastasis, but, until now, the mechanisms underlying this activity were not clear," explained Paul Fisher, the program co-leader of Cancer Molecular Genetics at Virginia Commonwealth University Massey Cancer Center, in a prepared statement. "In addition to providing a new target for future therapies, there is potential for using these two genes as biomarkers for monitoring melanoma development and progression."

The team of investigators discovered that RKIP become attached to mda-9/syntenin, which resulted in limiting the expression of mda-9/syntenin. With the finding of this physical interaction, the scientists believe that they could possibly create small molecules that are similar to RKIP and the molecules could be used as drugs to treated metastasis in cancers like melanoma.

We depict this pathway below:

[19[2]] http://www.redorbit.com/news/health/1112732493/stopping-the-spread-of-melanoma-by-removing-protein-affecting-metastasis/ ; Ho, C., Stopping The Spread Of Melanoma By Removing Protein Affecting Metastasis, RedOrbit, November 15, 2012



The article continues:

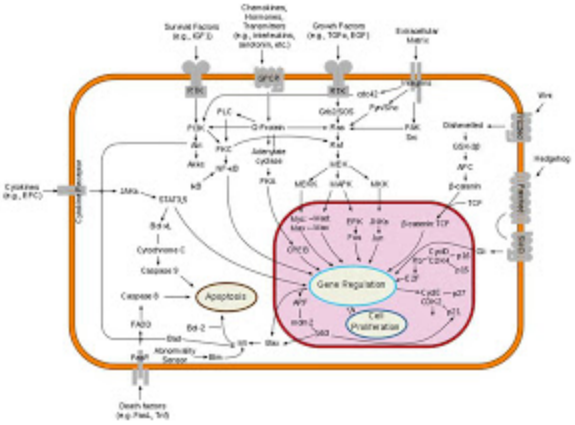
There was also a difference in terms of the level of mda-9/syntenin and RKIP. While malignant and metastasis melanoma cells had higher levels of mda-9/sytnenin compared to RKIP, the healthy melanocyte cells that create pigment in eyes, hair, and skin had higher levels of RKIP than mda-9/syntenin. The researchers believe that different levels in the proteins could be used in diagnosis, particularly in following the progression of a disease or tracking a patient's response to a particular treatment.

"Our findings represent a major breakthrough in understanding the genetic mechanisms that lead to metastasis in melanoma. Prior studies have shown that levels of mda-9/syntenin are elevated in a majority of cancers, including melanoma, suggesting that our findings could be applicable for a wide range of diseases," continued Fisher, who also serves as chairman of VCU's Department of Human and Molecular Genetics and director of the VCU Institutes of Molecular Medicine, in the statement.

Moving forward, the scientists plan to determine how they can develop small molecules that mimic RKIP. These molecules could potentially be utilized in new treatments for melanoma.

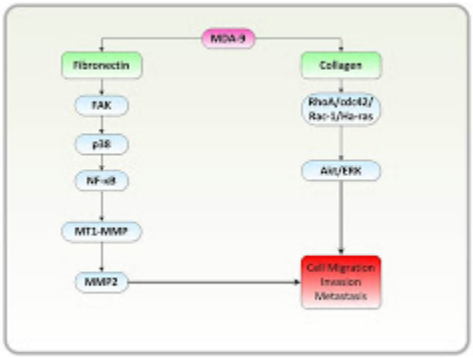
This is a fundamental result. It demonstrates another pathway element and at the same time connects the intracellular pathways with the extra cellular matrix and their pathways. Potentially this is diagnostic, prognostic and a treatment as well.

The following Figure is a repetition of the standard intra-cellular pathways. We have discussed these at length.



What is different from what we have detailed previously is the Extra Cellular Matrix connection via the integrins. This yields the controlling FAK path using FAK and Src. Note that this activates RTK and Ras and thus as we have described many of the other internal pathways this is the first time we have involved the ECM directly. The ECM is a significant element in cancer proliferation, it is the sea in which the changing cells sail metaphorically but at the same time it allows communication with the environment as well as presenting ligands to receptors.

As depicted in Sarkar et al, we have the following sets of paths and the results:



We shall be examining these in some detail. Let us first characterize some of the above identified elements controlled by the extracellular matrix path. The others we have examined in detail elsewhere.

FAK

FAK is also known as; PTK2, FADK; FAK1; FRNK; PPP1R71; p125FAK; pp125FAK. It is located at 8q24.3. It is a kinase.

NCBI states its function as follows:

This gene encodes a cytoplasmic protein tyrosine kinase which is found concentrated in the focal adhesions that form between cells growing in the presence of extracellular matrix constituents. The encoded protein is a member of the FAK subfamily of protein tyrosine kinases but lacks significant sequence similarity to kinases from other subfamilies. Activation of this gene may be an important early step in cell growth and intracellular signal transduction pathways triggered in response to certain neural peptides or to cell interactions with the extracellular matrix. Several transcript variants encoding different isoforms have been found for this gene, but the full-length natures of only three of them have been determined.

Src

SRC is located at 20q12-q13. As noted in NCBI[20][3]:

This gene is highly similar to the v-src gene of Rous sarcoma virus. This proto-oncogene may play a role in the regulation of embryonic development and cell growth. The protein encoded by this gene is a tyrosine-protein kinase whose activity can be inhibited by phosphorylation by c-SRC kinase. Mutations in this gene could be involved in the malignant progression of colon cancer. Two transcript variants encoding the same protein have been found for this gene.

p38

The p38 gene has multiple names. It is MAPK14, RK; CSBP; EXIP; Mxi2; CSBP1; CSBP2; CSPB1; PRKM14; PRKM15; SAPK2A; p38ALPHA. It is located at 6p21.3-p21.2.

Its function described by NCBI is as follows[21][4]:

The protein encoded by this gene is a member of the MAP kinase family. MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development.

This kinase is activated by various environmental stresses and proinflammatory cytokines.

The activation requires its phosphorylation by MAP kinase kinases (MKKs), or its autophosphorylation triggered by the interaction of MAP3K7IP1/TAB1 protein with this kinase. The substrates of this kinase include transcription regulator ATF2, MEF2C, and MAX, cell cycle regulator CDC25B, and tumor suppressor p53, which suggest the roles of this kinase in stress related transcription and cell cycle regulation, as well as in genotoxic stress response.

Four alternatively spliced transcript variants of this gene encoding distinct isoforms have been reported.

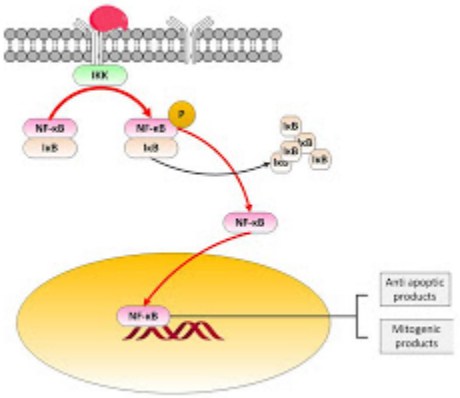
[20][3] http://www.ncbi.nlm.nih.gov/gene/6714

[21][4] http://www.ncbi.nlm.nih.gov/gene/1432

NF-κB

We have discussed this before. We reiterate what that discussion contains. NF-κB is a transcription factor that resides in the cytoplasm. It is called Nuclear Factor and was identified by David Baltimore as an enhancer factor for the κ chain of Ig light chain in B lymphocytes. When activated it moves to the nucleus and is a transcription factor in activating over 400 genes. It is activated by a large number of stimuli and its action of a large gene set causes significant DNA activity. NF-κB appears on 10q24 and is somatic and acts in a dominant manner.

We now depict this putative pathway based upon the work of Kwang and Aggarwal. This is shown below. Activated NF-κB is clearly an activator of an anti-apoptosis process in the nucleus. The paper by Huang et al shows that blockade of NF-κB is an effective suppressor of angiogenesis, invasion and metastasis of prostate cancer.



MMP-9

As NCBI states[22][5]:

Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. Most MMP's are secreted as inactive proproteins which are activated when cleaved by extracellular proteinases.

The enzyme encoded by this gene degrades type IV and V collagens. Studies in rhesus monkeys suggest that the enzyme is involved in IL-8-induced mobilization of hematopoietic progenitor cells from bone marrow, and murine studies suggest a role in tumor-associated tissue remodeling

We shall discuss MMP in detail when we summarize the ECM.

[22][5] http://www.ncbi.nlm.nih.gov/gene/4318

cdc42

As NCBI states[23][6]:

The protein encoded by this gene is a small GTPase of the Rho-subfamily, which regulates signaling pathways that control diverse cellular functions including cell morphology, migration, endocytosis and cell cycle progression. This protein is highly similar to Saccharomyces cerevisiae Cdc 42, and is able to complement the yeast cdc42-1 mutant.

The product of oncogene Dbl was reported to specifically catalyze the dissociation of GDP from this protein. This protein could regulate actin polymerization through its direct binding to Neural Wiskott-Aldrich syndrome protein (N-WASP), which subsequently activates Arp2/3 complex. Alternative splicing of this gene results in multiple transcript variants.

The Extracellular Matrix

The ECM has often been neglected when discussing cancer pathways. Weinberg has multiple references but does not seem to place it in any specific spotlight. In Lewin, Cell, the discussion is quite well focused but yet there is but passing reference to the impact on cancer pathways. Specifically in Lewin on p 850 there is reference to MMP-9, here a metalloproteinase, and melanoma[24][7].

The ECM is the collection of molecules that lie between the cell walls. The ECM provides for structural integrity as well as facilitates and even participates in cell to cell communications. The ECM is a highly complex and quite active element in the ongoing life of the cells. In addition we all too often look to what happens in a cell, with at best a nod to ligands, and we do not look at the cell internals as well as the ECM as a holistic system totality. The work of the Fisher Team in a small way may help refocus this effort on the complex as a working whole.

We will follow Lewin and deal with the principal participants in the ECM. There are a wealth of books which focus on this area.

Collagen

[23][6] http://www.ncbi.nlm.nih.gov/gene/998

[24][7] As NCBI states: "*Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. Most MMP's are secreted as inactive proproteins which are activated when cleaved by extracellular proteinases. The enzyme encoded by this gene degrades type IV and V collagens. Studies in rhesus monkeys suggest that the enzyme is involved in IL-8-induced mobilization of hematopoietic progenitor cells from bone marrow, and murine studies suggest a role in tumor-associated tissue remodeling.*" see http://www.ncbi.nlm.nih.gov/gene/4318

Collagens provide structure support. They are triple helical proteins wrapped to provide that supporting structure between the cells. There any many types of collagen and the actually assembly commences within the cell and the semi-finished product passes through the cell wall to the ECM. For our purposes the collagen complexes are at this time of limited interest.

Fibronectin

Fibronectin facilitates the process of connecting cells to matrices of collagen. Fibronectin proteins have a six element structure. Cells bind to fibronectin via receptors called integrins. The fibronectin binding thus activates pathways within the cell, thereby establishing an intra and intercellular pathway complex. The pathways activated control growth, movement and cell differentiation.

We can now examine some of the relevant literature on fibronectin and melanomas. As Yi and Ruoslahti state:

Fibronectin is a prototypic extracellular matrix (ECM) protein that is deposited by various types of cells into an adhesive fibrillar meshwork of protein (1). Fibronectin, and ECM in general, control many cellular functions, including growth, migration, differentiation, and survival. The signals that control these behaviors are transmitted from the ECM to the cell by integrins, a family of transmembrane receptors (2, 3). Malignant cells often bypass the ECM–integrin signaling system; they are not bound by the spatial constraints imposed by the ECM on normal cells, and they no longer require ECM contact for survival

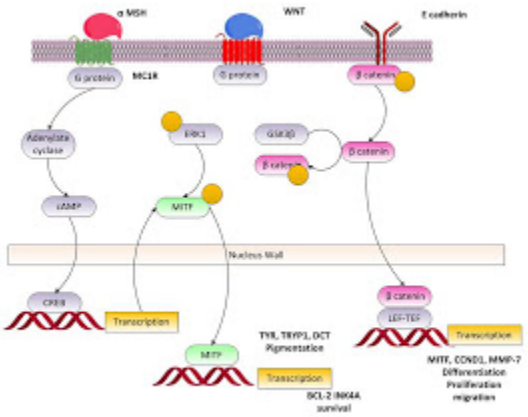
Liu et al state:

Tumor cells frequently exhibit decreased adhesiveness due to failure to deposit stromal fibronectin (FN), permitting more rapid proliferation, migration, invasion, and metastasis. Although up-regulation of FN has been noted in gene profiles of carcinomas compared with normal tissue, reduced FN expression has been described at the peripheral margins of invading tumors. In this study, we investigate the role of FN in cancer behavior. … Neoplastic transformation is often characterized by changes in the organization of the cytoskeleton, decreased cell adhesion, and aberrant adhesion–mediated signaling (2). Disruption of normal cell adhesion contributes to enhanced proliferation, migration, and invasion leading to metastasis. Fibronectin (FN) is an extracellular matrix protein with putative roles in mediating these actions. Indeed, tumor cells with decreased adhesiveness frequently fail to deposit stromal FN (3). In particular, reduced FN expression has been noted in transformed cell lines and primary tumors (4), including thyroid cancer (3, 5, 6), where diminished FN has been identified at the periphery of invasive tumor margins. In this context, we found that down-regulation of FN stimulates thyroid cancer cell proliferation and tumor growth (7). Conversely, 1, 25-dihydroxy vitamin D3 treatment increases cell adhesiveness and inhibits cell proliferation and tumor growth through enhanced FN expression.

We will come back to fibronectin in out later analysis.

E-cadherin

We have discussed E-cadherin at length in previous work. It plays a critical role in stabilizing cell adhesion and localization. Loss of E-cadherin results in loss of cell localization and thus cell movement. Specifically in melanocytes the cells begin to leave the basal layer and migrate upward as in melanoma in situ and downward as in superficial spreading melanoma.



As Swiatoniowski et al state:

Integrins are molecules which play a significant role in cell-extracellular matrix (ECM) interactions. They interact with the RGD tripeptide of fibronectin (FN), one of the main components of ECM. Labile expression of FN has been proven to play an important role both in the normal developmental process (morphogenetic movements) and in the course of carcinogenesis … Many authors have implicated loss or decrease of EC expression as an independent negative prognostic marker in breast cancer patients (6-9). There is increasing experimental evidence for a relationship between the EC level and different features of breast cancer, including histological grade (7, 16) and axillary lymph node involvement (13-16)…. In conclusion, our experiment revealed no prognostic value for EC or FN expressions in a homogenous group of patients

Proteoglycan

Proteoglycans are single polypeptide with multiple sugars attached. They provide for hydration in the ECM.

Protease

The proteases are ECM proteins which function to degrade the refuse in the ECM. The metalloproteinases are a family of proteases. They are also called MMP. MMP-9 and MMP-2 are ones of the MMPs often associated with melanoma.

There has been extensive work examining the MMPs and melanoma some dating back to the 1990s, see that of Luca et al. A recent result by Hoffman et al state:

Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are involved in tumour progression and metastasis. In this study, we investigated the in vitro and in vivo expression patterns of MMP-1, MMP-2, MMP-3, MMP-9, TIMP-1 and TIMP-2 mRNA and protein in a previously described human melanoma xenograft model. This model consists of eight human melanoma cell lines with different metastatic behaviour after subcutaneous (s.c.) injection into nude mice. MMP-1 mRNA was detectable in all cell lines by reverse transcription polymerase chain reaction (RT-PCR), but the expression was too low to be detected by Northern blot analysis. No MMP-1 protein could be found using Western blotting. MMP-2 mRNA and protein were present in all cell lines, with the highest expression of both latent and active MMP-2 in the highest metastatic cell lines MV3 and BLM. MMP-3 mRNA was expressed in MV3 and BLM, and in the non-metastatic cell line 530, whereas MMP-3 protein was detectable only in MV3 and BLM.

None of the melanoma cell lines expressed MMP-9. TIMP-1 and TIMP-2 mRNA and protein, finally, were present in all cell lines. A correlation between TIMP expression level and metastatic capacity of cell lines, however, was lacking. MMP and TIMP mRNA and protein expression levels were also studied in s.c. xenograft lesions derived from a selection of these cell lines. RT-PCR analysis revealed that MMP-1 mRNA was present in MV3 and BLM xenografts, and to a lesser extent in 530. Positive staining for MMP-1 protein was found in xenograft lesions derived from both low and high metastatic cell lines, indicating an in vivo up-regulation of MMP-1. MMP-2 mRNA was detectable only in xenografts derived from the highly metastatic cell lines 1F6m, MV3 and BLM. In agreement with the in vitro results, the highest levels of both latent and activated MMP-2 protein were observed in MV3 and BLM xenografts.

With the exception of MMP-9 mRNA expression in 530 xenografts, MMP-3, MMP-9, and TIMP-1 mRNA and protein were not detectable in any xenograft, indicating a down-regulated expression of MMP-3 and TIMP-1 in vivo. TIMP-2 mRNA and protein were present in all xenografts; interestingly, the strongest immunoreactivity of tumour cells was found at the border of necrotic areas. Our study demonstrates that of all tested components of the matrix metalloproteinase system, only expression of activated MMP-2 correlates with increased malignancy in our melanoma xenograft model, corroborating an important role of MMP-2 in human melanoma invasion and metastasis.

We shall see the impact of MMPs as we examine the pathways.

Integrins

Integrins are for the most part the receptors for ECM proteins. They are one of many such cell surface receptors. The integrins play important roles in cell homeostasis and cell to cell communications.

MDA-9

Let us briefly examine the gene MDA-9 and its protein Mda-9 and what is known and how it has evolved. Now MDA-9 is located on (8q12). As the NIH data base states:

The protein encoded by this gene was initially identified as a molecule linking syndecan-mediated signaling to the cytoskeleton. The syntenin protein contains tandemly repeated PDZ domains that bind the cytoplasmic, C-terminal domains of a variety of transmembrane proteins. This protein may also affect cytoskeletal-membrane organization, cell adhesion, protein trafficking, and the activation of transcription factors.

The protein is primarily localized to membrane-associated adherens junctions and focal adhesions but is also found at the endoplasmic reticulum and nucleus. Alternative splicing results in multiple transcript variants encoding different isoforms[25][8].

In the paper, Src kinase activation is mandatory for MDA-9/syntenin-mediated activation of nuclear factor-κB, by H Boukerche, H Aissaoui, C Prévost, H Hirbec, S K Das, Z-Z Su, D Sarkar and P B Fisher, the author's state:

The scaffolding postsynaptic density-95/disks large/zonula occludens-1 (PDZ) domain-containing protein melanoma differentiation associated gene-9 (MDA-9)/syntenin is a tandem PDZ protein overexpressed in human melanoma, and breast and gastric cancer cells. MDA-9/syntenin affects cancer cell motility and invasion through distinct biochemical and signaling pathways, including focal adhesion kinase and p38 mitogen-activated protein kinase (MAPK), resulting in activation of the nuclear factor (NF)-κB pathway.

MDA-9/syntenin also promotes melanoma metastasis by activating c-Src, but how c-Src regulates NF-κB activation is unclear. Using a human melanoma model, we document that MDA-9/syntenin–c-Src interactions are positive regulators of NF-κB activation. Inhibition of c-Src by PP2 treatment, by blocking c-Src or mda-9/syntenin expression with small interfering RNA, or in c-Src (−/−) knockout cell lines, reduces NF-κB activation following overexpression of mda-9/syntenin or c-Src.

Deletion or point mutations of the PDZ binding motif preventing MDA-9/syntenin association with c-Src reveals that both PDZ domains, with PDZ2 being the dominant module, are required for activating downstream signaling pathways, including p38 MAPK and NF-κB. We also document that MDA-9/syntenin–c-Src complexes functionally cooperate with NF-κB to promote anchorage-independent growth, motility and invasion of melanoma cells. These findings underscore PDZ domains of MDA-9/syntenin as promising potential therapeutic targets for intervening in a decisive component of cancer progression, namely, metastatic tumor spread[26][9]*….*

(MDA-9 Acts as a PDZ domain-containing adapter protein. In adherens junctions, it couples syndecans to cytoskeletal proteins or signaling components. Seems to be required for the targeting of TGF-alpha to the cell surface in the secretory pathway. By virtue of its association with a large number of additional proteins, including class B ephrins, TGF-alpha,

[25][8] http://www.ncbi.nlm.nih.gov/gene/6386

[26][9] http://www.nature.com/onc/journal/v29/n21/pdf/onc201065a.pdf

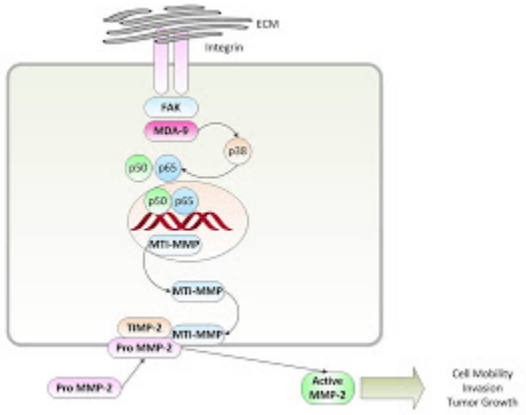
phosphotyrosine phosphatase, neurofaschin, neurexin, schwannomin/merlin, IL-5 receptor, various glutamate receptor subtypes, and the syndecan family of heparan sulfate proteoglycans, MDA9 has been implicated in diverse processes, including protein trafficking, activation of the transcription factor SOX4, cytoskeleton-membrane organization, and cell adhesion/migration….

(MDA-9) Its expression is induced by IFN-gamma in melanoma cells. Is believed to be involved in cancer metastasis. In melanoma, it promotes the metastatic phenotype by activating NFkB and focal adhesion kinase (FAK), which promotes induction of matrix metalloproteinase (MMP) and then migration and extracellular matrix invasion of melanoma cells. Syntenin is overexpressed and promotes cell migration in metastatic human breast and gastric cancer cell lines.

The gene product is also called by many other names, specifically:

1. MDA9
2. MDA-9
3. TGF alpha cytoplasmic domain interacting protein18
4. TACIP18
5. SYCL
6. Syntenin-1
7. Syndecan binding protein 1
8. SDCBP
9. Melanoma differentiation associated protein 9

From Das et al. we have the following modified figure[27[10]]:



Das et al state regarding the above pathway model:

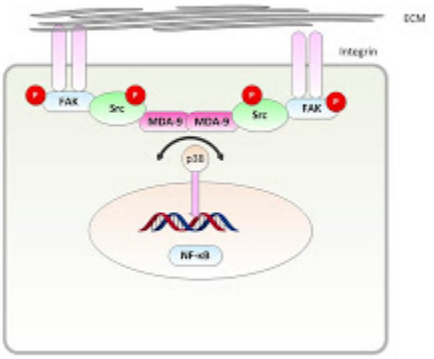
Schematic diagram for mda-9/syntenin mediated NFκB activation. Upon interaction with ECM (fibronectin), MDA-9/syntenin activates the p38/MAPK by augmenting FAK phosphorylation. This results in degradation of IκBα and movement of p65 from the cytoplasm where interaction

[27[10]] http://www.bioscience.org/2012/v17/af/3911/fulltext.asp?bframe=figures.htm&doi=yes

[27[11]] Pecorino, Molecular Biology of Cancer, Oxford (New York) 2nd Ed, 2005.

with p50 results in binding to target genes (MT1-MMP) resulting in enhanced production of MT1-MMP, which interacts with TIMP-2 activating pro-MMP-2 to produce active MMP-2. This product then enhances cell motility, invasion, and cancer cell growth. mda-9/Syntenin activates the NF-kB pathway.

The original Figure appears to be from Boukerche et al as shown with some mods below:

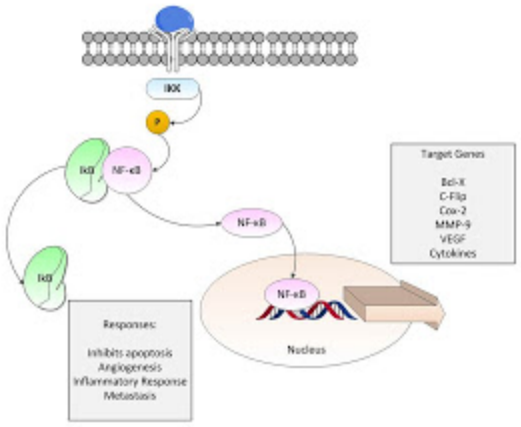


Note the differences. First the original shows multiple integrins and multiple FAK binding and in turn a binding of MDA-9 initiating the p38 pathway. Also note the explicit presence of NF-κB and its result of genes forcing mobility, invasion and metastasis. The authors state:

Hypothetical model of signal transduction pathways coordinately regulated by MDA-9/syntenin through its interaction with c-Src. MDA-9/ syntenin interaction with c-Src results in clustering of c-Src/FAK signaling complexes at high concentrations on the plasma membrane. The activated c-Src/FAK complexes activate the p38 MAPK/NF-κB pathways that regulate expression of genes involved in migration and invasion and thus play a crucial role in MDA-9/syntenin-mediated tumor progression.

The initiation of NF-κB is a significant factor since this transcription factor is what appears to be the instigator of the metastatic processes.

From Pecorino, p 220, we have again presented the details (as modified)[28][11]:



The above graphic clearly demonstrates the movement of the transcription factor into the nucleus, from a bound state with IkB to an unbound and active state. The target genes indicated includes an MMP gene which again goes into the ECM.

As Sarkar et al state:

*Melanoma differentiation associated gene-9 (*mda-*9), also known as syntenin, is a PDZ domain–containing adapter protein that is involved in organization of protein complexes in the plasma membranes, regulation of B-cell development, intracellular trafficking and cell-surface targeting, synaptic transmission, and axonal outgrowth. Recent studies now define a seminal role for* mda-*9/sytenin in cancer metastasis.*

Thus, Sarkar who is part of Fisher's Lab at Virginia, have had a focus on Mda-9. They continue:

Adapter proteins play an essential role in modulating signal transduction from the extracellular environment to the intracellular milieu by virtue of their association with key regulatory molecules … mda-*9 was originally cloned as a gene differentially expressed in human melanoma cells reprogrammed to terminally differentiate by combination treatment with IFN-h and the protein kinase C activator mezerein … Analysis of the subcellular distribution of mda-9/syntenin revealed its localization at the areas of cell-cell contact in cells of epithelial origin in colocalization with F-actin, syndecan-1, E-cadherin, h-catenin, and a-catenin (12). In fibroblasts, mda-9/ syntenin localizes to focal adhesions and in stress fibers. Overexpression of mda-9/syntenin in different cells induces the formation of plasma membrane structures, including ruffles, lamellipodia, fine extensions, and neurite-like structures, showing its role in regulating the structure and function of the plasma membrane…*

They continue:

The major characteristic of malignant tumor cells is their ability to invade foreign tissues and form metastatic foci at distant locations in the body. Such a process requires tumor cell attachment to various matrix proteins, degradation of the extracellular matrix (ECM) mainly by matrix metalloproteinases (MMP), followed by migration into the surrounding stroma by tumor cells…A model of progression of melanoma suggests that it begins by conversion of a normal

melanocyte into a benign nevi, subsequent transformation into a radial and then a vertical growth phase primary melanoma, and finally evolution into a metastatic melanoma.

Finally Sarkar et al outline the overall set of functions which MDA-9 is involved in. Specifically they state:

1. ***Interleukin-5 signaling.*** *mda-9/syntenin interacts with interleukin- 5 (IL-5) receptor a and the transcription factor Sox4, thus mediating IL-5–induced Sox4 activation …*

2. ***Cell-surface trafficking.*** *Although mda-9/syntenin is located predominantly in the plasma membrane, it is also identified in the early secretory pathway such as the endoplasmic reticulum, intermediate compartment, and cis-Golgi, thus facilitating cellsurface trafficking of secreted molecules such as proTGF-a, an epidermal growth factor receptor ligand…*

3. ***mda-9/syntenin and ephrin signaling.*** *Ephrins and their cellsurface tyrosine kinase receptors are implicated in controlling axon guidance and fasciculation …*

4. ***Mediation of cohesiveness of epidermal stem cells.*** *In the basal layer of interfollicular epidermis the stem cells are clustered, a feature known as cohesiveness. These cells express high levels of Notch ligand D1, which is important for maintaining cohesiveness …*

5. ***Regulation of glutamate signaling.*** *The excitatory neurotransmitter glutamate interacts with its cognate receptors and regulates postsynaptic excitatory currents. Glutamate receptors interact with mda-9/syntenin, …*

6. ***Regulation of axon outgrowth.*** *Unc51.1 is a serine/threonine kinase that is important for neurite extension/parallel fiber formation in cerebellar granule neurons. mda-9/syntenin interacts with Unc51.1 and Rab5, a member of the Ras-like small GTPases that is a marker of early endosomes and is essential for endocytic membrane fusion and trafficking. …*

Boukerche et al in 2005 stated:

Studies using an enhanced green fluorescent protein mda-9/ syntenin fusion protein showed that endogenous mda-9*/syntenin colocalized with the E-cadherin complex and syndecan-1 at adherens junctions as well as with focal adhesions and stress fibers at cell-substratum contact in fibroblastic and epithelial cells. These findings suggest that* Mda-9*/syntenin might promote cytoskeletal organizational changes and intracellular signaling.*

The organization of these dissimilar focal contacts is complex but was shown not only to contain the appropriate integrin but also cytoskeletal proteins (vinculin, talin, and a*-actinin) as well as several cytoplasmic protein tyrosine kinases, including members of the src family and focal adhesion kinase (FAK). Despite extensive research documenting an ability of* mda-9*/syntenin to form multivalent interactions, little is known about the role of* Mda-9*/syntenin in cancer development.*

Boukerche et al (2008) state:

Prior studies confirm that Mda-9/*syntenin stimulates motility through pathways involving FAK, p38MAPK, and NF-κB, leading to secretion of MMP-2 (4, 9). However, despite these intriguing observations, it is not fully understood how* Mda-9/*syntenin orchestrates these signaling molecules to enhance cancer cell motility and metastasis. A complex network of protein-protein interactions characterizes the structural organization of focal adhesions, involving known signaling molecules that play functional roles in various cellular activities and other less well-defined pathways.*

We presently show that Mda-9/*syntenin interacts with c-Src through its PDZ domain and activates the c-Src/FAK signaling pathway to maximize tumor cell motility and anchorage-independent growth of melanoma cells.* Mda-9/*Syntenin levels directly correlate with increased c-Src activity in a human melanoma model that closely mimics the early events of metastasis in humans.*

In 2010 Boukerche et al report (also in Fisher's Lab):

MDA-9/syntenin affects cancer cell motility and invasion through distinct biochemical and signaling pathways, including focal adhesion kinase and p38 mitogen-activated protein kinase (MAPK), resulting in activation of the nuclear factor (NF)-kappaB pathway.

MDA-9/syntenin also promotes melanoma metastasis by activating c-Src, but how c-Src regulates NF-kappaB activation is unclear. Using a human melanoma model, we document that MDA-9/syntenin-c-Src interactions are positive regulators of NF-kappaB activation. Inhibition of c-Src by PP2 treatment, by blocking c-Src or mda-9/syntenin expression with small interfering RNA, or in c-Src (-/-) knockout cell lines, reduces NF-kappaB activation following overexpression of mda-9/syntenin or c-Src.

Deletion or point mutations of the PDZ binding motif preventing MDA-9/syntenin association with c-Src reveals that both PDZ domains, with PDZ2 being the dominant module, are required for activating downstream signaling pathways, including p38 MAPK and NF-kappaB. We also document that MDA-9/syntenin-c-Src complexes functionally cooperate with NF-kappaB to promote anchorage-independent growth, motility and invasion of melanoma cells.

These findings underscore PDZ domains of MDA-9/syntenin as promising potential therapeutic targets for intervening in a decisive component of cancer progression, namely, metastatic tumor spread.

Observations

This set of papers from the Fisher Lab present several interesting connections between the ECM and the intra-cellular signaling paths. We have had prior arguments that one can develop models for metastasis by examining the cell as a target entity and then by modeling the environment, both the ECM and surrounding cells as influences on the target cell. In this work we can expand it to include ECM factors in some detail.

The suggested control of other pathway elements, beyond just the B-RAF control that we now have may be proven productive. Notwithstanding it does establish a research path that is based upon established cell dynamics.

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Labels: Cancer

MONDAY, NOVEMBER 26, 2012

WHAT IS AN EDUCATION?

I have been following the growth of the MOOCs closely including taking several for a better understanding. Posner has recently opined on the topic and I suspect he has not sampled the broth so to speak. So far I have tried MIT and Harvard, and as noted regarding the MIT course I had taught it a few decades ago.

Posner states:

The format seems superior to the conventional lecture. The average quality of the lecturers is much higher, because there is no limit on the number of students "attending" the lectures and so no reason why any student should be stuck with a mediocre lecturer. The online format has other advantages. The student can scroll back, or fast forward—in short can go at his own speed, which he could not do in a live lecture. A first-rate lecturer can communicate more effectively than a textbook (and of course the student can supplement the lecture with a textbook), and, of great importance, one doesn't have to travel anywhere to attend an online lecture. One can obtain in effect a first-class American college education wherever one lives and however little money one has. All you need is a laptop computer and an Internet connection. There is a problem of asking questions of the lecturer in a class of ten thousand students, but some MOOCs solve it by allowing students to post questions that the student body votes on, and only the most popular questions are put to the lecturer.

Well yes and no. I have found them a bit disorganized. They seem to take what may work in a classic lecture format and then throw together what they think works on a web based system. My major concerns are of a bit higher level. For example:

1. Why are the universities doing this? It costs money and they already spend like drunken sailors. Just look at any campus today and you see the costs in buildings, one after the other. Build a building and you have a century or two of costs keeping it up. That in may analysis is the major driver in the exploding costs base. So the issue is why add more costs.

2. What is success? How do you know you succeeded?

3. What is failure? This is the all too critical factor. When do you call it quits. Or does this just

keep going on?

4. Who is the target market? What are the quality measures? etc.

5. How do we avoid ambiguity of expectations. The university is we assume altruistic just trying to help people. But what do the people expect, say the student in India. Is a certificate from MIT worth anything? First we have no idea who took the course, not necessarily the person whose name is on the certificate. There is no authentication. If the student wants more than say just better understanding the material, how is that done. Will there be a back lash?

6. Posner states that one can get a first rate college education. Perhaps, but doubtful. The experience oftentimes require the preparation for admission, the peering relationships inside a university, the interaction with faculty. I had 350 students and between myself and my staff we knew each student personally, their strengths and weaknesses, their problems and their capabilities. That can never be accomplished here as presently structured.

Posner continues:

On the supply side of the MOOC market, there is the problem of developing a viable business model. As long as the market for MOOCs is limited to the first two groups of demanders—persons seeking intellectual enrichment and persons seeking marketable skills—the costs of providing the product are very low. They primarily consist of modest bonuses for the lecturers—modest because most lecturers would consider a huge expansion in their audience to be a substantial bonus in itself, as well as auguring a likely very large market for their textbooks, though the overall market for textbooks will decrease as MOOCs catch on. On the benefits side, even without sale of advertising space or the charging of an enrollment fee, MOOCs provide cheap advertising for the colleges and universities that provide the lecturers.

Indeed the viable business model is key. If MIT raises tuition $10,000 per year because they want to do this charitable work, then the students who are paying and who competitively got admitted are bearing the burden, or the alumni who have been cajoled to contribute, at least for the first round or two. Then again without a viable business model this may all come to naught.

Is there something here? Yes, indeed there is. In the mid 1950s I took College Chemistry on what became PBS today at 6 AM. It was in a TV series called Continental Classroom. Every morning there was a lecture, you had to watch at 6AM, take notes, do the problems, and send them in. Did it work? Yes for a short while, but I guess there may have been 10 to 20 other kids like me who would do that religiously. This was before AP Chemistry, and besides I had 4th Year Latin and First Year Greek instead at school.

The challenge will be to find the business model. It must be a business, the students must contribute something, perhaps based upon a country standard, and there must be some authentication. Then and only then is this something which makes sense.
Labels: Academy

SATURDAY, NOVEMBER 24, 2012

3500 KCAL PER POUND

I am always amazed by the "researchers" seeking genes for obesity. Seek and ye shall find. You can find a gene for anything. But as we have said over and again, 3500 Kcal equals a pound, almost always. You eat too much you get fat. Simple. Why we are wasting money studying this in a genetic manner befuddles me. In a recent piece they state:

A large international study has identified three new gene variants associated with body mass index (BMI) levels in adults. The scientific consortium, numbering approximately 200 researchers, performed a meta-analysis of 46 studies, covering gene data from nearly 109,000 adults, spanning four ethnic groups....

The researchers uncovered three novel signals, from the genes TOMM40-APOE-APOC1, SREBF2 and NTRK2) that were significantly associated with BMI in adults. All had previously been linked to other important disorders. The APOE locus is well known to be involved in blood lipid regulation and circulation, and plays an important role in Alzheimer's disease. The SREBF2 gene is in the same family as SREBF1, linked to type 2 diabetes in another CardioChip study. Finally, NTRK2 codes for a receptor of the BDNF protein, which is known to be related to BMI and is associated with the eating disorder anorexia....

Guo concluded that "while the individual effects of each gene may be small, they may provide fundamental clues to the biology of adult obesity." He added that further studies will investigate gene-gene interactions for the same trait.

Stop in a fast food restaurant and what does one see, volumes of food, obese people. What effect does any gene have in general, none. It is input, less output, equals net accumulation. The individual effects are indeed small, it is the over consumption. It is the massive plate size, the pile of french fries, the shakes. One need just wait on line at a super market and see the morbidly obese food stamp recipients adding more to our health care burden. This is a real problem and trying to hide it in the genes if creating an excuse for an epidemic. Cancer is genetic in many aspects, why no spend time and money there. Why spend a single penny on obesity genes when we know the answer.
Labels: Obesity

MORE ON EDUCATION

As one spends time on a holiday it often revolves around re-reading books on the shelves which are good friends, ones worth coming back to again and again. For me it is Copleston and his History of Philosophy. In describing the Later Stoics Copleston states:

IN the early Roman Empire the chief characteristic of the Stoa is its insistence on the practical and moral principles of the School, which take on a religious coloring, being bound up with the doctrine of man's kinship with God and his duty of love towards his fellow-men. The noble morality of the Stoa is strikingly displayed in the teaching of the great Stoics of the period, Seneca, Epictetus and the Emperor Marcus Aurelius.

At the same time a certain tendency to eclecticism is visible in the Stoa as in other Schools. Nor was the contemporary scientific interest absent from the Stoa: we may think, for example, of the geographer Strabo. We are fortunate in possessing an extensive Stoic literature from this period, which enables us to form a clear idea of the teaching of the School and the characteristics of its great personalities. Thus we are well provided in regard to Seneca's writings and we have four of the eight books in which Flavius Arrianus reported the lectures of Epictetus, while the Meditations of Marcus Aurelius show us the Stoic philosopher on the Roman throne.

L. Annaeus Seneca of Cordoba was tutor and minister to the Emperor Nero, and it was in obedience to the latter's command that the philosopher opened his veins in A.D. 65.

As we would expect of a Roman, Seneca emphasizes the practical side of philosophy, ethics, and—within the sphere of ethics—is more concerned with the practice of virtue than with theoretical investigations into its nature. He does not seek intellectual knowledge for its own sake, but pursues philosophy as a means to the acquirement of virtue. Philosophy is necessary, but it is to be pursued with a practical end in view. Non delecter.: verba nostra, sed prosint—non quaerit aeger medicum eloquentem .'

His words on this topic not infrequently recall those of Thomas a Kempis, e.g. plus scire quam sit satis, intemperanliae genus est. To spend one's time in the so-called liberal studies without

having a practical end in view is waste of time—unum studium ver; liberate est quod liberum facit...

I believe that this makes my point about education and perhaps the intellectually stranded Harvard undergraduates may find some wisdom in places perhaps they have avoided, the past.
Labels: Academy

FRIDAY, NOVEMBER 23, 2012

THE PURPOSE OF AN EDUCATION

The Harvard Political Review has a piece on the attack on liberal arts. They state:

If you plan to major in philosophy, the American government will stop at nothing to prevent you.

"Become an engineer. Study science or math," politicos of every rank and label say. "Don't bother with the mushy humanities."

In almost all places, they'll try to convince to put down Proust and pick up an engineering textbook; in some states, they'll incentivize you monetarily.

Now there are some issues here.

First, very few are competent to become engineers. You do not train engineers, they are educated. The effort is considerable and the time spent often exhausting. Harvard does not have an Engineering school, they call it something like Applied Technology. A small center hidden between the Law School and the main campus. Engineering is hard, just as hard as science. You just do not change from English or Fine Arts and get a degree i Chemical Engineering or Pure Math.

Second, the engineer always studies some amount of liberal arts; I did philosophy, history, psychology, logic etc. Thus the statement that the engineer or scientists is devoid of the arts is nonsense.

Third, to be successful I needed to understand the language and history of each country I worked in. That I learned prior to entry into the market. I understood Czech and Russian history, I understood the Greeks, I spoke Greek and Russian, but it was necessary to effect a good business relationship, and having an engineering degree I readily had the tools to learn what was needed.

They continue:

John Dewey, the United States' most enduring educational scholar, saw the virtue of vocational education. But unlike today's policymakers he also saw the necessity of the liberal arts. "The world in which most of us live is a world in which everyone has a calling and occupation, something to do," he wrote in his 1900 book, The School and Society. "But the great thing … is that [through a broad curriculum] each shall have had the education which enables him to see within his daily work all there is in it of large and human significance." A welder should be taught not just to weld, nor a tailor just to sow, nor a computer scientist just to type code. Each should be taught to appreciate his or her profession, appreciate why it is vital to the world around them. An education should satisfy and demystify, not just teach a single task that may be quite menial and, by itself, unsatisfactory.

First, Dewey was a socialist, and at times a Communist, after all he defended Trotsky, and his educational views were the antithesis of the Individualism that made America. He was the inventor of Group Think, the education of the masses to act as a mass. Dewey was an advocate of Trade Schools, training students in a collective manner to be "citizens", namely automatons in a collectivist society. One need just read Dewey, painful as it may be.

Second, somehow we have abandoned Trade School education, focusing on that goal of a liberally educated person. There was a time that one could be trained to be an electrician, a plumber, a carpenter. Then the Unions took over, drove the education and training out of the schools and embedded it in their collective and closed groups for self aggrandizement.

The Harvard student may most likely obtain employment due to connections, not necessarily due top an ability to be productive. I have found High School grads often more capable than most Liberal Arts grads. Perhaps the change in the current economy may make a shift to an education that leads to a productive and profitable "job". It really is not a bad idea.
Labels: Academy

WINDMILLS OF THE MIND

As a guest blogger, I have taken this opportunity to provide some of my insight on the state of alternative energy development in our country. Recently, I have seen many alternative energy sources at work, or at least attempting to work. As you may know, our current president has attempted to implement new energy resource plans to help "create jobs." In a recent speech the same individual actually said that "We've doubled our use of renewable energy."

From the photo above, it is readily seen that this is in fact not in the slightest of way true, at least for the systems which I have encountered. The above windmills were motionless, several dozens of such motionless windmills. You see, there is just not enough wind, unless of course there are flocks of birds flapping their wings to get them moving. I suppose this was not in the Nobel Prize winning physicist's plan who enacted them in out wonderful Department of Energy.

As we have gone through these many states, I have been able to see innumerable instances of our tax dollars going to waste, windmills at the top of hills barely moving, generating is any, just enough to power a normal one hundred watt light bulb. Is this success? I think not.
Labels: Guest Blogger

THURSDAY, NOVEMBER 22, 2012

HAPPY THANKSGIVING

The Mayflower, as displayed in the MIT lobby, a small craft which somehow defines this country. Then again there were all those Spanish trips and the Dutch who in 1609 ran about on the Hudson River. Thanks to the local and the turkey we manage to consume in excess. But no matter, have a happy Thanksgiving.

Labels: Commentary

SATURDAY, NOVEMBER 17, 2012

COASE AND EXAMPLES

Coase's Theorem is a powerful statement. I have used it an dozens of examples over the years, especially in contradistinction it with Pigou Taxes. They are not exactly parallels or even perpendiculars but they do present some ways to viewing them.

The classic Coase example is the farmer and the railroad. The farmer grows corn and the railroad goes past the farmers field, it sets out sparks. From time to time the sparks may burn down the farmers corn. Should the Government establish rules and regulations to prevent this or do we just the courts, assuming zero transaction costs, settle the argument. Note the zero transaction cost issue.

Let me go a bit further, Let us assume that we allowed the death penalty in civil cases, especially one regarding financial fraud. Would we be better off not having Government regulation but just having Civil Courts with Death Penalty ability to mediate claims. Would Madoff have done what he did, would Bear Stearns still exist? Just think of the extreme.

Now Frances Wolley has raised some fine discussions regarding this. As she states:

In The Problem of Social Cost, Ronald Coase argues that the outcome is "the same whether or not the cattle-raiser is held responsible for the crop damage brought about by his cattle". As long as it is clear who is liable for the crop damage, and there are no costs of negotiating a settlement, "the ultimate result (which maximises the value of production) is independent of the legal position".

In other words, it doesn't matter who is responsible for building the fence, as long as the cost of the fence is less than the cost of the crop damage, the fence will be built - and in the least costly fashion.

Now I have never taken the approach of detailing a Coase example, I have just argued its application and its consequences in extreme cases as above.

Now Frances has raised several interesting issues as do the comments attached thereto. I think my examples of Coase may add a bit to the discussion, but one must always remember the zero transaction costs assumption. Now with the over abundance of Administrative Laws, it may be said that we may never ever again see even close to zero transactions cost.
Labels: Economics

WHY USE SOCIAL MEDIA?

I was an early Facebook user, back when I was still at MIT. I can from time to time see what is happening via my grandson's portal to Facebook. Not that I understand any of it. You see, social media has become a clutter of concatenated comments by people who have not the faintest idea about what they are commenting on.

Now here comes the comment police, the algorithms from Silicon Valley types who believe that they hold the key to societal and cultural norms. At least that seems to be the gist of the NY Times piece. The article states:

... fighting obscenity can be good for business. Impermium, a Silicon Valley company that helps Web sites deal with unwanted reader comments, has begun marketing technology that identifies "all kinds of harmful content — such as violence, racism, flagrant profanity, and hate speech — and allows site owners to act on it in real-time, before it reaches readers." Impermium will police the readers — but who will police Impermium?

Interesting. This is from California, not known for anything much other than entertainment, some high tech, high taxes, and well a few other strange things. They will now establish our cultural norms in a social media context. But this really poses the question on how do we get our ideas out there. I often wondered about this, I even wrote a paper on it a few decades ago, pre-Web.

But I have made several observations:

1. In my blog, you may be reading it now, about 50% of my ever increasing readers are from outside the US. This is unlike so many other blogs which tend to focus on local issues or concerns.

2. I decided to no allow comments on my blog. The reason, if someone wanted to comment send it to me and I will reply. I will even post the comment and reply if worth the effort. Well just look at Facebook, are any of the comments of any value, many are just automatic additions. If someone thinks through an issue it is clearly worth a discussion.

3. On my company site I have taken to posting updated drafts of books. One of them had had 20,000 downloads! For a relatively obscure site I often wonder how anyone has gotten there. From time to time I get comments.

4. The Web Police as of this time do not seem to be out sanitizing blogs or company sites. But if one reads this article perhaps they soon will be doing so as well. You see this blog is a free gift of Google, nice of them but it does give them editorial rights. What if I said something they do not approve of? Will they edit what I say? They did so apparently for the Chinese at one time.

This article raises many interesting issues, but mostly it raises the issue of social media. What use is it? If you can be edited, and if so much detritus ends up posted on it, what is the value? Or frankly was there ever any value. I have been off Facebook for a few years now. Never missed it for a second. Never really found any value, before censoring.
Labels: Commentary, Internet

MONDAY, NOVEMBER 12, 2012

MY PHONE WORKS, WHERE IS MY ELECTRICITY?

During the hurricane, at every instance, my land line telephone worked. Dial tone, calls, in and out, no problem. But within minutes of the start of the storm, down went the power. Heavy dew or fog knocks out the electricity. Why?

They work over the same telephone poles, they both come from central stations, they both are wires, they both require power sources, and they both have repair trucks. So why?

Simple, you see that the telephone network is changing by the day, we now have broadband, wireless, sophisticated communications devices, world wide networks, and the list goes on. Power production and distribution has frankly not changed one bit in almost 150 years! They still use the same generators, same wires, same poles, same transformers, and frankly the same sockets.

One of the reasons is education. We have thousands of highly skilled telecom engineers, making changes to modulation, multiple access, network management, protocols. We have hundreds of universities educating them, and the industry absorbs them at a premium. Yet when was the last time we had a PhD in power engineering? MIT no longer teaches it, it has not taught it since before 1960 to my memory. I found this out when I took a Doctoral written exam at Northwestern, just to try it, and they did there, DC motors and power transmission lines. But I suspect that 1966 was the last time they did that. They even had vacuum tubes, but alas that was the end of that as well.

We just have no quality power types, no high tech capability in an entire industry. I remember back in the 50s, if you were smart you tried to get to Bell Labs or ATT, if you were a slacker you went to Con Ed.

Thus the key problem is that the industry has no R&D, no place for smart innovative people, and it seems to be managed by "managers" whose best talents are in keeping the maximum rate of return for a utility.

The industry is shameful for its long lack of investing in high tech solutions. The national grid network is an example. It is on a par with water distribution or sewer pipes. Can Government do anything? The answer is also a simple, no! Just look at DoE, since the early 1970s it has wasted hundreds of billion on electric cars. Sound familiar. Then batteries, then solar. It is clear that there is a major set of challenges, but to meet them will require a major upheaval of the utility mindset, the mindset that seems to see it fine to have tens of millions sent to the darkness while the dial tone still work.
Labels: Energy, Politics, Technology

WHAT THE EUROPEANS THINK

There is an interesting piece from Le Monde:

Nombreux sont ceux qui voient en la chancelière allemande la reine sans couronne de l'Europe. Quand on pose la question de savoir d'où Angela Merkel tient son pouvoir, on est renvoyé à l'une des caractéristiques qui définissent sa façon de faire : une habileté machiavélique.

NOW THAT IS A RATHER STRONG ACCUSATION EVEN FROM A FELLOW GERMAN!

Labels: Europe

C-MYC, SYSTEMS MODELS, AND CALIBRATION

We briefly examine the result and then we attempt to place it in the context of a full system model.
There has been a recent set of papers regarding the proper reference setting of microarray DNA expression data. The authors of the study argue that the methodology used in ascertaining the effects of one transcription protein, c-Myc, may exhibit significant and substantial errors.

The c-Myc Analysis

A review of the papers and related discourse has been provided in Science[29[1]].

[29[1]] See Marshall, in Science 2 Nov 2012, http://www.sciencemag.org/content/338/6107/593.full

The author of the Science review states:

(The authors)…argue that Myc*'s cancerous effects are much broader than most people have assumed, and that a flawed experimental method may have thrown off a decade's worth of* Myc *research…*

The problem highlighted by the Myc *studies may sound modest, but after thinking about it for a year, Levens and Young don't see a simple fix. The only way to update the older work on* Myc *and gene expression, they say, is to go back to the lab and redo the experiments. That view, Young says, causes "the most angst" among biologists. He says he understands the "desperation" of bioinformaticists seeking a way to tweak existing data into better shape, but he can't offer one that doesn't require lab work.*

Levens suggests that this problem arose partly because scientists viewed Myc *as a "master regulator of master regulators," one that sends a signal along defined pathways to an array of specific targets that send out additional signals, creating a dizzying pattern of interactions. In reality, Levens says, "*Myc *is not a high executive making lots of decisions but a dumb bureaucrat enforcing a rule." And the rule itself seems pretty simple: If a gene is expressed, increasing* Myc *in nearly all cases increases that gene's level of expression. Genes that are already highly expressed are boosted more, so the impact of* Myc *is "exponential," Levens says.*

The broad effects of Myc *were overlooked, according to Levens and Young, because the standard procedure in gene-expression experiments has been to use similar quantities of RNA from the samples being compared and to normalize results to mean RNA. Young calculates that this practice erroneously deflates* Myc*'s effects two- to threefold. He says it also creates the impression that some genes are turned down when they are not.*

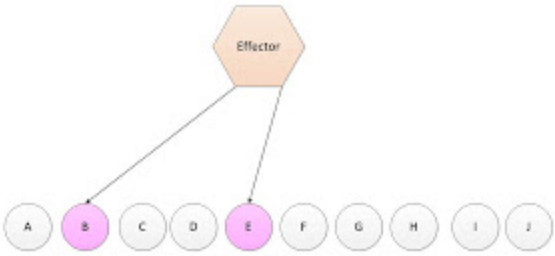
The paper by Louven et al states[30[2]]:

Gene expression analysis is a widely used and powerful method for investigating the transcriptional behavior of biological systems, for classifying cell states in disease, and for many other purposes. Recent studies indicate that common assumptions currently embedded in experimental and analytical practices can lead to misinterpretation of global gene expression data. We discuss these assumptions and describe solutions that should minimize erroneous interpretation of gene expression data from multiple analysis platforms.

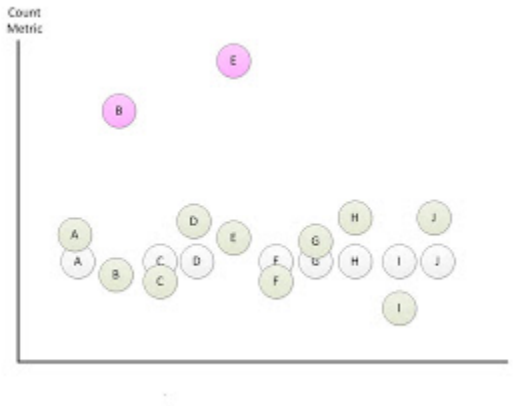
Let us examine what they are saying. We shall slightly reproduce their argument. Let us consider two cases.

First, we assume a limited transcriptional response. Namely we assume that say c-Myc activates and transcribes genes B and E. We demonstrate this below where we show what we believe nature is truly doing:

[30[2]] Louven, et al, Revisiting Global Gene Expression Analysis, Cell, 151, October 26, 2012.



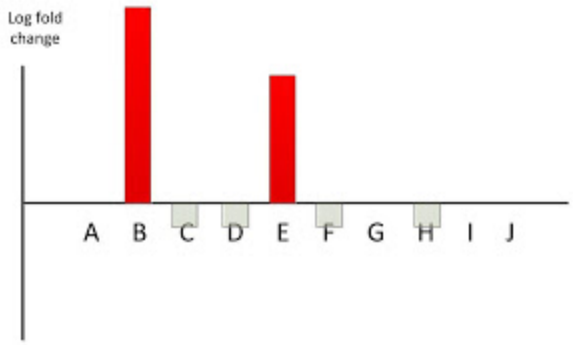
Now we examine via say a microcell analysis the expression of the transcribed RNA and we plot the expression for each gene when we have the effector and when we do not. Namely when a condition such as a cancer is present and when we know it is not. The objective is to ascertain whether there is some gene expression which we can then putatively relate to say this specific cancer. Perhaps we can use it as a target for therapy. If we were to plot for each gene the intensity of expression as measured in a microarray analysis we may get the following chart.



Note in the above that we have a cluster of unexpressed genes and just two expressed genes. The expressed genes have a higher count and thus stand out. Now what the authors propose is that we:

1) Normalize the chart above. Namely set a normalized value of say 1.0 count metrics,

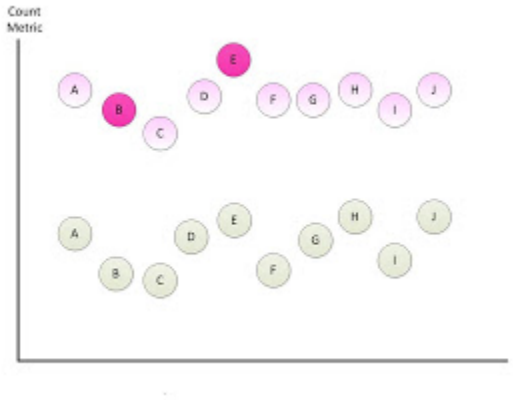
2) Then plot a log of what they call the fold changes. Simply this is a plot which accentuates large variations while de-emphasizing small ones. The resulting chart is as follows:



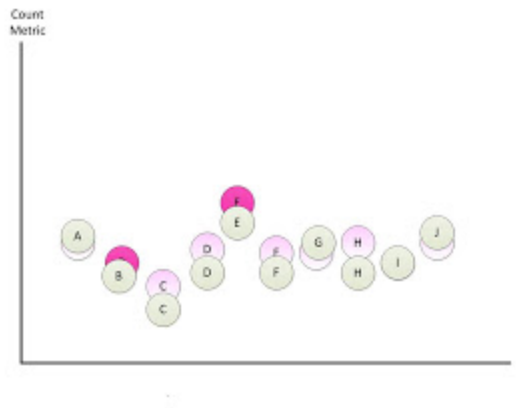
Thus we see that the two genes putatively expressed are identified as standing out in the process. This they authors argue is what researchers have assumed and have been doing.

Now the authors argue that in fact a protein like c-Myc actually activates a whole set of transcriptions. They call this transcription amplification. It results in all genes being activated and transcribed.

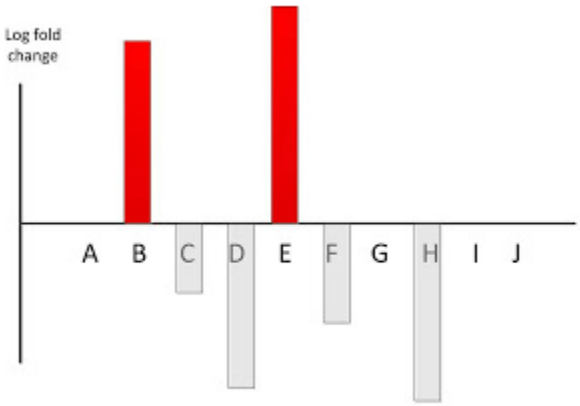
In the case of transcriptional amplification we obtain a plot as follows:



But now when we normalize it we obtain:



Note that now they align somewhat closely but using the log metric again we can get them to be expressed.



We may not be seeing the correct answer it is argued. The normalization is a concern and, it is argued, fails to truly represent the expression involved. The solution is to use “spiked in” RNA standards. When that is done we have the following:

Note that now we have all positive expressions. This is the response that was anticipated and it is obtained by using the reference set of RNA to standardize the data.

The authors conclude:

Our results indicate that spike-in controls of the type described here are a robust, cross-platform method to allow normalization to cell number and thus enable more accurate detection of differential gene expression and changes in gene expression programs. The clear implication is that the use of spike-in controls normalized to cell number should become the default standard for all expression experiments, as opposed to their more limited use in experiments where gross changes in RNA levels are already anticipated, as exemplified by transcription shutdown experiments …

When cell counting may be problematic, as for expression experiments from solid tumors or tissues, DNA content may be used as a surrogate if ploidy and DNA replication profiles are also characterized to prevent the introduction of a DNA content-based artifact.

The discovery of transcriptional amplification and the realization that common experimental methods may lead to erroneous interpretation of gene expression experiments has implications for much current biological research.

How prevalent is misinterpretation of genome-wide expression data due to the assumption that cells produce similar levels of total RNA? The answer is likely related to the prevalence of regulatory mechanisms that globally amplify or suppress transcription. What are the implications for classifying cell states in disease? Significant effort is being devoted to expression profiling cancer cells and these studies use standard normalization methods …

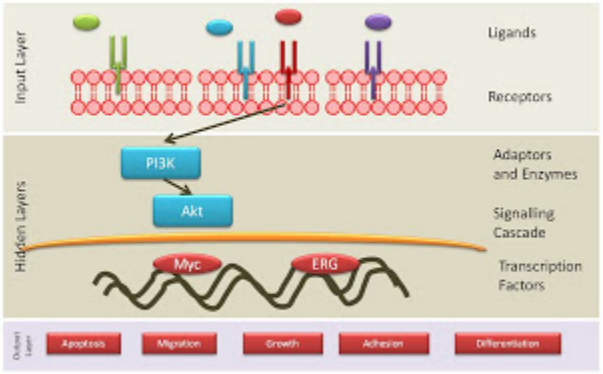
Because c-Myc expression occurs at widely varying levels in various tumor cells, transcriptional amplification is likely having a profound impact on cancer cell signatures. Where expression data are being used to gain insights into cancer cell behavior and regulation, it should be interpreted with added caution.

There is great validity to these conclusions but as the Science article states it may force a massive re-examination of many of the results from prior analyses.

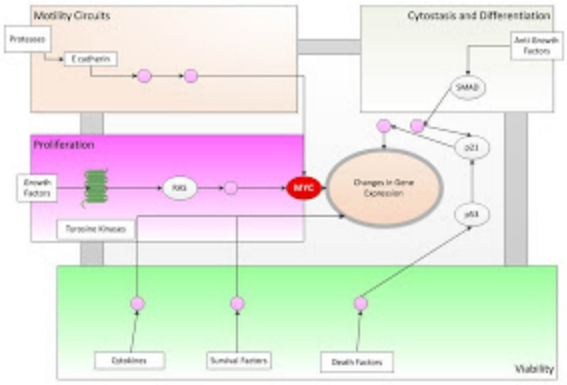
Pathway System Models

c-Myc is a strong transcription factor and is implicated in many cancers. It also is examined as we look for other gene expressions which may be diagnostic, prognostic as well as targets for therapeutics. Thus there is undoubtedly a great significance. We briefly look at the system elements of c-Myc.

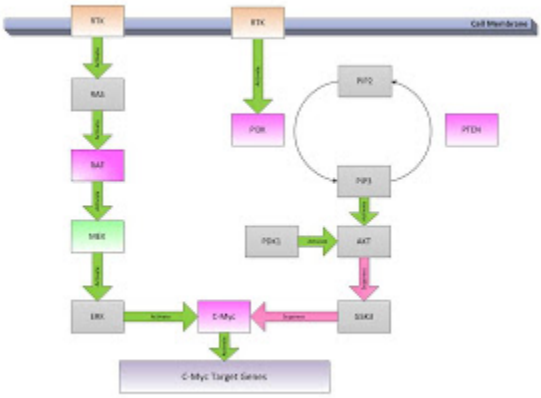
First, we display the generic Weinberg model below. This is the ligand, receptor signalling and transcription factor model with the resulting elements of growth, migration, apoptosis, adhesion and differentiation. When we look at c-Myc we are looking at one element in a chain, with inputs and outputs and resulting changes in state. We must always remember that we are examining a system of interconnected elements.



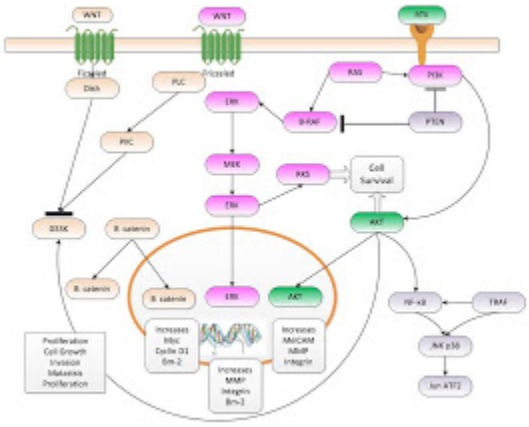
Now we can take the detail a layer below. Here we show c-Myc being the dominant transcription factor in the changes in gene expression. It is a driver, it makes genes transcribe more than they would usually in many cases and this in turn is one of many elements that result in the change of state in cells. Remember it is one of many. Remember also that it is single elements in a chain of related, more importantly, interrelated, genes which are expressed.



Let us examine two driving pathways. We have detailed these is our studies of melanoma and prostate cancer. We have seen in them the drivers above such as PTEN and B-RAF genes and their protein products.

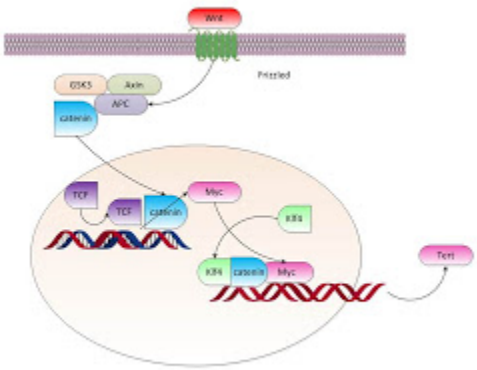


Finally the total complexity can be modeled as we show below.



Ultimately we have multiple genes and gene products which are arranged in a system manner and which we are seeking the driving models for these elements. We have discussed this previously, namely we know that there are scores of interrelated genes which "drive" other genes, directly as transcription factors or indirectly as drivers of transcription factors.

In the final description of c-Myc below we show the actual transcription of c-Myc and then its use as a transcription factor and the resulting down chain products. This complete analysis will be critical when assembling a measurement methodology and validation.



1 OBSERVATIONS

As with many other results of this kind they often raise more issues than they solve. We will just comment on a few.

1. Normalization: Normalization and reference levels are always key to understanding the results. We have examined this factor in microarrays before. We have also examined this in our analysis of flower color tessellation, attempting to reconstruct pathways from spectroscopic analysis of cell by cell anthocyanin expression. It is a standard problem. However we have argued that by having a system model and using identification techniques we have two key factors: first, we have a model which link elements together; second, we have a model with end points which allow for consistency testing.

2. System Models: We have argued that having a system model for gene and gene product interaction is essential to validate measurements. We believe that system models allow for three key results:

- Linkages: The system models expressly stipulate linkages between products and in turn their activation capacities. These provide substantial added elements for normalization.

- Boundary Constraints: The system models allow for the checking of boundary values. Namely do the results make sense?
- Identification Metrics: The system models also provide a strong basis for identification methodologies to be used to identify new linkages.

3. Validation: Validation of data is key. This means more than just calibration. Validation means true causality. As we have noted it seems that each and every day one sees more genes related to more diseases than ever before. But one must always question the issue of causality.

Labels: Cancer

SUNDAY, NOVEMBER 11, 2012

VETERAN'S DAY

In honor of our veterans, now and then.

Above an advancement ceremony aboard the USS Constitution. Below the officers and men of the USS Albert W. Grant, 1943.

Commissioning Exercises A. W. GRANT Charleston Navy Yard November 1940

Dr. Mathieu 2nd row left. Crissy just right of "Mike". BB Lyon just right of lecturn. Jerry Marsh. 2nd row between Crissy and Lyon. I'm on the far end front row.

Some of the above did not survive WW II. They lost their lives in service to their country in the Battle of Leyte Gulf, October 1944. To their memory.
Labels: Commentary

SUNDAY, NOVEMBER 11, 2012

MIDLAND BEACH AND THE HURRICANE

I worked as a lifeguard at Midland Beach for five years. I remember as a young teenager in the early 50s the results of the then hurricanes flooding up to Hylan Boulevard. I remember taking a dive with my father along Hylan Blvd looking at the hundreds if not thousands of flooded beach houses, still under water a day or two after the hurricane. But then they were sparsely occupied, most of the land was grass, Floyd Bennett Field had just closed, but all the homes were flooded out. I do not recall any loss of life but the damage was complete. This happened several years in a row, a hurricane cycle.

I wrote just before this current hurricane that perhaps this was the time again for extreme flooding. Regrettably I was right, it came as it had before. The NY Times writes as if it were a once in an eternity even but the result of global warming etc.

But perhaps we should beware. In the early 50s before global warming, the hurricane came year after year for almost five years. Midland Beach was always under water, before people moved there in droves. It was a natural flood plain. It will always fill up under the right circumstances, again and again.

Perhaps a trillion dollar flood wall would help but also perhaps not building there would help as well. There is really nothing new. It will happen again, and if the past is any indication, it may happen again soon, global warming or not. Thus the question is if there should be a rebuild. Nothing has changed. Mother Nature will do what she does, and we suffer the consequences.

It is the same with the outer banks, the barrier sand bars which we call the Jersey Shore. Beautiful, but they are subject to the ravages of the ocean. Perhaps we should have a conversation regarding just how far we want to defy the ocean.

As the Times notes:

Asked if the deaths in Midland Beach reflected a failure of the city's evacuation efforts, he responded that the term "failure" might apply "if the city didn't have a plan and this came upon us and we were going on the fly." But he added: "A hurricane is a foreseeable thing." "We have a plan for that," he said, "and we've done it."

There were warnings, there were notices, there was even history, if one dared look. Midland Beach had many tragedies, but the warnings were there. The past also tells us that soon after one hurricane, there may very well be another. One cannot stop them.

Labels: Weather

SATURDAY, NOVEMBER 10, 2012

RULES FOR SPIES, OOOPS

Back in the 70s I inherited a few folks who had been in MI5 in earlier times. Traveling around with them, between scotches and awful cigarettes, I heard many a tale. But I was always told about the three rules of spydom.

They were simply:

1. Trust no one.

2. Never put it in writing.

3. Always have a second exit.

Now I had an Irish friend who expanded in the first; Never trust anyone, not even your father. I suspect the Mossad would have said "Mother" but one gets the point.

Now the recent flap in DC is somewhat startling. It seems to have violated all three rules at once. Trust no one, not even your biographer. Never put in writing, especially in your gmail account. And where was that second exit?

What is especially strange is that affairs are more common than tennis lessons in DC. It seems that power has some strange effect. Money, as in New York, is more exhausting and much less tuned in on the fancies of the DC market.

But also strangely, back in the 70s, I knew a retired DDA when the Agency decided that gays could stay as long as everyone knew about it. Sort of the opposite of "Don't ask, don't tell." It was "Ask whatever, and I tell you all.". It worked, once out in the open you were no longer a target. Thus affairs in that environment were a non issue as long as everyone knew. Thus an even more strange result.

Thus one suspects that in this world of spydom, where nothing is ever what it appears to be, the others shoes will inevitably drop, one at a time.
Labels: Commentary

THURSDAY, NOVEMBER 8, 2012

RATIONING?

As I had indicated with theory and fact that rationing of any form exacerbates the problem, it seems that the insanity is catching on. As the NY Times states:

With gas lines in New York City still stubbornly long and no relief for gas shortages in sight, Mayor Michael R. Bloomberg imposed an odd-even gas rationing rule Thursday that goes into effect at 6 a.m. tomorrow. Identical rules are going into effect in Nassau and Suffolk Counties on

Long Island tomorrow..

The mayor said the measure, imposed by emergency order and similar to one put in place in 12 New Jersey counties by ***Gov. Chris Christie on Saturday that has been considered effective,*** *should cut down lines and allow gas stations to stay open later. ...*

Violations of the gas rule are class B misdemeanors, punishable by up to three months in jail...

In New Jersey, by comparison, Governor Christie said Thursday morning, "I've driven around the state the last two days and I've barely seen any fuel lines any more. There's order, there's plenty of gas."

Now we are criminalizing human existence. And by the way, the who considers them to be effective. The stations are still closed by Government dictum, the shortage still exists and it is a creation of Government. I just drove a few miles and see station after station closed by the local police. The police have not for one second looked at aged residents to see if they are alive and well, they are assigned gas station closing duty. It is worse than any poorly managed Communist country.

It is truly a shame where this country is headed.
Labels: Commentary

HARVARD CONSERVATIVES' POST

The Harvard Conservatives' Blog has an interesting post:

Tonight's biggest loser and biggest winner

Tonight's biggest loser in the Republican Party, looking forward, is Chris Christie. His career in presidential politics is over. Ironically enough, he was probably the only R who could have beaten Obama this year. Tonight's biggest winner? Marco Rubio.

There is a certain amount of truth to that. We really do not have any Marcus Aurelius types around. As the snow encircled, as the Government created gas shortage increased, as the power remained off, I longed for the jungles of Thailand, where one could get gas, water, electricity, good health care, the King is a Harvard Med grad, and even a good hot meal. New Jersey has collapsed totally and I suspect it will not be forgotten.
Labels: Politics

MONDAY, NOVEMBER 5, 2012

COMMON SENSE ON MEDICARE

In NEJM there is a brief note regarding Medicare and corrections which can and should be made to it. They state:

Medicare was always intended not just to increase access to care but to protect the elderly from financial ruin.

We agree and we had proposed that with our various plans. Although I do not agree with all the proposals there should be some core propositions which must be addressed:

1. Move age eligibility upwards to 70 as life span increases.

2. Increase Medicare from 3% to 4% over some time frame.

3. Make it for catastrophic coverage, it should help the truly needy.

4. Have some payments from the participants.

5. Provide essential coverage not total coverage.

6. Scale back or scale up costs for those with higher incomes.

There must be a dialog here. Catastrophic coverage is essential, we want to make certain that people are not left destitute. However total coverage must be addressed. We currently pay for too much. Means testing will become essential and age adjustments are critical as well. It is readily solved, if we want to.
Labels: Health Care

WHAT BUSINESS ARE YOU IN GOOGLE?

My adventure with my now defunct Nexus 7 continued today. As expected when I called Google Customer Service their approach was the "I feel your pain" approach, namely avoid solving the customer's problem by talking in a soothing manner. It is the "California way". Well it does not work in New Jersey on a New Yorker after a week without power in a 100 year hurricane. I never understood psychiatry anyhow, just load them with haldol.

All I wanted was to find out how to get a replacement. All "Jon" wanted was to make certain I never got one. He "sensed" my stress. Why for the good Lord's sake there was no stress, stress was when the 80 mph gust knocked the 200 foot ash tree on my roof when I was sitting inside, mild stress at that.

So did I get anywhere, did any of the disappointed customers seem ever to get anywhere? Not really. Google seems to have trained its CSRs, in my opinion based on doing this stuff for 50 years, so as to "calm" the irate customer but to accomplish nothing. Not a good way to solve a customer problem.

Thus, I again ask; what business is Google in? Their flag ship search business is splendidly executed and has tremendous bran loyalty. I love it. However when you go into a different field, specifically hardware and products, customer service is essential. Quality of the product is sine

qua non, and resolving your own problems must be seamless. It is not.

I thus did what I said I would do, sent it to the Chairman, he an I sat on some Government panels in the past, and frankly I await no response. Just a few hundred dollars down the proverbial drain.

The most important thing for a company to do is to protect its reputation. The actions taken by Google are, in my opinion, counter to that approach.
Labels: Google

SUNDAY, NOVEMBER 4, 2012

CARTER AND CHRISTIE

Now I am old enough to remember all the gas shortages, 1973 and 1979. In 1979 with Carter there was the odd and even dictum, as Christie has instituted in New Jersey. Lines of cars waiting for gas.

Now this is a simple queueing problem. In queues there are three inputs and one output for example.

The inputs are:

1. The Arrival Rate

2. The Holding Time

3. The Number of Servers.

Now there are other subtleties as well but let us look at a simple queue. The output in a simple analysis is say the average queue length.

Now let us examine what odd and even does.

1. Arrival Rate: The arrival rate is driven by human factors here. If there were no restrictions, say during a normal period, people will wait till their tank is well below half knowing that they can get gas anywhere. Thus they get gas at say a quarter a tank. Now when you restrict gas, say by this odd and even deal you get people getting anxious. They see then tank below 3/4 or 2/3 and they start looking to top off. So the arrival rate then doubles or triples.

Also the State has limited open hours, that further increases the arrival rate. The less hours the more people arriving during the alleged open hours. Thus by reducing open hours from 16 to say 4 we further increase an arrival rate by a factor of 4.

The total increase in arrival rate would be 8-12 time normal all due to Government action.

2. Holding Time: Frankly the time to fill a tank is dominated by delays and getting a gas server, a human. In new Jersey you must have a person pump the gas so the holding time is increased and as such it is almost independent of how much gas you get. Thus the holding time is constant.

3. Number of Servers: Well as a result of DHS and NJ restrictions not to mention the lack of electricity the number of servers is cut to less than a third, and then add the police setting limited times and controlling flows, the servers are cut even lower, I estimate to one tenth.

Now the State has further exasperated the problem by forcing certain stations in congested areas from even opening, thus withdrawing the number of servers.

The result, tremendous queue lengths. You have Government control rather than the free market, Christie has become Carter. Amazing. Now back in 1980 the analysis which I just outlined was done and it was compared to the data from the Carter lines, same as the Christie lines. The solution, get Government out of the way.

Namely the use of Odd/Even has just made things worse. They did so in 1979 under Carter and are repeating under Christie in 2012. Same theory and same data. The only problem here is that NJ license plates are a mess, very few end in numbers. So how does one choose odd and even if you end in a Z? Do you go back to the last digit, and use that, it is not what the Executive Order states. So we have more confusion. See what Government does.

Regrettably Christie has morphed into Carter. There appears to be no one who has any understanding of simple queues, some folks did at Bell Labs, but they are gone. Politicians always seem to make the same mistakes. History is doomed to repeat itself.
Labels: Commentary

NEXUS VS KINDLE

I got a Nexus 7 when it first came out. It was wonderful. Then as the hurricane came in it just died. Just sat there and went black.

So I decided to write a review commenting on the fact. I stated:

The device was wonderful, while it worked. I had a Kindle Fire which is much more durable but much less functionality. The Google SW and OS worked splendidly but the ASUS product appears to be a fiasco, especially if one reads the reviews. I have always had concerns in Google overextending their brand. The ASUS quality seems to be grossly poor in my opinion. This is not something that Apple under Jobs would have allowed. I will attempt to resolve it with Google but given the reviews I have little hope. This will unlikely be a severe blemish on Google and I anticipate a nice note attached to this review by some ASUS entity but quite frankly automated comments do not remedy poor execution. Unfortunately, I ordered five more for my grandchildren and I now anticipate the money down the drain! I also suspect ASUS will not be responsive, but time will tell!

As expected, within seconds of posting there was a negative review. It must be some ASUS automaton. Or perhaps a Google robot. Let's see how we can track this! As I watch the negatives increase, I find it impossible that any potential buyer noticed this review. There must be some automatic responding mechanism, as I have found with certain other Amazon reviews, such as Microsoft. This only adds to the negative review by having the vendors, in my opinion, "smash" down the review so that it is not seen! Smart but people do talk and perhaps they should find out who they are smashing.

Now a decade ago Eric Schmidt and I were Chairman and Co Chair of the Presidential Commission on Internet 2. We got to know each other well and as Google proceeded I had concerns that they must focus on what they do well. Thus the Motorol deal was in my opinion a bad one, good for the patents but the hardware business is not compatible with the service business. Now the Nexus was a good idea for expanding the Nexus platform. But! That assumes that your vendor, ASUS delivers a quality product. Looking at the reviews it is clear that ASUS has some real problems.

Further it appears that either ASUS or Google is smashing reviews which are negative on Amazon. Frankly that may be on the verge of legality, in my opinion, namely using the wirelines to suppress free speech. But I leave that to the Department of Justice. In a matter of less than one hour there were over 6 negative reviews. That makes no sense given it is an obscure review. Clearly the vendor in my opinion is hammering down any and all negative reviews. Rather unethical, even more a reason not to purchase from Google et al. Pity, watch the reputation dissolve!

But the problem is that Google will be tainted by the ASUS poor quality. Google will be the recipient of the bad name, frankly no one in my opinion ever would buy an ASUS anything. But what is interesting is the almost real time attempt to smash down negative reviews. I will keep all posted! Especially after I send Eric the defunct Nexus 7.
Labels: Google, Quality

MONDAY, OCTOBER 29, 2012

SAT, TEST PREP, AND REALITY

Now I am old enough to have taken the PSAT and SAT in the 50s. Yes, that long ago. I went to a classics oriented secondary school where the emphasis was on Latin, Middle English, Solid Geometry, etc and less on what was becoming contemporary requirements in the public arena. So one day in early Junior year we all got called into to take what was the PSAT. Frankly I had no idea what it was and just punted, after all I was in the midst of Cicero and who really cared about wasting a morning on a test. Needless to say I did not do well and it was not until the results came in that I realized that these tests had some importance.

Now as a student of a good Catholic school I knew that my best chances were to ask my friends at the local Jewish Community Center what to do. The CYO just played basketball and that would not be a viable career option. So off to the intersection of Forest Avenue and Victory Blvd and seeking wisdom, the answer was the Bronstein and Wiener course at the Commodore Hotel in NY (now the Hyatt) on Saturday mornings. So I took my lifeguard funds, signed up and every Saturday, for what I believe was ten weeks, I went amidst this crowd of intent exam passers and along with the exam review book, of which I did every problem and memorized every word, I then was prepared for the December SAT.

Now there is also a technique for taking the SAT. It was at Curtis HS near Port Richmond. I was primed. I arrived dressed casually, as one did in the 50s, and just sat with no evidence of last minute preps. I did not even have a pencil! I looked around saw some acquaintances and just asked what they thought of the dance last evening. Dance!

They all were studying! What I wondered. I had a secret, I prepped with the most aggressive mental animals in New York City for months, my group would make the products of Tiger Moms look like wimps, my group was the descendants of Feynman, Rockaway Beach, Stuyvesant, Bronx Science, Brooklyn Tech, mad intellectual animals, all seeking MIT admission, no one ever thought of wasting time at Harvard and Princeton was after all in New Jersey and Yale could never be found amidst the mess there in New Haven. Besides MIT was a factory, we all understood factories.

The next trick is to finish with more than half the time left. I accomplished that task easily, then stride outside and wait on the corner until the others come out. The look on the faces of the exam takers as you walk up less than half way trough looking totally at ease and hand in your exam. It terrifies the rest, and I would guess drop their scores at least 100 points!

Now for the results. Not only perfect but I found mistakes, yes my readers the SAT had errors. Not only had they told me that prep was useless and that was totally wrong but they had made mistakes. I wrote then but all I received was a form letter informing me of the fact that others had also informed them. Were they sorry? No, after all they are the SAT!

Now to why this rant if you will. In the NY Times there is a brief discussion regarding SATs and prep. It states:

Q: Several readers have found incredible your assertions that test-prep activities and tutoring have only minimal impact on students' scores. Are you truly suggesting that such resources are not beneficial enough to pursue? Why do you offer test-prep materials on your Web sites, and what is your response to tutors who write that their test-prep techniques have been successful?...

***Ms. Juric**: While the idea that test-prep activities do not materially improve SAT scores may seem counterintuitive, several highly respected independent organizations — including the National Association for College Admission Counseling (Nacac) — have conducted research showing that to be the case.*

My response, Balderdash! Those kids with me at Bronstein and Wiener in the Commodore, they showed up at MIT. Personally I just about doubled my score from the PSAT, adjusting for baseline. If you do not know the vocabulary then you will not do well, if you have not read extensively, you will not do well, if you have not drilled the math style, you will not do well.

The answer was evasive at best, use someone else to cover for you perhaps. Counter-intuitive, to say the least. What is clear is that a personal commitment to excel is essential. But it is like studying for the Medical Boards or the Bar, you just have to consume many facts but at the same time you must not have to spend time understanding the question, it should be clear from prior practice.
Labels: Education

SUNDAY, OCTOBER 28, 2012

WAITING FOR THE HURRICANE

In the early 1950s, when I lived on Staten Island, I remember the hurricanes that hit New York, especially Staten Island. The areas down by the beaches were well under water, today there must be billions of dollars of homes and major hospitals. I wonder how they will fare.

This will be an interesting exercise in human response. We have buttoned down everything, have batteries, water, secured the outdoors, generator, sump pumps, back up sump pumps, hand pumps etc. Prior planning prevent poor performance, perhaps.

It will be undoubtedly a total loss in power for days, that after all is how the power company operates, they get paid only after a disaster and at premium prices. It seems that our Government officials really do not give a shilling. But alas the following week is election week, we shall see the effect.

One good thing, it hopefully keeps the teenage monsters from our door on Halloween. God acts in strange ways. Or be careful what you pray for!
Labels: Commentary

WEDNESDAY, OCTOBER 24, 2012

PSA TESTING AND CONCENSUS

NEJM just released a poll regarding the continuing use of PSA tests. They state:

We received 958 votes from readers in 67 countries. A little over half (55%) of all voters recommended PSA screening for the man in our clinical vignette — a split that revealed the lack of clinical consensus surrounding this important issue. North American voters preferred to screen with PSA testing: 59% of 489 voters from the United States and 67% of 46 Canadians voted in favor of PSA screening. European voters were less enthusiastic, with only 47% of 217 voters in favor of PSA screening.

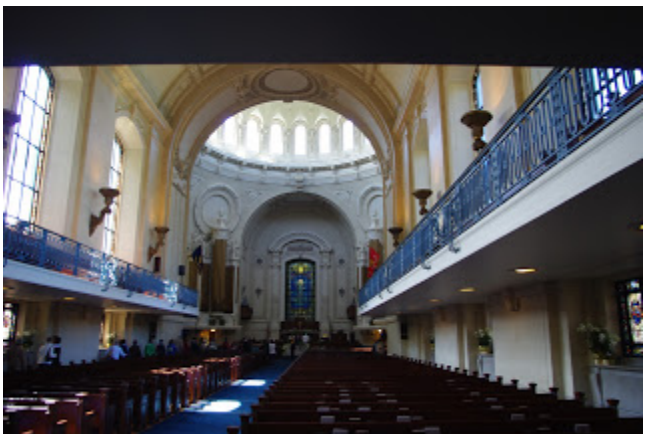
They continued:

A large number of respondents remarked that they recommended PSA screening on the basis of personal experience with elevated PSA levels that led to life saving treatment. Other respondents believed that data from the European Randomized Study of Screening for Prostate Cancer provide compelling evidence that PSA screening saves lives. Finally, a number of comments touched on patients' fears with regard to cancer diagnosis, and some clinicians were of the opinion that measuring the PSA level can reassure a patient that his physician is actively performing surveillance.

But as we had noted before the European Trial did PSA tests with 4 year intervals. As we have argued before the 4 year interval is the equivalent of not even testing. Thus it can be argued that the European tests are invalid in terms of their conclusions.
Labels: Cancer, Health Care

TUESDAY, OCTOBER 23, 2012

THE US NAVY, WHERE DOES IT GO



The US Navy has had and continues to have a unique role in US international presence. On the one hand it has the function of protecting the ocean borders of the United States, apart from the policing actions of the Coast Guard. Second, it has the duty to ensure that US interests are protected abroad, from threats, from attacks, and the like. For example if an enemy fleet of whatever type were to attempt to breach the borders of the United States by sea then the Navy has the duty to protect those borders. Also if U.S. ships, persons, or even business were under threat on foreign seas or lands then the Navy has the prime duty to send defense to protect those interests. That is assuming they are allowed to.

Thus two decades ago the 6th Fleet roamed the Med and if a Libyan attack had occurred then the fleet could launch jet attack aircraft in minutes and helicopter relief ships in less than two hours. Now we have most likely a few tugs in the Med, thus the Libyan disaster. Naples is at best a port of repair, and the Med is open to all comers.

The Admirals of the type of King, Nimitz, and Spruance seem no longer to exist, those there are politically tuned and thus avoid conflict and in my opinion confuse the mission.

Let us examine the current fleet. There are 287 Deployable Battle Force Ships. Amongst that there are only six Aircraft Carriers composed of the following**:** [31[1]]

USS Enterprise (CVN 65) - 6th Fleet
USS Nimitz (CVN 68) - Pacific Ocean
USS Dwight D. Eisenhower (CVN 69) - 5th Fleet
USS George Washington (CVN 73) - South China Sea
USS John C. Stennis (CVN 74) - 5th Fleet
USS Harry S. Truman (CVN 75) - Atlantic Ocean

Also there are only 6 Amphibious Assault Ships comprised of the following:

USS Peleliu (LHA 5) - port visit Phuket, TH
USS Wasp (LHD 1) - Atlantic Ocean
USS Bataan (LHD 5) - Atlantic Ocean
USS Bonhomme Richard (LHD 6) - port visit Sepangar, MY
USS Iwo Jima (LHD 7) - 5th Fleet
USS Makin Island (LHD 8) - Atlantic Ocean

The typical Carrier Group is composed of 6-10 ships:

1. 1 Carrier: The carrier provides a wide range of options to the U.S. government from simply showing the flag to attacks on airborne, afloat and ashore targets. Because carriers operate in international waters, its aircraft do not need to secure landing rights on foreign soil. These ships also engage in sustained operations in support of other forces.

[31[1]] http://www.navy.mil/navydata/nav_legacy.asp?id=146

2. 1 Guided missile cruiser multi-mission surface combatant. Equipped with *Tomahawks* for long-range strike capability.
3. 2 Guided missile destroyers multi-mission surface combatants, used primarily for anti-air warfare (AAW)
4. 1 Attack submarine in a direct support role seeking out and destroying hostile surface ships and submarines
5. 1 Combined ammunition, oiler, and supply ship provides logistic support enabling the Navy's forward presence; on station, ready to respond

Now a ship is at sea for 4 months at a time. That means that despite the fact that we have 6 Carrier groups we have only 2 at any one time deployed under full condition. Thus given the current strength of the Navy we have a truly weak presence. Thus, there most likely no way to react to Libya.

What should a naval strategy be? That is an oft debated question. Do we still need a stealthy nuclear attack fleet? Would we use it and against whom. Should the littoral fleet be expanded? Are we concerned about in close warfare, and how complex should the littoral fleet be? One of the typical Naval and DOD problems is that they take a simple ship concept such as the littoral craft and turn it into a multi-billion dollar affair. Why not keep them at say the old Fletcher class destroyers, sleek, light, and mobile. That is a swarming attack and defense force. I have written extensively about this in the past and rapid deployment and mobility at low costs are essential.

Reconnaissance can now be accomplished by various means and methods from drones to the NRO fleet of satellites. C^3I should be well developed. The Navy should have an expansive mission with plans for flexible roles in many theatres. China has one rebuilt nuclear carrier, not that they cannot build a half dozen, but deploying them would take time. Russia has reduced its presence. The nature of the enemy has changed. It is pirates in the Indian, and frankly concerns about the shores of the homeland.

Thus frankly the dismissive comments by the current president are not only to be concerned about but frankly they should be terrifying. One should remember that on 9-11 we had only 2 unarmed Massachusetts National Guard jets available for New York City. There were more Czech jest available for Prague! The prior administration had gutted national defense assuming a new century of peace and when it comes to protecting ourselves we had not one bullet.

Now the threat is magnitudes higher and the planning and execution must meet the challenge. We need Admirals who can articulate a plan, reasons for why they need what. We must not retreat into the slumber of the 1930s, with not even the fuels to set the few ships asail.

Labels: Military

TUESDAY, OCTOBER 23, 2012

COST OF DRUGS

In a recent paper by Siddiqui and Rajkumar the authors detail the costs of some of the recent cancer drugs[32[1]]. They state:

Last year, ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY) was approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma. The benefit in survival over and above standard treatment arms was 3.7 months in previously treated patients and 2.1 months in previously untreated patients. The cost: $120,000 for 4 doses. As staggering a figure as that is, the drug is hardly alone in its lofty price. We believe that the immense cost of contemporary cancer drugs signals even greater costs for future drugs.

The following Table is from their paper as modified. Note the annual costs. What are not presented are the survival rates, for example melanoma extends survival 4 months for $120,000. That is $30,000 per month.

Generic drug name	***Cancer***	***Cumulative drug cost for 1 y ($)***
Ipilimumab	Melanoma	120,000
Sipuleucel-T	Prostate cancer	90,000 for 3 doses
Bevacizumab	Various cancers, including lung and colon cancer	90,000
Paclitaxel, protein-bound	Breast cancer	80,000
Lenalidomide	Multiple myeloma	90,000
Bortezomib	Multiple myeloma	60,000
Imatinib mesylate	Chronic myeloid leukemia	70,000
Alemtuzumab	Chronic leukemias	70,000
Ofatumumab	Lymphomas and chronic lymphoid leukemias	120,000
Brentuximab vedotin	Hodgkin lymphoma	100,000
Dasatinib	Chronic myeloid leukemia	110,000

32[1] http://download.journals.elsevierhealth.com/pdfs/journals/0025-6196/PIIS0025619612007380.pdf

Now the authors proceed to argue why they are so expensive and argue as to what can be done to reduce costs. In a sense this is still health care research financed by the public and not really beneficial drug disbursement. Almost all of these drugs are at best minimal life prolongers. Perhaps we are at a very early stage where we use large populations to fund experimental protocols as well as drugs.

Labels: Health Care

MONDAY, OCTOBER 22, 2012

WAS THIS ALSO A CAUSE OF THE HOUSING COLLAPSE

We have heard a great deal about what caused the collapse of housing and the exploding US Debt. There have been many reasons for it but perhaps there is one which may truly have been at its heart, a tax policy.

In 2007 Congress passed and the President signed a change to the Tax Code, called The Mortgage Forgiveness Debt Relief Act and Debt Cancellation. Before this if you lost your house in a bad deal and the bank wrote off he mortgage you were on the hook for taxes on the loss. Short sales had the same effect. Namely the individual had an incentive to not take a lass, there was a dire penalty at the end.

As the IRS says:

If you owe a debt to someone else and they cancel or forgive that debt, the canceled amount may be taxable.

The Mortgage Debt Relief Act of 2007 generally allows taxpayers to exclude income from the discharge of debt on their principal residence. Debt reduced through mortgage restructuring, as well as mortgage debt forgiven in connection with a foreclosure, qualifies for the relief.

This provision applies to debt forgiven in calendar years 2007 through 2012. Up to $2 million of forgiven debt is eligible for this exclusion ($1 million if married filing separately). The exclusion does not apply if the discharge is due to services performed for the lender or any other reason not directly related to a decline in the home's value or the taxpayer's financial condition. ...

If you borrow money from a commercial lender and the lender later cancels or forgives the debt, you may have to include the cancelled amount in income for tax purposes, depending on the circumstances. When you borrowed the money you were not required to include the loan proceeds in income because you had an obligation to repay the lender. When that obligation is subsequently forgiven, the amount you received as loan proceeds is normally reportable as income because you no longer have an obligation to repay the lender.

Namely you had strong disincentives prior to this but now you can just walk away with no

penalty. That meant that the downside risk was zero. That meant that many people just walked, took no responsibility and let the house drag down everything

There is talk that this may be revised and renewed. I believe that such a down side risk would actually stabilize the market.
Labels: Economy

SUNDAY, OCTOBER 21, 2012

HOW WRONG CAN ONE GET

The former White House CEA head, Ms Romer, has written an amazing piece in today's NY Times. She states:

After listening to Representative Paul Ryan in the vice-presidential debate, you might think that careful evaluation isn't needed. In his view, we spent $800 billion on the stimulus, yet unemployment still rose to 10 percent — so obviously it wasn't helpful.

To understand what's wrong with that reasoning, think of someone who's been in a terrible accident and has massive internal bleeding. After lifesaving surgery, the patient still feels rotten. But we shouldn't conclude from this lingering pain that the surgery was useless — because without it, the patient would have died...

The ultimate verdict on the Recovery Act will depend in part on further studies. I believe that as more research occurs and the political rancor fades, the fiscal stimulus will be viewed as an important step at a bleak moment in our history. Not the knockout punch the administration had hoped for, but a valuable effort that improved the lives of many.

There is no ultimate verdict. Month by month, since she put out her paper, I have tracked and reported on her grossly inaccurate predictions. Fact! She has never even been close in her predictions.

The surgical analogy is absurd! In this case she promised specific improvement, by the month and by the numbers. Never Happened!

If a surgeon performed an operation and charged you a fortune and promised certain levels of specific improvement and it did not happen, welcome to a lawsuit! But in her case it just needs further study. I have been viewing the fiscal stimulus in the light of what she and her colleague said would happen, I did not make up the numbers, she did. How can one have the gall to write this?

No wonder with people like this we are in such a mess, and we keep educating more of them, or perhaps we should call it indoctrination.
Labels: Economics

SATURDAY, OCTOBER 20, 2012

FOCUS, FOCUS, FOCUS

I had commented on the Google acquisition of Motorola Mobile as at best problematic and at worst a very bad decision. Google is really in the service business. Namely people get a service from Google, search or ads, and they do not have to assemble it, it comes prepackaged. There is no inventory needed and the infrastructure is generally unseen.

The product business is quite different. Motorola Mobile is in the product business, it makes things, and the customer really does assemble them, and you need inventory. The customer sees your product for better or worse.

The culture between a product and service business is dramatically different. One sells boxes and the other the "experience" Google is great at experience, and the box business is really tough, it is competitive and one really wonders of Google made the right choice.

The patents were worth the price, the operations of the company may very well not be worth anything, in fact as we see this week they may be costly.

As the NY Times noted:

The challenges of making money in a mobile world were not the only reason that Google's net revenue and earnings per share fell significantly below analysts' expectations. Motorola Mobility, the ailing cellphone maker it recently acquired, is bleeding money.

This was not a surprise for me, the surprise is that it did not happen sooner.

As the Times continued:

Google executives took pains Thursday in the conference call with analysts to reassure investors that it was prepared for the challenges from mobile, and that it was already shifting its business models to adjust.

"Monetization on mobile queries right now is a significant fraction of desktop," Larry Page, Google's chief executive, said.

He said Google was exploring new ways to make more money as people increasingly used phones and tablets in addition to and instead of desktop computers, and said it was "uniquely positioned to get through that transition and to profit from it."

"I am not worried about this in terms of our business at all," Mr. Page said. "I think it's an opportunity for us."

The problem is that you do not have to own the farm to get the milk. One should focus on what one does well, and do it again and again, always improving it. Going astray always gets you in trouble.

Further the release of the quarterly filing the way they did should result in significant staff changes in the Finance Department, specifically extreme measures and replacements with those who understand the consequences. Too many free lunches make people sloppy.
Labels: Google

YOU REALLY CANNOT MAKE THIS UP

The Hill has a piece on the UN sending monitors to US Polls this November. They state:

United Nations-affiliated election monitors from Europe and central Asia will be at polling places around the U.S. looking for voter suppression activities by conservative groups, a concern raised by civil rights groups during a meeting this week. The intervention has drawn criticism from a prominent conservative-leaning group combating election fraud.

From central Asia, the Taliban from Afghanistan? You really cannot make this up? One wonders whence this arose. This is either the silly season or this is one of the most blatant violations of US sovereignty ever.
Labels: Politics

WAITING ON THE CORNER FOR THE BUS

I just read a piece by Posner on Luck versus Hard Work. He concludes:

In short, I do not believe in free will. I think that everything that a person does is caused by something. It is true, and is the basis of belief in free will, that often we are conscious of considering pros and cons in deciding on a course of action; "we" are deciding, rather than having the decision made by something outside "us." But calculation and decisionmaking are different. Deciding may just mean calculating the balance of utility and disutility; the result of the balance determines the decision. No doubt when a cat pounces on a mouse, it has decided to do so; but the decision was compelled by circumstances—the feline diet, the presence of the mouse, etc. A complete description of the incident would not require positing free will.

Namely he sides with Luck versus Hard Work. I more than humbly disagree. I often tell folks that to be successful you must be on the corner when the bus goes by, and you must get on the right one. The bus does not come to your house, you must walk to the corner and be prepared for the ride.

I have seen far too many people who want a job, to be told what to do, and then bemoan their fate when the lose what they may have had.

I recall many of my ventures, taking the full risk of no income, focusing on a new idea, selling the idea to others to form a team, raising more capital, and expanding the business. I have never been a Government employee, unless you count my summers as a NYC Lifeguard or my winter shoveling snow for the NYC Sanitation Department. Learning experiences but not jobs.

Posner does not understand that one must do a great deal to be prepared for luck. Many people turn luck down, they really do. They are offered opportunities, which require risks, and they say no. Many would never have the luck because they were not educated enough to realize it when it comes.

As for free will, I totally disagree with Posner, we all too often chose, for better or worse. The "path not taken" was a choice. We are not compelled. There are many who have not become alcoholics, who have not smoked cigarettes, who have lost weight and kept it off, who have not consumed various illegal substances. That was by choice. In fact the very presence, the existence, of those who avoid obesity is proof of choice. If once obese and then no longer, that is a choice, that is a sine qua non example of free will.

SATURDAY, OCTOBER 20, 2012

EDX REDUX

I have commented on the MIT 6.002X course and now I will get a chance to comment on a Harvard one, PH207X, the statistics course from the Harvard School of Public Health.

Now as before some bona fides. I have taught probability and statistics in graduate level course at MIT from 1969 through 1975 and at GW University from 1976 thru 1980. That is as I measure it some 11 years. Then I wrote my first book in 1969 and published in 1974 on Stochastic Systems and State Estimation (Wiley). I also published some fifty plus papers in this area as well. Thus I may have a leg up. I also took a Board Review course at HMS back in 1994 I believe which used the book by the instructor, good book, early undergrad level, somewhat cook bookish but does the task. Thus like 6.002X I come with some experience in the area.

I was again disappointed, left after the middle of the first problem set. Now why? Simple, the student had to download a cumbersome statistics package, figure out how to use it from some video by some person who was using Valley Speak, and waving hands all about the place, and I never could find the data set. This is another example of never getting to the material, being encumbered by some generally useless piece of interference.

It is akin to the First Year Latin Instructor at some expensive private school demanding that homework have been written with a blue ball point, with names on the top right on each page in green ball point and dates on the top right in red ball point and a staple ¾" from the top and ¾" from the left, and parallel with the top of the paper. How about the Latin? Form and not function. I saw the same problems in 6.002X but not to this extreme.

Why must a student waste so much time on acquiring and learning some generally useless software package? It would have been much better to have the student lean the theory and then using Excel for example work through the analysis in detail.

In my experience for example performing an analysis of variance process one learns a great deal by actually doing every step in the analysis and not by using some software package that spits

out the answer. Raw data is what we deal with and the student should and must become familiar with that data, must work with is, must live with it.

For example, dealing with outliers is a key issue. I wrote an oft quoted paper on this back in 1975 I believe. What is an outlier and when do we disregard it and when is the data in an outlier the most important data element? You learn that only by dealing with all the data.

The instructor does teach a good course and his insights are quite useful. He provides the novice with a window to statistics as used in the Medical field. However he does not take the user to the extreme, nor is that expected in such an introductory course. Thus getting bogged down in the first step by some third party piece of software is really a waste of time.

It again begs the question of what is the whole purpose of this venture. Will someone learn, perhaps, but would I ever teach this way, never. I want the student to understand the principles and to work with the data, to make the mistakes and to recover from them. I want to the student to even go as far as saying that the wrong question was asked and the data may be correct and properly analyzed but you asked the wrong question.

For example take the NEJM studies on prostate cancer and PSA. They asked if performing PSA measurements in some manner and using a threshold of 4.0 as a marker for say a biopsy, did that result in the saving of lives. They concluded that it did not.

But the right question should have been and what procedure and what data would result in a material change in mortality and morbidity? Perhaps the answer was 2.0 and not 4.0 and perhaps the answer also required velocity and percent free PSA as well as normalization on prostate volume. Namely what was the right question and how do we develop tests to get answers to the right question.

I come back again to what is the purpose of this course? To learn how to use a software package or to learn how to employ statistical analyses in the field of medical trials. I suspect it should have been the latter.
Labels: Education

SUNDAY, OCTOBER 14, 2012

ROCKS FROM HEAVEN

The ten year old who suddenly develops a high fever and has swollen lymph nodes, it turns out to be leukemia, an acute variety, the 30 year old mother who upon awakening stumbles and cannot stand up and has a glioma, the 25 year old who suddenly looses sight and has MS, the 15 year old who suddenly break a leg bone, and has osteosarcoma, these are those rocks from heaven that hit many people day after day. Medicine may help, a bit, and perhaps more every day,

But upon reading an article in today's NY Times I was a bit confused. Here was a fifty year old man who decided to avoid any form of health care until the top caved in and the opinion writer tries to infer that it is the Republican's candidates fault. How far can this be stretched. Every

obese person has assumed a certain risk for their behavior, every substance abuser as well, these are life style choice diseases. Every person who spends too much time in the sun also takes on a risk, one mitigated by subsequent follow ups to spot a pigmented lesion early and excise it, but with the risk is responsibility.

In the Times case there was abject and deliberate abrogation of any personal responsibility. It recounts a person who decides to leave a job and health coverage to go out a enjoy life and who neglects some key points, the result is terminal cancer. It is one of those things many a young physician often thinks but should never say, "Why didn't you come here earlier?" It is the case of seeing a 65 year old woman in the ER who has been both constipated and bleeding for six to eight months, only to discover that she has stage IV colon cancer, and she had insurance. Why did you not come here earlier? Terror, not cost.

As the writer states:

Yet remember also that while .... was foolish, mostly he was unlucky. He is a bachelor, so he didn't have a spouse whose insurance he could fall back on in his midlife crisis. In any case, we all take risks, and usually we get away with them. Scott is a usually prudent guy who took a chance, and then everything went wrong.

The Mitt Romney philosophy, as I understand it, is that this is a tragic but necessary byproduct of requiring Americans to take personal responsibility for their lives. They need to understand that mistakes have consequences. That's why Romney would repeal Obamacare and leave people like Scott to pay the price for their irresponsibility.

To me, that seems ineffably harsh. ***We all make mistakes, and a humane government tries to compensate for our misjudgments.*** *That's why highways have guardrails, why drivers must wear seat belts, why police officers pull over speeders, why we have fire codes. In other modern countries, ... would have been insured, and his cancer would have been much more likely to be detected in time for effective treatment.*

This is preposterous. The person in question may not have ever gone to a physician, the behavior seems to indicate as such. Furthermore under the ACA and the new CEC Panel they would have outlawed PSA tests anyhow. Yes, you do have consequences for your actions. Take illegal drugs, then possibly HIV or overdose, smoke, lung cancer, sun tanning, melanoma, obese, well just dozens of things. Personal responsibility is key to a stable society. If no one is responsible but we all are for those who refuse then what is left, chaos. One can pity this person, one should, but he made a choice, choices have consequences. Ride a motorcycle without a helmet and speed on sandy highways and perhaps you will have an accident.

Is it harsh that the 10 year old has AML? Yes it is, the 10 year old had no choice. Should we as a society take care of the child, without a doubt. But a Harvard educated 50 year old who decides to make a choice which has possible serious consequences, well that is a different story. People have duties, responsibilities, not to be deliberate burdens on others. The counter is that society does have a duty or responsibility to deal with the rocks from heaven, the people who for no reason of their own making find themselves distressed.

Is this Romney's fault that this individual made a personal choice which had consequences. If I chose to bet all my money in Black Jack games and lost is society to reimburse me for my bad luck, or stupidity, I think not. Is that 65 year old woman with terminal colon cancer responsible for her state, perhaps. Is the 10 year old child, never.

We are in a society where there are well placed warning signs. Some are confusing, made so deliberately by Government, such as the PSA test, but others clear such as smoking bans. Some which should be more clear such as obesity. But one would assume that a Harvard graduate would have some semblance of both intelligence and insight, and is it Romney's fault, doubtful, after all it is the current president's administration which wanted to do away with PSA tests as it stands, thus the end point may not have changed. Perhaps this is just a very poor example to prove one's alleged case.

Perhaps the most severe misstatement in the piece is that we all make mistakes but a "humane" government makes up for our misjudgements. Wow. Think of all the dumb things we have done in our lives, in the past we learned from them, not to repeat them. Now the left wants the Government to take away that primal learning experience. As I have said before to my children, every action you take has a consequence, think it through and act accordingly, you must live with the result.
Labels: Health Care

SATURDAY, OCTOBER 13, 2012

COMPUTER ATTACKS

The recent articles on cyber attacks are interesting in that many of these can be prevented and the whole issue has been analyzed for decades. The NY Times reports on some of the latest updates but I wonder why the big concern especially if one take a modicum of care.

Back in the 70s there were similar issues:

1. Red and Black: Secure rooms and un-secure were black and red. Namely one took some care to close the rooms down, secure them from snooping, have screens, bury them etc.

2. Carefully vet your people. The classic tale of the Falcon and the Snowman about the drugged up workers in the TRW vault in the 70s trying to sell the Soviets highly classified data in Mexico, is an example of what not to do. People are always the most insecure element. Today we share everything across the board, before we were quite circumspect.

3. The Internet is an open network. If you want to operate a secure network the DO NOT USE THE INTERNET. When I started my VOIP business in the mid 90s I had dedicated lines, it guaranteed levels of service and security. I owned all my routers and they were secure. I never thought otherwise.

4. Kernelized Operating Systems: Back in the 70s we worried about people getting into out OS environments so we developed kernelized security, and it seemed to work. Now we have more holes in any OS so that almost weekly we have security patches. That is amazing in that we had

developed quite secure systems 40+ years ago. One wonders where Microsoft was.

The problem is simply allowing the wrong people to have access to open systems with poor security. Having the Government control it is the wrong approach. They controlled the old ATT network before divestiture. ATT even sat in the Pentagon, and this never really did anything useful

Thus the best way is a Coasian way, let the failure occur and then have the users sue the devil out of the fool company that allowed it to happen.

Labels: Cyber Warfare

THE AUTO BAILOUT

Was the auto bailout the only way to save General Motors, or in fact was and is General Motors worth saving? The current President believes that it was the sine qua non approach. But we do have bankruptcy courts and the airlines seem to have been able to work their way there many times. It appeared as if GM had grossly incompetent management and labor unions whose grabs went much too far. That is what bankruptcy is for. You cram down the equity holders and convert the debt holders, find new management, and restructure the union deals. It works every day of the year but not here.

Now bankruptcy does not mean you fire everyone. Airline operate in bankruptcy almost half the time. They still fly. GM could have still made cars. Any lawyers should know the law of bankruptcy, they allegedly teach it at law schools, even Harvard. Thus what has happened is a distortion of our legal system, the debt holders were wiped out, the Government rewarded the unions and replaced management with God knows what, two telecom guys. Will it get better, the jury is still out.

One thing for certain, debt holders will be very wary next time, try and raise debt when you have a Government which bumps you out no matter what the law. That type of action places a very chilling effect on the economy, as if anyone has noticed!
Labels: Politics

OUTLAWING CREATIVITY

The Hill reports on the intentions of many countries via the ITU to take control over the Internet. They state:

Proposals to expand the U.N.'s International Telecommunications Union's (ITU) authority over the Internet could come up at a treaty conference in Dubai in December. European telecommunications companies are pushing a plan that would create new rules that would allow them to charge more to carry international traffic.

Just a reminder to all, back just 20 years ago it costs $5.00 per minute to place a call to or from Paris. It was not costs or capacity it was this same group of internationalists who collect massive

salaries and destroy creativity. With luck if they get control we will all become Greece!

I spent a decade finding ways around this using the Internet as one element. Letting the ITU and the UN of all useless entities take control of high tech is one of the most absurd ideas ever conceived of by the Genus Homo.

They state:

The proposal by the European Telecommunications Network Operators' Association could force websites like Google, Facebook and Netflix to pay fees to network operators around the world.

These operators already get paid as I have noted many times, by their customers. This is intrusion to the extreme and will set society back even more so than what happened with the banks!
Labels: Internet, Telecom

FRIDAY, OCTOBER 12, 2012

GENES, OBESITY AND WHAT?

There is another recent article in NEJM which I cannot fully grasp. Namely the authors contend that it is a genetic driver that children who over consume sugar based drinks get fat!

They state:

In conclusion, our data provide consistent evidence from three separate cohorts that greater consumption of sugar-sweetened beverages was associated with a more pronounced genetic predisposition to elevated BMI and obesity risk among women and men.

Now as usual they try to shift the blam to some "disease state". In this case they state:

We selected 32 single-nucleotide polymorphisms (SNPs) that represent all 32 loci that are known to be associated with BMI

One may have a SNP but one must consume the calories. SNPs do not force one to over consume.

They continue:

The genetic-predisposition score was calculated on the basis of the 32 SNPs with the use of a previously reported weighting method; scores range from 0 to 64, with higher scores indicating a higher genetic predisposition to obesity.

Is this correlative or causative. The details seem to be missing.

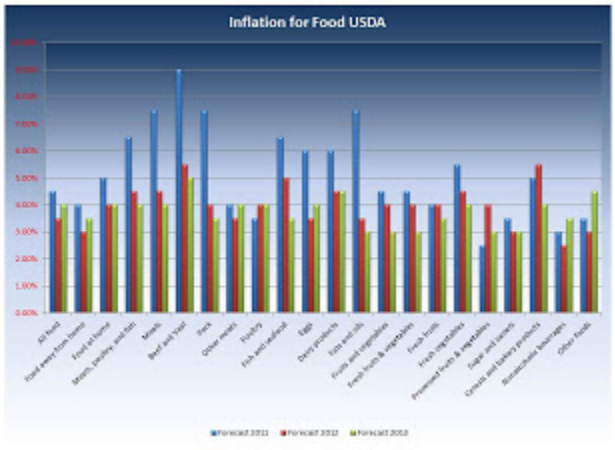
Yes obesity is a problem, but as is well known all too frequently it is driven by one and only one factor, over consumption. Reduce the consumption and in almost all cases the obesity goes,

genes or no genes.

I am afraid that this type of argument makes into a disease what is merely individual responsibility. It will just drive up health care costs.
Labels: Health Care, Obesity

FRIDAY, OCTOBER 12, 2012

FOOD INFLATION Q4 2012



Food inflation as per the USDA seems to be low. However when examining certain specific elements it is extraordinarily high. For example:

Milk has gone from $3.00 to $4.50 a gallon

Coffee from $3.00 to $8.00 a pound

and it continues.

One suspects that energy costs as reflected in gasoline at $5.25 a gallon will get reflected here as well for Q4. I believe that this pressure along with heating costs will hit heavily in Q1 2013.

Labels: Economy

CICERO, DEBATES AND THE SENATE

QUO usque tandem abutere, Catilina, patientia nostra? quam diu etiam furor iste tuus nos eludet? quem ad finem sese effrenata iactabit audacia? Nihilne te nocturnum praesidium Palati, nihil urbis vigiliae, nihil timor populi, nihil concursus bonorum omnium, nihil hic munitissimus habendi senatus locus, nihil horum ora voltusque moverunt? Patere tua consilia non sentis, constrictam iam horum omnium scientia teneri coniurationem tuam non vides? Quid proxima, quid superiore nocte egeris, ubi fueris, quos convocaveris, quid consilii ceperis, quem nostrum ignorare arbitraris?

As every third year Latin student knows, Cicero as a great orator went after Cataline with his fingers bared. His eloquence was compelling and his style lasting. Rhetoric in Rome has unending value amongst those who ruled.

However the debate on the fore night was anything but. Too bad our Senate has lost class, perhaps is never had a great deal, then again there was Webster.
Labels: Commentary

CANCER MARKERS: WHAT IS THE VALUE

There has been a continual flow of markers for proposed use in cancer identification and management. For example:

1. The recent prognostic blood borne markers for prostate cancer prognostication.

2. BRAF V600 marker for certain types of melanoma

and many others.

It usually works as follows:

1. Some group publishes a paper announcing a new marker or markers. This is all too often devoid of any discussion of why they are good markers such as describing pathway issues. BRAF is a clear exception.

2. The trade press then blasts this "discovery" across its pages and it all too often includes comments by some of the authors all too often making illusions to great things to come.

3. Then the popular press gets a hold on it and generally having o idea what they are saying explode it to a level never anticipated.

Thus the issue is what value and at what cost.

Take the prostate markers, all it tells one is that you will die soon or sooner. Is that valuable? Possible to estate planning but any good clinical physician could come close to the same answer.

Then BRAF V600, we can now extend life 6 months at the cost of $100,000. The same end point, but at significant costs, not to mention 6 months of physician care etc. Is this worth the cost?

Perhaps it is all in the eye of the beholder. Perhaps the researchers should temper their enthusiasm.
Labels: Cancer

PROSTATE CANCER, PROGNOSIS AND WHY

We have examined many studies looking at genetic prognostic markers from a causative basis. Namely we look at genes in specific pathways which are altered result in malignant conditions for cell growth and proliferation. In this note we look at a two recent articles examining blood borne proteins which have some putative prognostic value. They have been extensively discussed in the press and whereas they have some uses it is our opinion that perhaps they have been extended well beyond their significance. This is a brief note therefore focusing on issues raised by the results.

Both reports we discuss herein are prognostic in their approach. They are prognostic, however, for androgen resistant PCa. Although it is always good to understand what the prognosis is, even if you cannot do anything about it, it does raise the concern of what benefit is this to either the physician or patient. The results seem to say that the prognosis is that one has 9-10 months versus 3-4 years of expected life. There is nothing that can be done, and even care of the patient is in question. No matter what it is palliative. Although the results are interesting the question is are they beneficial, to anyone. One may ask why waste the money to find out something that you can do nothing about. That is both an ethical and an economic issue.

A summary reported in the press states[33][1]:

The first study, demonstrating that a nine-gene signature could distinguish between lower and higher risk castration-resistant prostate cancer (CRPC), was led by Johann de Bono, MD, of the drug development unit at the Royal Marsden NHS Foundation Trust in Sutton, United Kingdom, and was conducted with colleagues in both Europe and the United States.

The second study, which found a six-gene signature that also stratified CRPC into different risk groups, was led by William K. Oh, MD, of the division of hematology/oncology at the Tisch Cancer Institute at Mount Sinai School of Medicine in New York.

One of the findings was related to immune system genes not those normally thought of in pathway control. The authors state[34][2]:

The result that immune function is key to prostate cancer outcome is very surprising, said Dr. de Bono.

"The biggest surprise of this study was that the most significant six genes which predicted survival were not primarily cancer-related genes, but were involved in immune function," said Dr. Oh. "In some ways, this is not a surprise, since it suggests that the patient's innate immune response to cancer may be a strong predictor of the impact of the cancer." Dr. Oh added that the

[33][1] http://www.cancernetwork.com/prostate-cancer/content/article/10165/2106848

[34][2] http://www.cancernetwork.com/prostate-cancer/content/article/10165/2106848

function of the identified genes in the immune system is not yet understood. Nor is it understood how the genes may interact and lead to a difference in survival for patients.

Both authors of the studies see the RNA analysis as highly applicable for the clinic. Dr. Oh said that the particular six-gene signature his study identified "could be translated fairly easily to the clinic, since it uses simple technologies such as PCR to identify the genes of interest." Dr. Oh and colleagues collected the RNA in blood using a special preservation tube (PAXgene), which are widely available. Dr. de Bono and colleagues are currently testing whether a DNA analysis could provide the same information.

Dr. Oh highlighted the different approaches of the two teams: "What is interesting about the Royal Marsden paper is that they took a very different analytic approach, which in fact looked at more genes and was thus potentially more unbiased, and found that the most prognostic genes were again driving immune function in patients." Both teams ended up with a similar result: "The blood contains a molecular signature in patients with advanced prostate cancer which predicts survival based on the functioning of the immune system."

Now it must be emphasized that these studies examined prognostic factors and not diagnostic and that further they examined patients who were already androgen resistant, namely the PCa had progressed extensively. Thus the implication of immune system elements is not unexpected. Also this analysis is not diagnostic in any way and further is not prognostic in any manner related to a watchful waiting strategy. As the authors suggest survival in his risk is about 8 months and in "low" risk is about 35 months. In either case the patient is terminal.

1 Recent Finding

There are two recent papers regarding this issue. The first is a recent Lancet article by Ross et al, entitled, *A whole-blood RNA transcript-based prognostic model in men with castration-resistant prostate cancer: a prospective study*[35[3]], the authors state:

Survival for patients with castration-resistant prostate cancer is highly variable. We assessed the effectiveness of a whole-blood RNA transcript-based model as a prognostic biomarker in castration-resistant prostate cancer. Peripheral blood was prospectively collected from 62 men with castration-resistant prostate cancer on various treatment regimens …

A six-gene model (consisting of ABL2, SEMA4D, ITGAL, and C1QA, TIMP1, CDKN1A) separated patients with castration-resistant prostate cancer into two risk groups: a low-risk group with a median survival of more than 34·9 months (median survival was not reached) and a high-risk group with a median survival of 7·8 months ....Transcriptional profiling of whole blood yields crucial prognostic information about men with castration-resistant prostate cancer. The six-gene model suggests possible dysregulation of the immune system, a finding that warrants further study.

[35[3]] http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2812%2970263-2/fulltext?_eventId=login

We wish to examine this in some detail. There are several issues we wish to look at.

First, what pathways do these genes participate in and thus how do they play a role in the management of the homeostasis of the cell. Why would one want to consider these genes?

Second, are these genes causative or reflective of a cancer state? If reflective are there causative genes related thereto which may merit more detailed examination.

Third from a prognostic perspective, why are these expressed as they are?

Fourth from a treatment perspective are these markers useful in targeting gene aberrations so as to mitigate further uncontrolled growth and in fact reduce what is present.

Fifth, is there a holistic picture of how most likely metastatic growth is identified by such expression and how one may ascertain the spread of the metastatic cells?

There is also a second paper entitled, *Prognostic value of blood mRNA expression signatures in castration-resistant prostate cancer: a prospective, two-stage study* by Olmos et al which notes[36[4]]:

Biomarkers are urgently needed to dissect the heterogeneity of prostate cancer between patients to improve treatment and accelerate drug development. We analysed blood mRNA expression arrays to identify patients with metastatic castration-resistant prostate cancer with poorer outcome.

Whole blood was collected into PAXgene tubes from patients with castration-resistant prostate cancer and patients with prostate cancer selected for active surveillance. In stage I (derivation set), patients with castration-resistant prostate cancer were used as cases and patients under active surveillance were used as controls. These patients were recruited from The Royal Marsden Hospital NHS Foundation Trust (Sutton, UK) and The Beatson West of Scotland Cancer Centre (Glasgow, UK).

In stage II (validation-set), patients with castration-resistant prostate cancer recruited from the Memorial Sloan-Kettering Cancer Center (New York, USA) were assessed. Whole-blood RNA was hybridised to Affymetrix U133plus2 microarrays. Expression profiles were analysed with Bayesian latent process decomposition (LPD) to identify RNA expression profiles associated with castration-resistant prostate cancer subgroups; these profiles were then confirmed by quantative reverse transcriptase (qRT) PCR studies and correlated with overall survival in both the test-set and validation-set.

LPD analyses of the mRNA expression data divided the evaluable patients in stage I (n=94) into four groups. All patients in LPD1 (14 of 14) and most in LPD2 (17 of 18) had castration-resistant prostate cancer. Patients with castration-resistant prostate cancer and those under

[36[4]] http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2812%2970372-8/fulltext

active surveillance comprised LPD3 (15 of 31 castration-resistant prostate cancer) and LDP4 (12 of 21 castration-resistant prostate cancer).

Patients with castration-resistant prostate cancer in the LPD1 subgroup had features associated with worse prognosis and poorer overall survival than patients with castration-resistant prostate cancer in other LPD subgroups (LPD1 overall survival 10·7 months [95% CI 4·1—17·2] vs non-LPD1 25·6 months [18·0—33·4]; p<0 span="span">

A nine-gene signature verified by qRT-PCR classified patients into this LPD1 subgroup with a very low percentage of misclassification (1·2%). The ten patients who were initially unclassifiable by the LPD analyses were subclassified by this signature. We confirmed the prognostic utility of this nine-gene signature in the validation castration-resistant prostate cancer cohort, where LPD1 membership was also associated with worse overall survival (LPD1 9·2 months [95% CI 2·1—16·4] vs non-LPD1 21·6 months [7·5—35·6]; p=0·001), and remained an independent prognostic factor in multivariable analyses for both cohorts.

Our results suggest that whole-blood gene profiling could identify gene-expression signatures that stratify patients with castration-resistant prostate cancer into distinct prognostic groups.

2 Summary of Prognostic Gene Markers

The following Table is a summary of the prognostic gene markers.

Gene	*Description*[37][5]	*Location*
ABL2	This gene encodes a member of the Abelson family of nonreceptor tyrosine protein kinases. The protein is highly similar to the c-abl oncogene 1 protein, including the tyrosine kinase, SH2 and SH3 domains, and it plays a role in cytoskeletal rearrangements through its C-terminal F-actin- and microtubule-binding sequences. This gene is expressed in both normal and tumor cells, and is involved in translocation with the ets variant 6 gene in leukemia. Multiple alternatively spliced transcript variants encoding different protein isoforms have been found for this gene.	*1q25.2*
SEMA4D	CD100; SEMAJ; coll-4; C9orf164; M-sema-G. Semaphorin 4D (Sema 4D) is an axon guidance molecule which is secreted by oligodendrocytes and induces growth cone collapse in the central nervous system. By binding plexin B1 receptor it functions as an R-Ras GTPase-activating protein (GAP) and repels axon growth cones in both the mature central nervous system. In the immune system, CD100 binds CD72 to activate B cells and dendritic cells, though much about this interaction is still under investigation. During skin damage repairs, SEMA4D interacts with Plexin B2 on gamma delta T cells to play a role in the healing process	*9q22.2*
ITGAL	ITGAL encodes the integrin alpha L chain. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. This I-domain containing alpha integrin combines with the beta 2 chain (ITGB2) to form the integrin lymphocyte function-associated antigen-1 (LFA-1), which is expressed on all leukocytes. LFA-1 plays a central role in leukocyte intercellular adhesion through interactions with its ligands, ICAMs 1-3 (intercellular adhesion molecules 1 through 3), and also functions in lymphocyte costimulatory signaling. Two transcript variants encoding different isoforms have been found for this gene.	*16p11.2*
C1QA	This gene encodes a major constituent of the human complement subcomponent C1q. C1q associates with C1r and C1s in order to yield the first component of the serum complement system. Deficiency of C1q has been associated with lupus erythematosus and glomerulonephritis. C1q is composed of 18 polypeptide chains: six A-chains, six B-chains, and six C-chains. Each chain contains a collagen-like region located near the N terminus and a C-terminal globular region. The A-, B-, and C-chains are arranged in the order A-C-B on chromosome 1. This gene encodes the A-	*1p36.12*

[37][5] http://www.ncbi.nlm.nih.gov/gene

Gene	*Description*[37][5]	*Location*
	chain polypeptide of human complement subcomponent C1q.	
TIMP1	This gene belongs to the TIMP gene family. The proteins encoded by this gene family are natural inhibitors of the matrix metalloproteinases (MMPs), a group of peptidases involved in degradation of the extracellular matrix. In addition to its inhibitory role against most of the known MMPs, the encoded protein is able to promote cell proliferation in a wide range of cell types, and may also have an anti-apoptotic function. Transcription of this gene is highly inducible in response to many cytokines and hormones. In addition, the expression from some but not all inactive X chromosomes suggests that this gene inactivation is polymorphic in human females. This gene is located within intron 6 of the synapsin I gene and is transcribed in the opposite direction.	*Xp11.3*
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. Multiple alternatively spliced variants have been found for this gene.	*6q21.2*

3 TIMP-1

TIMP-1 is a tissue inhibitor of metalloproteinases. Metalloproteinases (matrix metalloproteinases, MMP) are zinc dependent proteases which have the ability to cleave cell walls[38][6]. Transcription of this gene and thus increase in its product are activated by cytokines and various hormones. However, in this analysis, it is most likely the excitation from the immune system cytokines which activate the response.

[38][6] For example the use of doxycycline as a suppressor of MMP at low doses is used to treat corneal abrasions and certain types of dental erosions.

There has been extensive work performed analyzing TIMP-1 recently in various other cancers. The work of Wang et al examines Gastric cancers, Lee examines Colorectal cancers, and Bloomston looks at pancreatic cancers. Other detailed analyses have been done by Vaghooti et al as well as Wang. Thus is should be no surprise as to the use of TIMP-1 in this specific case as well.

In addition as per Marks et al[39][7], The TIMP, tissue inhibitors of metalloproteases, MMP, are within the class of ADAM proteins which are membrane bound.

The following is a summary by Bigelow et al and although it focuses on breast cancer issues it does provide a reasonable summary as applied to this case:

TIMP-1 (Tissue inhibitor of matrix metalloproteinase-1) is typically associated with inhibition of matrix metalloproteinases (MMP) induced invasion. However, TIMP-1 is overexpressed in many malignancies and is associated with poor prognosis in breast cancer.

The mechanisms by which TIMP-1 promotes tumorigenesis are unclear. Reduced levels of TIMP-1 mediated by shRNA in MDA-MB-231 breast cancer cells had no effect on cellular physiology in vitro or tumor growth in SCID mice compared to vector control MDA-MB-231 cells.

However, overexpression of TIMP-1 in MDA-MB-231 cells resulted in inhibition of cell invasion and enhanced phosphorylation of p38 MAPK and AKT in vitro. Additionally, treatment of parental MDA-MB-231 cells with purified TIMP-1 protein led to activation of p38 MAPK and MKK 3/6. cDNA array analysis demonstrated that high expression of TIMP-1 in MDA-MB-231 cells resulted in alterations in expression of approximately 200 genes, 1.5 fold or greater compared to vector control cells ($P < 0.1$).

Real-time RT-PCR confirmed changes in expression of several genes associated with cancer progression including DAPK1, FGFR4 and MAPK13.

In vivo, high TIMP-1 expression induced tumor growth in SCID mice compared to vector control cells and increased tumor vessel density. Affymetrix array analysis of vector control and TIMP-1 MDA-MB-231 xenograft tumors revealed that TIMP-1 altered expression of approximately 600 genes in vivo, including MMP1, MMP13, S100A14, S100P, Rab25 and ID4.

These combined observations suggest that the effects of TIMP-1 differ significantly in a 2-D environment compared to the 3-D environment and that TIMP-1 stimulates tumor growth.[40][8]

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[39][7] See Marks et al, pp. 455-459.

[40][8] TIMP-1 overexpression promotes tumorigenesis of MDA-MB-231 breast cancer cells and alters expression of a subset of cancer promoting genes in vivo distinct from those observed in vitro, Rebecca L. H. Bigelow, Briana J. Williams, Jennifer L. Carroll, Lisa K. Daves and James A. Cardelli, Breast Cancer Research and Treatment Volume 117, Number 1 (2009), 31-44, DOI: 10.1007/s10549-008-0170-7. http://www.springerlink.com/content/a61k12012441l672/

Thus we have the question that TIMP-1 at an inhibitor of MMP is thus increased in response to cytokines which may themselves be increased as a result of the PCa metastatic expansion. The question then becomes; is this just a natural and expected result, is this just consistent with PCa evolution, or is there something special here.

4 ABL2

BCR and ABL are genes closely related to CML. In a 2002 paper in NEJM by Katarjian et al we have:

Chronic myelogenous leukemia (CML) accounts for about 20 percent of newly diagnosed cases of leukemia in adults. The course of the disease is characteristically triphasic: a chronic phase lasting three to six years is followed by transformation to accelerated and then blast phases of short duration. The cause of CML is the translocation of regions of the BCR and ABL genes to form a BCR-ABL fusion gene. In at least 90 percent of cases, this event is a reciprocal translocation termed t(9;22), which forms the Philadelphia (Ph) chromosome. The product of the BCR-ABL gene, the BCR-ABL protein, is a constitutively active protein tyrosine kinase with an important role in the regulation of cell growth.

Thus this fusion product has been found to result in a cancerous growth of the immune system. ABL2 is a product which is a tyrosine kinase resident in the cytoplasm.

Considerable work has been done on ABL and reference is made to that of Wong and Witte as well as O'Hare. Also there is the recent work of Sirvent et al examining Abl in normal and cancer cells.

In the work by O'Hare et al the authors note:

The BCR-ABL signaling network and ABL kinase inhibition.

A, BCR-ABL signaling pathways activated in CML. Dimerization of BCR-ABL triggers autophosphorylation events that activate the kinase and generate docking sites for intermediary adapter proteins such as GRB2. BCR-ABL– dependent signaling facilitates activation of multiple downstream pathways that enforce enhanced survival, inhibition of apoptosis, and perturbation of cell adhesion and migration.

A subset of these pathways and their constituent transcription factors, serine/threonine-specific kinases, and apoptosis related proteins are shown. A few pathways that were more recently implicated in CML stem cell maintenance and BCR-ABL–mediated disease transformation are shown.

Of note, this is a simplified diagram and many more associations between BCR-ABL and signaling proteins have been reported. BCR-ABL is unstable upon disruption of primary CML cells; therefore, pharmacodynamic evaluation of BCR-ABL activity is performed by monitoring

the tyrosine phosphorylation status of either CRKL or STAT5, with CRKL phosphorylation considered the most specific readout.

B, Predicted effectiveness of ABL kinase inhibitors in three therapeutic scenarios: to inhibit native BCR-ABL , to inhibit mutated BCR-ABL, and as a component in the control of CML involving a BCR-ABL–independent alternate lesion[41][9].

Now ABL by itself has certain control mechanisms. They are well known and reviewed extensively, refer to Wong and Witte.

5 SEMA4D

SEMA4D is also known as CD100. The CD or cluster of determination molecules often are receptors and frequently found on immune system sourced cells. CD100 specifically is characterized as one of Mono migration; with T and B activation; T cell-B cell and T cell-DC interaction. Thus SEMA4D is another immune cell related marker and not one of internal pathway control.

From the work of Gelfand et al we have:[42][10]

(a) *Sema4D signaling in the nervous system. Proteins in the R-Ras pathway are shown in red: in the presence of Sema4D, Rnd1 is recruited to Plexin-B1. Plexin-B1 R-RasGAP activity is activated and downregulates the active form of R-Ras. The decrease of active R-Ras inhibits PI3K–Akt activity, decreasing GSK3β phosphorylation and, thus, activating it. GSK3β then phosphorylates and deactivates CRMP2 and causes microtubule disassembly.*

(b) *Sema4D signaling in the vascular system. Proteins in the RhoA pathway are shown in blue: in the presence of Sema4D, the receptor tyrosine kinase Met binds and phosphorylates Plexin-B1 and then activates PDZ–RhoGEF and LARG, which activates RhoA and leads to endothelial cell migration through the ROCK, Pyk2 and PI3K pathway. It is not clear how this pathway affects actin dynamics or microtubule dynamics in vascular system.*

(c) *Sema3A signaling in the nervous system. Rac1-regulating proteins are shown in green: in the presence of Sema3A, FARP2 is released from Plexin-A1 and actives Rac1. Rac1 then activates PAK and LIMK and, as a result, phosphorylates Cofilin, which finally causes actin depolymerization. R-Ras-regulating proteins are shown in red: in the presence of Sema3A,*

(d) *Sema3A signaling in the vascular system. Sema3A, through an unknown mechanism (possibly through Npn-1 and/or a co-receptor, shown as a dashed line and '?'), inhibits VEGF-induced activation of Src and FAK and contributes to angiogenesis. Sema3A might also function through Npn-1 to inhibit integrin-mediated adhesion of endothelial cells to the ECM. Sema3A can induce*

[41][9] http://clincancerres.aacrjournals.org/content/17/2/212.full.pdf+html

[42][10] http://www.sciencedirect.com/science/article/pii/S096289240900018X

VE-cadherin phosphorylation and causes vascular permeability through unknown mechanisms (indicated by '?'), in which PI3K–Akt is involved.

In the work of Neufeld and Kessler we have:

The main signal transduction pathways by which SEMA3A and SEMA4D activate plexin A1 (PLEXA1) or PLEXB1…[43][11]*. The information is derived mainly from the study of neuronal cells. The activation of PLEXA1 by SEMA3A (left side) or PLEXB1 by SEMA4D (right side) induces activation and sequestration of RAC1 and RND1 by the plexins.*

Sequestration of RAC1 results in reduced phosphorylation of p21-activated kinase 1 (PAK), inhibition of LIM domain kinase 1 (LIMK1) activity and activation of cofilin, which causes actin depolymerization.

Activation of PLEXA1 by SEMA3A also results in the activation of the tyrosine kinases FYN, FES and FER, which is followed by the recruitment and activation of cyclin-dependent kinase 5 (CDK5), which in turn inactivates collapsin response mediator proteins (CRMPs) such as CRMP2. CRMPs affect microtubule dynamics and the organization of the actin cytoskeleton.

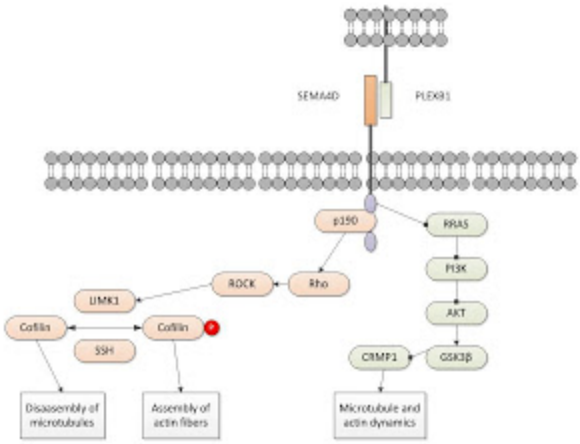
The activation of PLEXA1 also leads to the activation of MICALs (molecules interacting with CasL), which form complexes with CRMPs and are also essential for the effects of SEMA3A on the cytoskeleton.

In the case of SEMA4D, activation of PLEXB1 can also lead to the inactivation of CRMPs through inhibition of phosphoinositide 3-kinase (PI3K) and AKT activation that leads to GSK3 activation and as a result to the inactivation of CRMPs.

In addition to these short-term effects there are also long-term effects. In the case of SEMA3A, activation of PLEXA1 induces apoptosis of neuronal and endothelial cells, which is manifested by inhibition of extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2) phosphorylation and activation of caspase 3 (indicated in purple). The insert shows the effects of SEMA3A on the actin cytoskeleton of endothelial cells.

We depict below a modified version of their pathway description.

[43][11] http://www.nature.com/nrc/journal/v8/n8/fig_tab/nrc2404_F5.html



Also below we have from the work of Siderovski and Willard the following discussion of pathway involvement[44][12]:

Membrane targeting strategies employed by multi-domain RGS proteins.

*(**A**) The R7 RGS proteins form obligate heterodimers with Gβ5 via a Gγ-like sequence (the "GGL" domain) N-terminal to the RGS-box. This GGL/Gβ5 interaction could allow R7 RGS proteins to act as conventional Gβγ subunits in coupling Gα subunits to 7TM receptors, thereby localizing RGS-box-mediated GAP activity to particular receptors. The DEP domain of RGS9-1 interacts with a membrane-anchoring protein (R9AP) analogous interactors may exist for the DEP domains of other R7 subfamily members.*

*(**B**) The PDZ domain of RGS12 is able to bind the C-terminus of the IL-8 receptor CXCR2 (at least in vitro). The RGS12 PTB domain binds the synprint ("synaptic protein interaction") region of the N-type calcium channel ($Ca_v2.2$); this interaction is dependent on neurotransmitter-mediated phosphorylation of the channel by Src.*

*(**C**) The AtRGS1 protein of Arabidopsis thaliana (thale cress) has a unique structure for an RGS protein: an N-terminus resembling a 7TM receptor and a C-terminal RGS-box. Although a ligand is not known for the 7TM portion of AtRGS1, a simple sugar is most likely.*

*(**D**) The transmembrane receptor Plexin-B1 couples binding of the membrane-bound semaphorin Sema4D to RhoA activation via an interaction with the PDZ domain of PDZ-RhoGEF (and of the related RGS-RhoGEF LARG). Domain abbreviations: IPT, immunoglobulin-like fold found in plexins, Met and Ron tyrosine kinase receptors, and intracellular transcription factors; PSI, domain found in plexins, semaphorins, and integrins; Sema, semaphorin domain.*

The pathway involvement is similar to what we have depicted above.

[44][12] http://www.biolsci.org/v01p0051.pdf

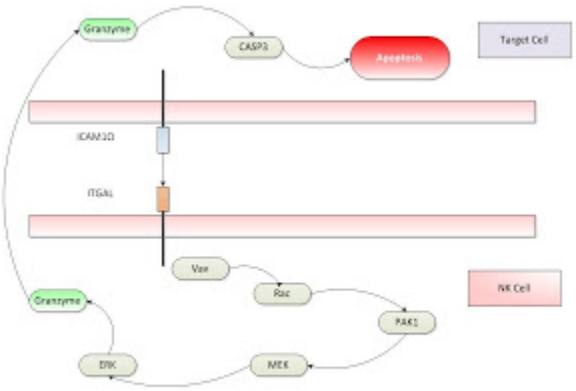
6 ITGAL

ITGAL is integrin alpha L and is also known as CD11, another CD protein and thus another immune response marker and not a pathway marker.

From the KEGG database we have the following additional information[45][13]:

Gene name	**ITGAL, CD11A, LFA-1, LFA1A**	
Definition	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	
Orthology	K05718	integrin alpha L
Organism	hsa	Homo sapiens (human)
Pathway	hsa04514	Cell adhesion molecules (CAMs)
	hsa04650	Natural killer cell mediated cytotoxicity
	hsa04670	Leukocyte transendothelial migration
	hsa04810	Regulation of actin cytoskeleton
	hsa05144	Malaria
	hsa05150	Staphylococcus aureus infection
	hsa05166	HTLV-I infection
	hsa05169	Epstein-Barr virus infection
	hsa05323	Rheumatoid arthritis
	hsa05416	Viral myocarditis

From KEGG we have the following pathway[46][14]:



[45][13] http://www.genome.jp/dbget-bin/www_bget?hsa:3683

[46][14] http://www.genome.jp/kegg-bin/show_pathway?hsa04650+3683

Note the connection between the target cell and the NK or Natural Killer sell from the immune system. ITGAL facilitates the apoptosis of the cell. If ITGAL is defective then we have a loss of natural apoptosis.

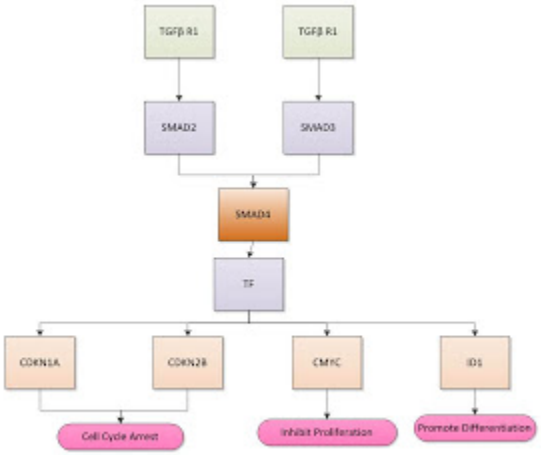
This then is another step in the immune system failing to manage the cell status.

7 CDKN1A

CDKN1A is controlled by SAD4. SMAD4 is an element in the TGF-β signalling chain. TGF is a cytokine, specifically a transforming growth factor cytokine. Like the Wnt-Apc pathway, the TGF pathway links defective development to cancer. The pathway is shown in part below (from Bunz p 199). Normal TGF signalling down-regulates the growth of most normal cells. Several of the genes in the TGF/SMAD pathway activation suppress growth. Specifically the genes CDKN1A and CDKN2B encode the cyclin dependent kinase inhibitors which suppress growth. Activated SMAD pathways also appear to suppress the transcription of other genes including c-Myc.

Kibel et al have recently examined CDKN1A and CDKN1B specifically in prostate cancers with extensive insight.

We show some of the TGF SMAD signalling below along with its control over the CDKN1A element. We will elaborate this later. Note here that CDKN1A controls apoptosis as well.



SMAD4 controls the G1 to S transition. As stated in NCBI[47][15]:

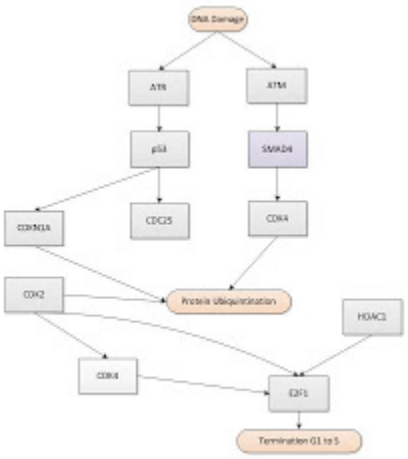
This gene encodes a member of the Smad family of signal transduction proteins. Smad proteins are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to TGF-beta signaling. The product of this gene forms homomeric complexes and

[47][15] http://www.ncbi.nlm.nih.gov/gene/4089

heteromeric complexes with other activated Smad proteins, which then accumulate in the nucleus and regulate the transcription of target genes.

This protein binds to DNA and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the Smad-binding element (SBE). The Smad proteins are subject to complex regulation by post-translational modifications. Mutations or deletions in this gene have been shown to result in pancreatic cancer, juvenile polyposis syndrome, and hereditary hemorrhagic telangiectasia syndrome.

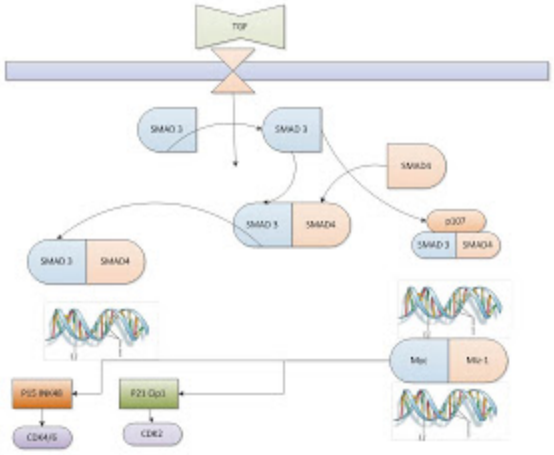
We use the NCI data set for its pathway[48][16]:



The SMAD pathway is also detailed by NCI and one is referred to that source for further detail. From Weinberg (p 291) we also have the SMAD4 pathway showing its immediate control of the DNA transcription.

48[16]

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



As Weinberg states (p 292):

"… Half of all pancreatic carcinomas and more than a quarter of all colon carcinomas carry mutant inactivated Smad4 proteins. Without the presence of Smad4 neither Smad2-Smad4 norr Smad3-Smad4 complexes can form. These two complexes are the chief agents dispatched by the TGF-β receptor to the nucleus with the important assignment to shut down proliferation."

This control mechanism is shown above.

8 C1QA

As NCBI states[49][17]:

This gene encodes a major constituent of the human complement subcomponent C1q. C1q associates with C1r and C1s in order to yield the first component of the serum complement system. Deficiency of C1q has been associated with lupus erythematosus and glomerulonephritis. C1q is composed of 18 polypeptide chains: six A-chains, six B-chains, and six C-chains. Each chain contains a collagen-like region located near the N terminus and a C-terminal globular region. The A-, B-, and C-chains are arranged in the order A-C-B on chromosome 1. This gene encodes the A-chain polypeptide of human complement subcomponent C1q.

Azzato et al have examined C1QA in breast cancer and they discuss it broadly based presence. They state:

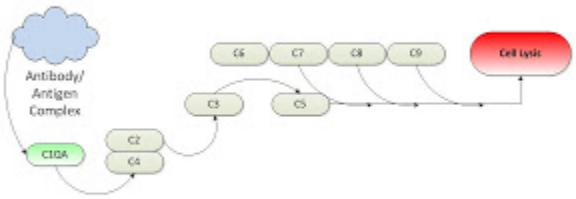
Complement is involved in the primary defence against intravascular microorganisms and has been reported to be involved in the clearance of tumour…. Recently, we have reported an association between expression of C1QA and prognosis in oestrogen receptor (ER)-negative breast cancer… in more than one cohort. We found that ER-negative tumours with overexpression of gene C1QA were associated with a better prognosis. The C1QA gene, located

[49][17] http://www.ncbi.nlm.nih.gov/gene/712

on chromosome 1p36.12, encodes for one of the components of the C1q complex. There are seven single nucleotide polymorphisms (SNPs) catalogued for C1QA on the NCBI database, of which there is only one common SNP (minor allele frequency 45%) located in an exon rs172378 is a synonymous SNP characterised by a G for A substitution at position 361 (A361G).

Thus we have another element from the immune system. It is part of the complement system, not the adaptive part and thus has primitive roots.

Now we depict a selection of its pathway as below (modified from KEGG)[50][18]:



Note that the expression of C1QA is controlling the chain of complement factors which result in cell destruction. Suppression of C1QA then results in loss of this function. C1QA is thus just another factor in the overall control of cell proliferation.

9 Observations

There is a seemingly endless progression of genes identified as related to various cancers. All too often they are just noted as almost an incidental finding and as we have discussed before they are often putatively posed with no detailed pathway implications cited.

In this case we see a preponderance of immune system genes expressed albeit in a late stage of cancer. As indicated it is expected that all of these patients are terminal and that we are arguing of how soon. The range is from 10 to 40 months. Survival is not an end point; we seem to be arguing over when death occurs. As we had indicated above although it has some prognostic capability it has de minimis quality of care capacity. Thus one wonders why even attempt it other than having some scientific value.

On the other hand we can always view this in a Rosenberg manner and see the immune system kicking in in all manners and fashions. Its failure may then result in metastatic results and rapid death. An interesting question for treatment would be if one could re-stimulate or activate these

[50][18] http://www.genome.jp/kegg-bin/show_pathway?hsa04610+712

broken elements and see if they can restore a protective barrier against metastatic results. Rosenberg sought this path in his years of melanoma research. Perhaps this is a means to rejuvenate that to but a later stage of the cancer. Namely we are seeing multiple immune elements failing so what can we achieve to mediate that result.

The problem seen in analyses of this type is that the press all too often exploits its ramifications. This is quite unfortunate for the patients in that they may somehow infer that this discovery may add hope to their plight when in reality it does nothing more than better estimate their demise.

For example there is a quote which states[51][19]:

"There is an urgent need for predictive models that help assess how aggressive the disease is in prostate cancer patients, as survival can vary greatly," said lead investigator William K. Oh, MD, Chief of the Division of Hematology and Medical Oncology of The Tisch Cancer Institute at The Mount Sinai Medical Center. "Our six-gene model, delivered in a simple blood test, will allow clinicians to better determine the course of action for their patients, determine clinical trial eligibility, and lead to more targeted studies in late-stage disease."

This set of tests is not what is desired. We are really desirable of tests which can predict the aggressive nature when the Gleason score is at 6 or less, namely when do we allow, with some sense of safety, for watchful waiting. This report is only for ultimately terminal patients, not those who could survive. This is a classic problem when results like this hit the media, even the professional media. In fact the reports get more exaggerated when we see the results in the popular media.

In summary we may pose the following:

1. There are many of these markers which are immune system related. Is this a common cancer response in the late stages, as much of the literature suggests. If so is the immune system attempting to isolate and defend the body.

2. How does this progress. Somehow one sees snapshots, namely patient A has such and such a profile and we then know when they reach that point the prognosis is bad or very bad. But what are the details of the evolution, do they all follow the same trajectory and if not why not and if so why and what does that mean.

3. Is there an interaction between the pathways and the immune system or is this just a normal, in the case of cancers, immune response. How much of this is prostate specific and how much is common across a wide variety of malignancies.

4. What does this tell us about potential treatment paths? Can we activate the immune system, can we target it, and is the complement system of special interest. Is this a call to further focus on immune system alternatives?

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[51][19] http://www.onclive.com/web-exclusives/Blood-Test-May-Stratify-Risk-in-Prostate-Cancer

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Labels: Cancer, Health Care

TUESDAY, OCTOBER 9, 2012

TOCQUEVILLE AND IRELAND

When I first returned to my ancestral home in Ireland, Mohill, what struck me was that the Protestant Church was lavishly built and the graveyard was tine and aside the Church. The Catholic Church had been built atop a hill and looked like so many Catholic Romanesque Churches in the US after WW II, red brick, long, crowded, lots of kids. The graveyard was down the street a piece, massive in size, hundreds if not a thousand or more gravestones, not as ancient as the Protestant Church. Those facts told a great deal as to what had transpired under centuries of brutal English occupation.

Tocqueville visited Ireland in the summer of 1835, after his trip to the States, and he recorded the brief trip in some notes transcribed and translated into his Journey in Ireland, translated masterfully by Larkin. This is a wonderfully written book, with a sense of immediacy and presence. It is the contemporaneous reflections, not the deep thought of his American journey. He recorded what he saw when he saw it.

On p 11 he states:

The Protestant minister is in general a holy man, whom God has not overwhelmed with work; he has twenty or so thousand francs [£800] income, forty parishioners, and a small gothic church, which is built at the top of the park. The Catholic priest has a small house, a much smaller dinner, five or six thousand parishioners who are dying of hunger, and share their last penny with him; and he fancies that this state of things is not the best possible one. He thinks that if the Protestant minister had a little less and the poor Catholic population a little more, society would gain by it, and he is amazed that five thousand Catholics are obliged to pay twenty thousand francs in taxes to support the religion of forty Protestants.

Tocqueville reflects upon the reality of the situation. At that time the starving Irish were forced to support the English Church of some small but elite class.

On p 49 Tocqueville states:

I have not yet met a man in Ireland; to whatever party he belonged, who did not acknowledge, with more or less bitterness, that the aristocracy had governed the country very badly. The English say it openly, the Orangemen do not deny it, the Catholics shout it at the top of their voices.

I find that the language of the aristocracy proves it more than all the rest. All the rich Protestants that I saw in Dublin speak of the Catholic population only with an extraordinary hatred and contempt. They are, to all intents, savages incapable of recognizing a kindness, fanatics led into every disorder by their priests.

Now, these same people who hold such language are those who have held, and still hold in part, the whole government of the country. How to expect that people animated by such feelings and imbued with such opinions rightly or wrongly, 1 do not know, can treat with kindness, country's money.

Aristocracy, British Aristocracy, was the burden of those occupied, distant owners of land who oppressed the people who tried to scratch an existence from land which could never again be theirs. The lands were taken from them and distributed to those friends of the crown, deprived of any means of existence, the people for centuries managed a mere pittance of a life, lower than slaves in England, they were not even considered as property. Their overseers thought them less than human, livestock had more value.

On page 51 Tocqueville states:

Asked if there is a Catholic church. Answer yes, a mile away. The parish is very large. A parish priest and two curates. Asked how many Protestants in the parish. Answer three. Where is the Protestant minister? He lives in Waterford. Do they still pay the tithe? No, they stopped paying it three years ago. How much did the tithe amount to? 10 shillings per acre of wheat or potatoes. 8 shillings per acre of barley. Meadows were exempt.

Mr. Plunkett, a Dublin lawyer, told me today (22 July 1835) it is only since 1782 that the Catholics can own land. Before that time the law prevented it. One should not be surprised therefore that the Irish population is so completely excluded from the land and that it is so little divided up.

Tocqueville is often amazed of the brutality amongst the locals but he seems from time to time to understand it. As noted above the notes the prohibition on land ownership until 1782. The over-abundance of Catholic clergy, the absentee nature of the Protestant.

On p 59 he states:

We went to see today (14 July 1835) Msgr. Kinsely, bishop of Kilkenny. We found him very simply lodged. He told us: My revenue is not large and still less fixed. 1 have only what comes to me by the voluntary gifts of the faithful, but 1 can sometimes give a dinner. I have a gig and a horse. I find myself rich enough and 1 would despair if the state wished to pay me. Last spring I went to London for the sole purpose of preventing such a measure from being proposed. It would break the union that now exists between the clergy and the people. Now the people regard us as their own work and are attached to us because of what they give us. If we received money from the state they would regard us as public officials, and when we should advise them to respect law and order, they would say, they are paid for that.

Monsignor Kinsley added: In 1828 I was in France. On arriving Rouen I saw two sentries at the gate of the archbishop. What is that? I asked a French ecclesiastic who was accompanying me. It is a guard of honor for the archbishop. I do not want such guards of honor, I explained, they make [people] think your archbishop as a representative of the king.

The observation here tells mountains. On the one hand the clergy understands the need for separation of Church and State, in fact it would be the only way. On the other hand the Irish clergy immediately saw the problem in France by its proximity and possible collusion.

Of all of Tocqueville's works this one is the freshest, most observant and worth a read at any time.
Labels: Politics

MEDICARE AND PUNDITS

The NY Times opinion writer Brooks again repeats a distortion regarding Medicare. In my paper of 2 plus years ago on Medicare Myths I demolished this myth, as reported subsequently in the Washington Post.

Now Brooks states:

According to the Urban Institute, the average couple in 2010 had paid $109,000 in Medicare taxes during their working years but would be able to receive about $343,000 in benefits. A chunk of that $234,000 gap will be paid for by their grandkids. That should weigh on the conscience of every American over 55. You're supposed to help your grandkids, not take from them.

Let us not go through the details let us just do a simple reality check. Let us do the following:

1. Medicare collects 3% of our total compensation each year.

2. Assume that the Government never invests this, in reality it just spends it, so no interest.

3. Let us assume that at 65 the worker has worked 45 years. Not a bad assumption.

4. Let us assume that they were paid the same every year, so their total salary was 45 X. They contributed 3% of 45 X. Brooks quotes that as $109,000.

5. Now solve for X.

X=$109,000/(45*0.03)=$80,074 per year.

Thus anyone making less than this has paid in less and similarly any one more than this pays more.

Now for benefit:

1. At 65 your life expectancy is 16 years.

2. Your averegae Medicare take is $11,000 per year.

3. Your total take is $176,000.

4. You over benefitted by $67,000.

But the Urban Instituted inflated the payout but did not do so with the pay in! Rather unfair I believe. Also the problem is that poorer people are more unhealthy, obesity etc. The poorer get more and pay less. Can we correct that, perhaps.

But the assumptions and facts in the above are almost totally wrong, so let that be, after all it is just the Times and furthermore it is just some opinion writer as well, we could expect no more. In reality the analysis is a bit more complicated, as is most of reality and yes, many people get a deal, and well Mr. Brooks many people get to pay for the others. And for those of us fortunate to be health and to still work past 65 we collect zero and pay 3% till the day we die.

Is the system fair? I do not know but at least we should all deal with the facts. Brooks seems to continuously ignore them. The Urban Institute has an agenda as does Brookings. Why follow that agenda.
Labels: Health Care

MONDAY, OCTOBER 8, 2012

PATENTS AND THEIR VALUE

I have a mixed view of patents. On the one hand it creates the patina of value for ideas. On the other hand it is an invitation for endless litigation. I have avoided patents my entire life, I publish and let the document suffice, or I have donated my patents to MIT if they see so inclined.

I feel this was due to my time on patent cases. In one I just happened to keep my lecture notes from the 1960s and in them I described a certain general implementation which some company thirty years after the lecture made a claim to have invented. It was common knowledge in the 60s but somehow the PTO never caught on.

But in the process it costs many entities millions each. To no avail in the end.

The NY Times has a telling piece on patents worth the read. As the Tomes aptly states:

One option is judicial activism. This year, Judge Posner, in an Illinois federal court, tossed out patent arguments made by both Apple and Motorola Mobility in a 38-page opinion that dismissed a lawsuit between the two companies. Cleaning up the patent mess, Judge Posner said in an interview, might also require reducing the duration of patents on digital technologies, which can be as long as 20 years. "That would make a big difference," he said. "After five years, these patents are mainly traps for the unwary."

Ideas have also come from policy experts and Silicon Valley. The Federal Reserve Bank of St. Louis recently published a working paper calling for the abolition of patents, saying they do more harm than good.

Another idea is to create different classes of patents, so that some kinds of inventions, like pharmaceuticals, would receive 20 years of ironclad protection, while others, like software, would receive shorter and more flexible terms.

In my view the patent is a double edged sword, on the one hand it conveys ownership and on the other it stifles creativity. What the best solution is one can but guess, however the problem is real. Anyone who develops technology recognizes the quick sands that are afoot, one cannot review all prior art, it is too massive, and ultimately one may accidentally cross a line set up by the PTO. On the other hand there are the patent collectors who set out to sue no matter what. Clearly the system is near being broken. How to fix it is the question.
Labels: Law

SATURDAY, OCTOBER 6, 2012

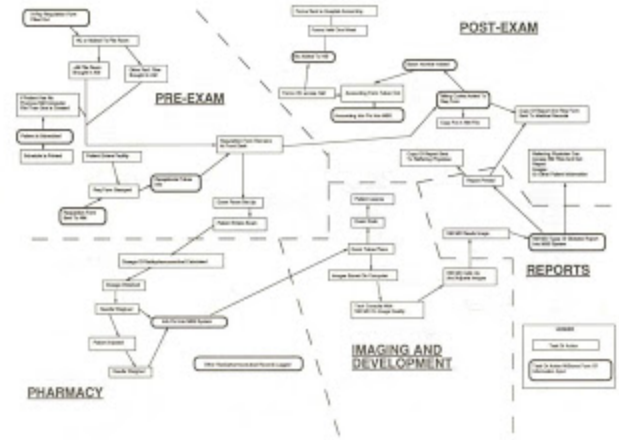
UNDERSTANDING HEALTH CARE COSTS

In the current JAMA there is an article describing how medical students should have a better grasp of the costs of health care especially the complexities of many procedures.

The article states:

Teachers can demonstrate the consequences of seemingly simple decisions. For example, an order for an inpatient chest x-ray requires the following: someone schedules the test, someone informs the patient that the x-ray is being done and why, someone transfers the patient from the bed to a stretcher or wheelchair and transports him or her through hallways to the radiology department where the patient spends time alone in the holding area, and then someone leads the patient through maneuvers to obtain the radiograph. These steps are reversed to return the patient to his or her room. A radiologist interprets the image and creates a report. The clinician who ordered the test examines the report and then makes a decision based on that information. Then, the patient and often several family members need to be informed of the findings and how those findings will affect the next steps in care. This is not a simple process. Now multiply this by the number of patients under a team's care and the number of tests ordered for each patient.

Consider the challenges of more complex diagnostic tests, such as colonoscopy. Then think about the influence of the patient's age and health status on that process. Having students observe each of these steps for tests they order on some of their patients would emphasize the effects of those decisions on patient comfort and resource utilization. This exercise would complement the strategy of showing trainees the prices of ordered health care services, an approach that has produced mixed results on cost reduction. It does so by translating prices in monetary units into real resource (primarily labor) requirements.



In 1991 I wrote a paper with Mike Sununu which examined the number of steps in performing a nuclear scan (see the steps above). We examined ways to reduce the steps and in turn the costs. The article in JAMA raises a much larger set of issues. Health Care providers as a result of Government regulation as well as legal liabilities are often forced to go through steps so arcane and complex that they drive costs to extreme levels.

Health Care administrators all too often focus on collecting maximum benefits and fails grossly to address the issue of cost reductions, and they do not understand the work flow environment. The JAMA article establishes a paradigm for a set of simple procedures. However the overhead is exploding. As we have shown in a prior posting the only growing industry is health care, not because we provide more and better care but simply because it is so complex and arcane. No business person would tolerate such inefficiencies. However it is the Government which all too often makes this worse, just look at ACA.

With the EHR now coming to the fore, I observe several phenomenon, they drive costs up and care down. Namely the use is as follows:

1. The physician enters the data looking at the screen and not the patient. Osler would not at all be happy.

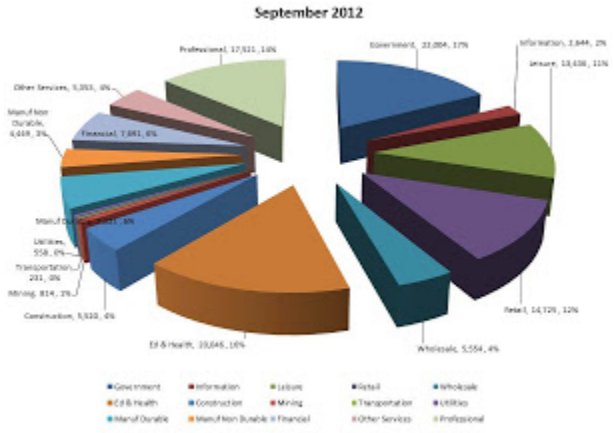
2. A second person follows the physician around typing into the system.

3. A physician takes notes and then has another person transcribe them after the fact into the EHR.

The variations go on. I have yet to see an EHR provide useful information for patient care. It is now just one more added burden. Using the work flow analysis as described above one could readily calculate costs, the benefit is de minimis but the cost is extraordinary.
Labels: Health Care

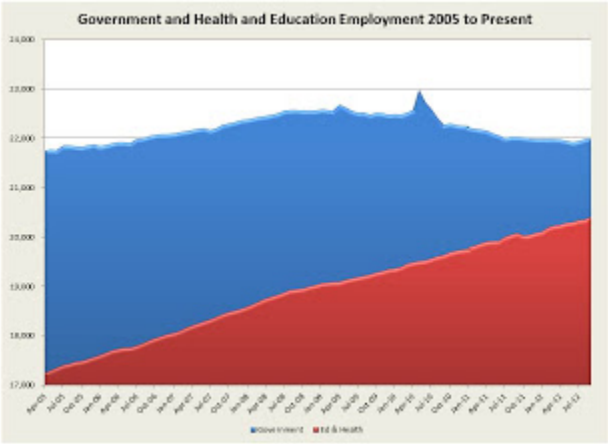
FRIDAY, OCTOBER 5, 2012

DIGGING INTO THE DETAILS

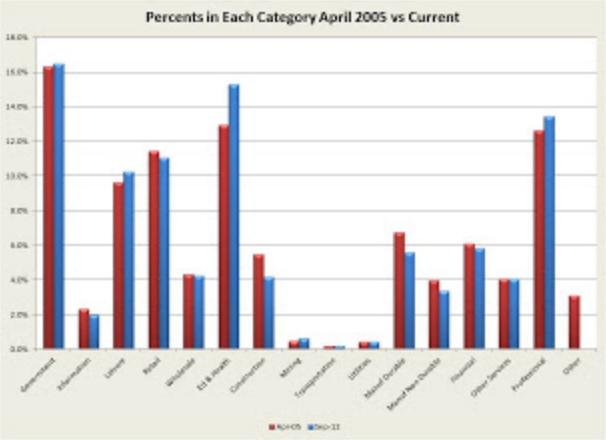


We have dug a bit deeper into the details of the employment report and show them here for a more detailed understanding. Above we show the breakout by sector as of September. Also just look at the total percents in Govt and Ed/Health.

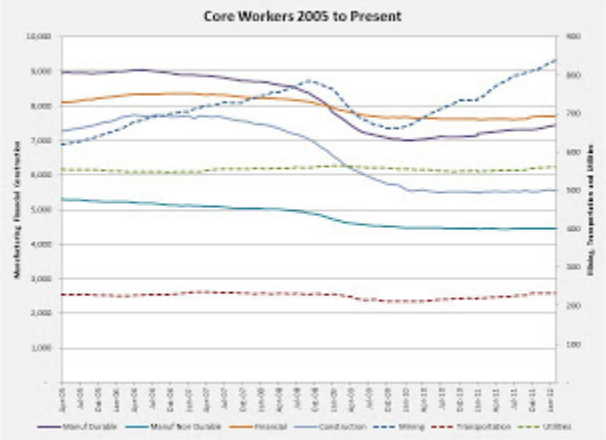
A closer look at Government and Education/Healthcare shows continuing explosive growth in Health Care.



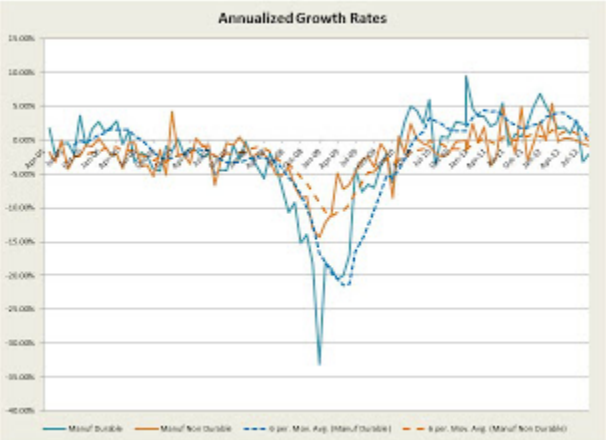
This I believe will be a serious problem going forward and will be uncontrollable unless major changes are made and that includes the removal of ACA and its demands.



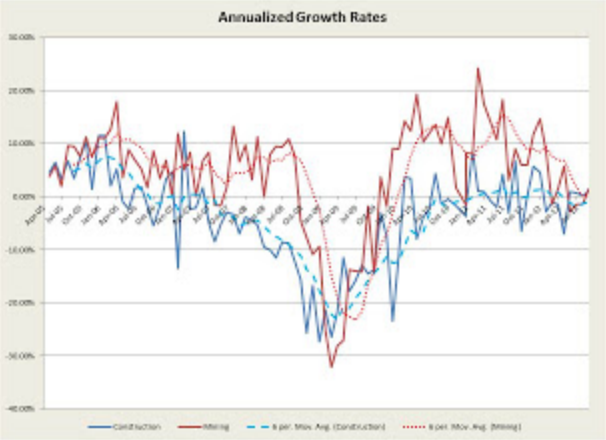
The above shows the change from the beginning of the collapse until now. Remember that the population has increased so that growth which may appear may actually be just a population effect. We see Ed/Health and Government are the largest contributors.



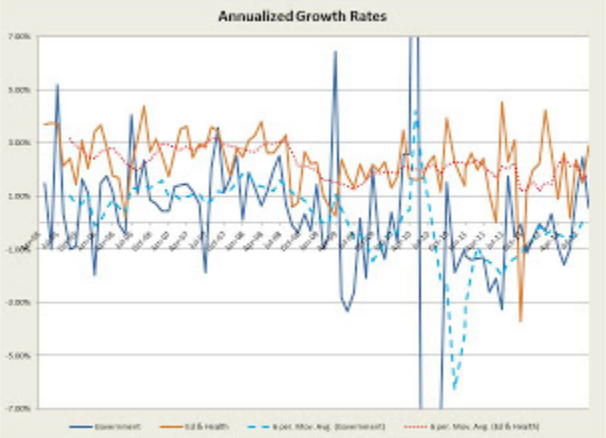
Above is the employment by month by sector. We see some growth in a few sectors but great weakness across the board.



The above and following two depict percent changes by a few sectors. Note above we have dropped in Manufacturing and have negative growth.



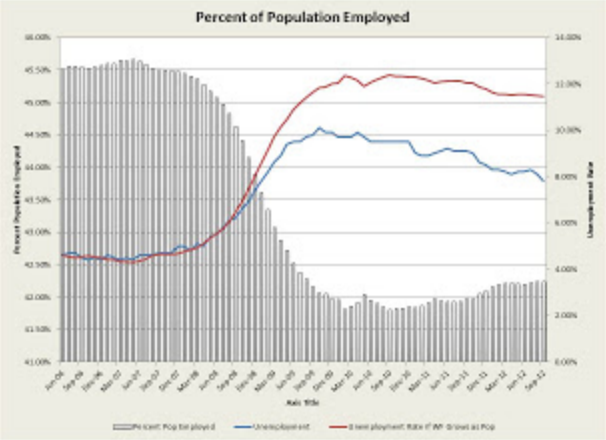
And finally:



The details are not positive despite the spin machines.
Labels: Economy

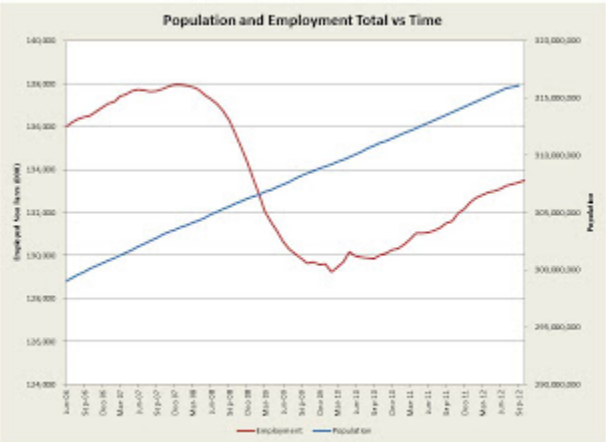
EMPLOYMENT UPDATE, NOT REALLY GOOD

The latest report is in and despite the claim of a 7.8% rate when examined in minor detail it is still poor. Let us examine in a bit of detail:

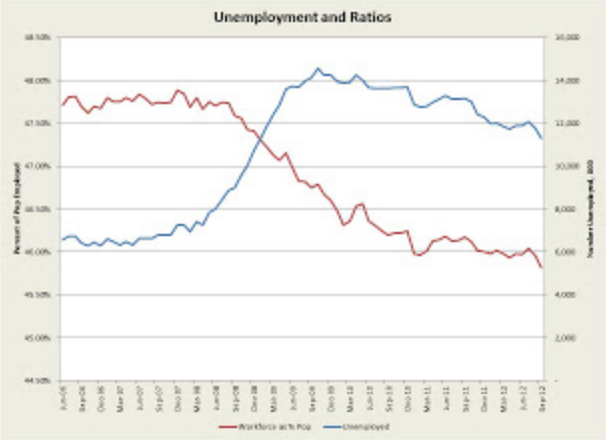


First as above we see that the unemployment based upon the Jan 2008 percent of population employed is still just under 12%. In fact is has frozen there. Remember that more than 47% of the population was employed then and that the population increases at 250,000 or more a month so that we need about 120,000 plus new jobs a month just to stand still. That is the issue of having a moving denominator, one can come up with whatever number one wants.

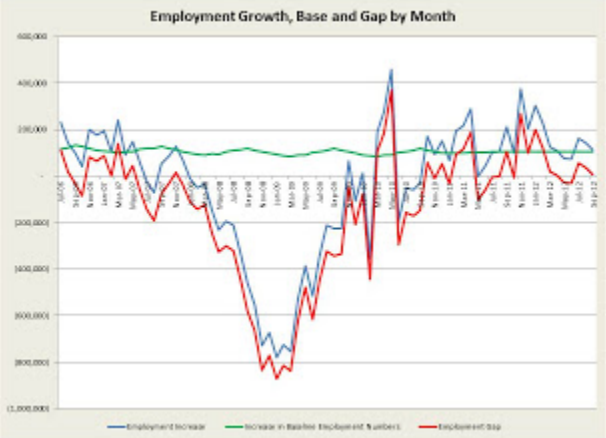
What is critical in the above is that we are stalled at about 42% of the population employed whereas before the crash we had 45% of the population employed. Thus we have about 12 million lost from the employment pool, just written off, the "Forgotten Workers". The 7.8% is thus frankly an arithmetic fluke, an insult to those written out of the pages of the employable. I would never expect the Press to even understand this no less report on it, it is against their core and is not within their limited intellect.



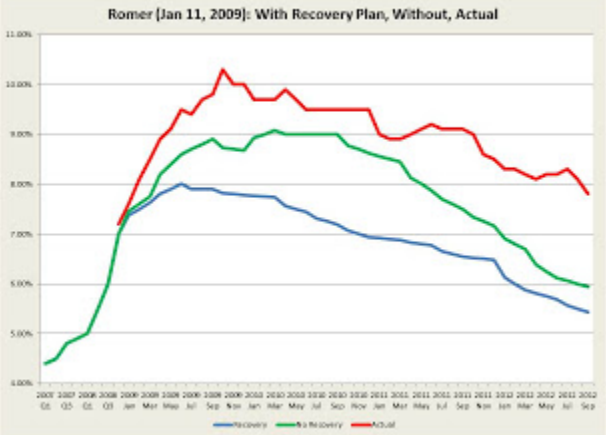
The above shows the details of what I have said above especially the growing population but the lagging employment. In fact September was downward sloping. The Devil is always in the details.



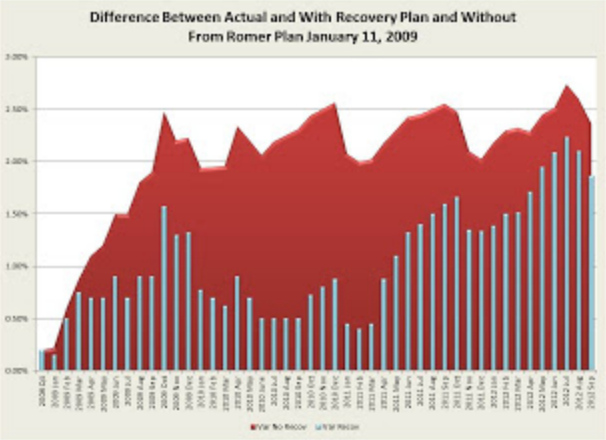
The above gives further insight showing what we have discussed.



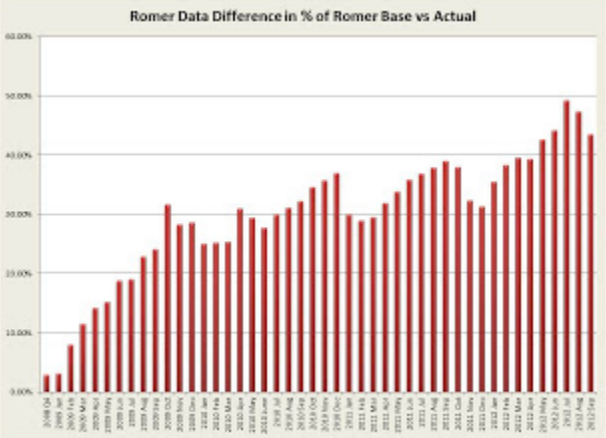
The red line shows whether we are gaining or losing. Here we show just about zero gain at best. Not what the DOL suggests.



Now my favorite. This is the Romer chart. She said we would be a booming economy by now. So much for left wing economists. Please don't have them build bridges.



The above is the error rate on Romer and below we show the percent error.



Labels: Economy

THURSDAY, SEPTEMBER 27, 2012

FROM CANADA

I like Canada, I married into a Canadian family, and in New Hampshire I live less than an hour from the border. I even like the AM French stations I hear late at night with the music so un American.

Now from north of our border comes the following statement:

The fact that Willard M. Romney is still running almost even in the polls despite his demiurgic implausibility as a candidate, afflicted by a one-person pandemic of foot-in-mouth disease, illustrates the concern of the American voters. Either Romney lucks through and numerate sanity starts to return to American public life, or the most self-destructively incompetent regime since James Buchanan brought on the Civil War, will come back and stoke up a truly spectacular inferno that will purify America in a mighty economic Jonestown. There will be no more tugging

at a trouser leg from Canada — either a comradely pat on the back, or a neighbourly blast with a fire extinguisher, but this operatic crescendo can't continue for one more full act.

Perhaps we should listen and heed it. From the time of Gov Thompson and his need to arm New Hampshire with nuclear weapons to defend themselves against the "Commies" in the North, to now with the North telling us that we are worse off than most others, and they are correct, it will be interesting to see if any down here are listening.

This is worth a read.
Labels: Politics

MONDAY, SEPTEMBER 24, 2012

SUETONIUS, POLITICIANS, AND GIVING AWAY THE PUBLIC MONEY

Suetonius, in his Twelve Caesars, reflects on the Emperor Vespasian as follows:

Vespasian behaved most generously to all classes: granting subventions to senators who did not possess the property qualifications of their rank; securing impoverished men of consular rank an annual pension of 500,000 sesterces; rebuilding on a grander scale than before the many cities throughout the empire which had been burned or destroyed by earthquakes; and proving himself a devoted patron of the arts and sciences.

He was the first to pay teachers of Latin and Greek rhetoric a regular annual salary of 100,000 sesterces from the imperial exchequer; he also awarded prizes to leading poets, and to artists as well, notably the ones who refashioned the Venus of Cos and the Colossus.

An engineer offered to haul some huge columns up to the Capitol at moderate expense by a simple mechanical contrivance, but Vespasian declined his services: 'I must always ensure', he said, 'that the working classes earn enough money to buy themselves food.' Nevertheless, he paid the engineer a very handsome fee.

When the Theatre of Marcellus opened again after Vespasian had built its new stage, he revived the former musical performances and presented Apelles the tragic actor with 400,000 sesterces, Terpnus and Diodorus the lyre players with 200,000 each, and several others with 100,000; his lowest cash awards were 40,000, and he also distributed several gold crowns. Moreover, he ordered a great number of formal dinners on a lavish scale, to support the dealers in provisions.

On the Saturnalia he gave party favours to his male dinner guests, and he did the same for women on the Kalends of March. But even this generosity could not rid him of his reputation for stinginess. Thus the people of Alexandria continued to call him 'Cybiosactes', after one of the meanest of all their kings.

One need only read between the lines, the Emperor gave money to engineers not to work and employed those who did the work, Shovel Ready Projects, he paid the teachers exorbitant sums, well we know where that is, then money to the theatre, or as we call them "green" jobs. Politics never changes, politicians remain somewhat the same. Suetonius was the Bob Woodward of Rome for a while, a bit more succinct, yet as telling and as insightful. Plus ca change, plus c'est la meme chose..
Labels: Politics

ECONOMISTS AND THE ECONOMY

I have a continuing spat with the economists who have all too often been wrong, both in predictions and worse in recommendations. In a recent blog entry by Mankiw, whose projections paralleled my comments for the past 4 years as regards to the actions of the current Administration has an interesting blog entry.

This post takes its title from a new article at Econ Journal Watch. Here is the abstract:

"In early 2009, the incoming Obama administration's Council of Economic Advisers predicted real GDP would rebound strongly from recession levels. In a blog post, Greg Mankiw expressed skepticism. In their blogs, Brad DeLong and Paul Krugman sighed. Of course there would be strong growth, they maintained, because the recovery of employment would mandate it via Okun's Law. Mankiw challenged Krugman to a bet on the issue, but there was no response. Of course we now have a good idea of the likely outcome, but I posit a hypothetical time series econometrician who, at the time of the blog entries, applies some standard forecasting methods to see whether DeLong and Krugman's confidence was justified. The econometrician's conclusion is that Mankiw would likely win the bet and furthermore that a rebound of any significance is unlikely. The econometrician has no idea how DeLong and Krugman could have been so confident in the CEA's rebound forecast."

Now my rants have been targeted at Romer and her now infamous January 11, 2009 paper from the "Office of the President Elect" stating what one would expect from the Stimulus. As we have chronicled for almost 4 years her projections never came close. Mankiw and others were more on target. One thus wonders where we may be in another 4 years if we are to continue this way.
Labels: Economics

VERIZON AND CABLE

There was an interesting article in today's Times about Verizon and the CATV folks. It states:

"We were all trained to believe cable operators and the phone companies were natural enemies," said Craig Moffett, an analyst at Sanford C. Bernstein & Company.

Cable operators and phone companies thought so, too, but the cable companies have largely ended efforts to compete in the mobile phone business because the cost of building their own wireless networks could be prohibitive.

Instead, they can use Verizon to attract customers without investing in a network of stores. "We've looked at a whole range of options for how to fulfill that customer need, including building our own cellular carrier, but we concluded we would be a late entrant in a highly competitive business," said Peter Stern, chief strategy officer at Time Warner Cable.

Cox, which tested the waters in the wireless market, now sells Verizon products and services in its Cox Solutions Stores in Tulsa, Okla., and Oklahoma City. Cox, which is based in Atlanta, has 130 retail locations and predicts Verizon will be a major part of its offerings.

Now let me refresh a few on the technical facts:

1. LTE/OFDM can accommodate 8 bps/Hz of bandwidth.

2. Verizon just got a tremendous amount of bandwidth.

3. Adaptive beam antenna can multiple OFDM by a factor of 10, thus almost 80 bps/Hz.

4. MPEG 4 runs at 2 Mbps and H.265 will half the rate of H.264 with HDTV.

5. Verizon can then provide direct to the home HD TV and everything else with their exiting bandwidth and cell sites.

What does this mean:

1. Cable companies will have near instantaneous competitors at marginally lower costs.

2. Verizon has a union problem on the wireline side. Thus the ending of FIOS, along with its costs. There is no union on the wireless side so by switching to all wireless means the end of the unions, and further reductions in costs.

3. Wireless is seamless between fixed and mobile, same techniques, and thus extends over the customer's life cycle.

4. By being the face to the customer you get to own the customer. Going forward Verizon could own all of the customers and the CATV guys are left behind.

So who thinks this is a good idea?
Labels: CATV, Telecom

WILL RATIONING HAPPEN HERE

The Telegraph in the UK states:

GPs believe the numbers of patients asking about paying for operations including cataract removal and joint replacements has increased markedly in the last year, according to a poll.

Dr Clare Gerada, chairman of the Royal College of GPs, said it was "incontrovertible" that increased NHS rationing was behind the increase in going private, a trend she described as "very sad".
The poll, carried out by ComRes for the firm BMI Healthcare, found that 70 per cent of GPs are now unable to refer a patient for further treatment on the NHS at least once a month because they do not qualify under local criteria.
Primary care trusts (PCTs) have increasingly been restricting access to treatments including cataract removals, hernia operations and hip and knee replacements, by raising the threshold of how ill or disabled a patient has to be.
It is suspected that the same will happen under the ACA especially for Medicare patients. Whether that is good or bad depends on what is rationed and to whom.
Labels: Health Care

TUESDAY, SEPTEMBER 18, 2012

OBESITY AND THE GOVERNMENT

Obesity is an epidemic and the major cause of Type 2 Diabetes. As we have argued in our draft online book on Obesity and Type 2 Diabetes (with some 10,000 downloads!), the solution is quite simple, stop eating. Or at least get down to where your caloric input equals or is less than you burn rate, generally about 1,800 to 2,200 kcal per day. Recall that a pound gain in weight occurs for every cumulative 3500 kcal above the burn rate. 200 Kcal sodas consumed at 17.5 per week add a pound. Pizza at 800 Kcal, well you can do the math.

Now in JAMA two authors, one being the head of NIH state:

The obesity epidemic is not the first major health crisis that the United States has faced. In recent decades, progress has been made against such daunting challenges as tobacco use, infant mortality, and HIV/AIDS. However, obesity may pose the most significant challenge yet because it involves changing approaches to 2 fundamental aspects of daily life: food consumption and physical activity. To have any chance of release from obesity's ever-tightening grip, the nation will require broad-based efforts in every corner of society: homes, schools, community organizations, all levels of government, urban design, transportation, agriculture, the food industry, the media, medical practice, and, without question, biomedical research....

To address this need, research must proceed swiftly on 2 parallel fronts. The first is to devise practical and effective strategies for intervention, with special emphasis on preventive strategies that can be rapidly implemented in health care and community settings. The second is to evaluate community-based efforts that will soon be launched or are already under way, to gather data about their effectiveness, and to use that information to develop evidence-based interventions that can be applied on a wider scale.

I respectfully disagree. Obesity is 50 to 100 times worse than AIDS, and it is simply controlled by controlling consumption. It does not require retroviral drugs it just requires reduction in calories. So let's look at the above.

First, intervention, as any GP or Internet knows if you get 1% of your patients to voluntarily control intake it is a miracle. You see them frequently, adjust the metformin or insulin, send them to specialists and at best they never really get any better. They must see this as an economic issue, they must pay more for the right to get fat, and then we must pocket the funds to pay for the inevitable. Frankly it worked with tobacco.

Now as a community issue, we all too often see obese families, obese groups of people, and they do reinforce one another. Thus Collins et al pose the need for some community approach. Again in my experience this is difficult if not impossible. "Mother" has food on the table, and often an excess. Societal pressure creates an accelerated demand. Again there is no motivator other than price, an economic motivator.

As we have argued before, there are two economic approaches, Pigou and Coase. Pigou taxes at the point of consumption, tax on carbs, and Coase at the point of impact, if your BMI exceeds 25.0 you are taxed. This thus is a medial problem ex post but an economic problem ex ante.
Labels: Health Care

MONDAY, SEPTEMBER 17, 2012

PELAGIUS, INDIVIDUALISM AND THE NUN

The NY Times recounts the speech of some nun at the convention a week or so ago. As they state:

The Catholicism of Sister Campbell and Mr. Biden is a natural fit for Democrats. It is the faith of social justice activists like Dorothy Day and Thomas Merton, the church whose pope pleaded for relief of the "misery and wretchedness pressing so unjustly on the majority of the working class" in an 1891 encyclical.

Now let me mention two excommunicated thinkers in the Catholic Church; Pelagius and Ockham. It was Pelagius, a British monk, who proclaimed that individuals can attain their salvation based upon the good acts they perform, that the individual has both the capacity and the ability to act in a way to do good deeds. Furthermore it was incumbent on the individual alone to do so, not through a group, it was the person's singular actions. Needless to say Pelagius lost and Augustine won. For Augustin was a classic Roman, one of the last, seeing man as a "subject" of

the Church as they were "subjects" of the Roman Empire. The very concept of the individual was a heresy to Augustine. Furthermore he rejected individual deeds and introduced the concept of grace and divine selection, God gives grace, and no matter what you do unless God decides on you, that is the only metric, thus predestination.

Now for Ockham, the first modern individualist. He argued against the Pope, he saw the Pope as just another individual, not as some supreme worldly pontiff, whose views went beyond any question. Indeed he questioned, and John XXII was most likely less than any pope we can envision.

Then in the 19th century we have the rise of socialism and the like and Rome's counterattack to more loss in its authority was infallibility of the Pope and the construct of social justice. Frankly they also grew from the loss of Papal lands and the pushing by Garibaldi and the nationalists of the papacy back to a religious only institution. From this comes social justice, a clear loss of individualism and demand for the global community to follow the Pope en masse. Thus the strange movement of nuns using social justice as a template but at the same time denying Papal supremacy is the cornerstone of the Democrat thrust into Catholicism.

Is it not truly what each person does, individually and on their own, is not the New Testament a document freeing the individual and at the same time demanding from each, each person, their due. Social justice is a movement wherein the collection of a few put demands on the many. What benefit does that have, it glorifies the few and oppresses the many. It does not allow the individual to act, to demonstrate the essence of their faith.

The recent document from the Vatican, Compendium of the Social Doctrine of the Church, presents the Vatican's view, and in many ways it both denies individualism, and in turn individual responsibility, and sets forth a doctrine of societal duty as a group. One may ask what happens when we seek collusion with Caesar, in stead of individually giving God what is due, individual acts. Pelagius may very well have some kernels of truth, Augustine was clearly hanging on to the City of Rome, both man's and God's. Furthermore Ockham and his arguments have strong merit especially in light of the many mis-steps of the papacy over two millenia.

Thus we hear from some nun about what we as a group should do, whereas the Gospels speak to us as individuals, letting Caesar get his piece apart from our duties elsewhere. The Times continues:

Mr. Biden is not a “cafeteria Catholic” who chooses his beliefs according to convenience. He stands in the tradition of the Rev. John Courtney Murray, the Jesuit theologian who asserted that the foundation of modern pluralist society is not perfect agreement but continuing “public argument” based on shared values. The laws that frame this evolving conversation cannot always align with religious teachings. “It is not the function of civil law to prescribe everything that is morally right and to forbid everything that is morally wrong,” he wrote in a 1965 memo advising the church to support the decriminalization of artificial contraception.

Two quick points, Catholics have to accept the total bundle, but what one suspects is that what the bundle is, is bounded by the four walls of the Gospel. Second, Jesuits and Vatican 2 have a

rather shaky record. I remember quite well that period, having spent pre-Vatican 2 in the Franciscan Seminary and Vatican 2 in a Catholic institution, and Murray is hardly the sine qua non expert to choose, nor Maritan.
Labels: Commentary

FRIDAY, SEPTEMBER 14, 2012

WORDS AND WISDOM

In the winter of 1960 the snow was wet, heavy, and the temperature just hung around freezing, making the streets a combination of ice and slush. For reasons I seem to have misplaced somewhere in my white matter my father had gotten me a job, full time, twelve hours a day and six days a week for six weeks in the New York Sanitation Department, in the Port Richmond Depot, shoveling snow from streets. Now he had arranged with my school's headmaster, since by that time I had finished all my requirements for graduation, had gotten early admission, had scholarships, and was I guess getting to feel my oats, so manual labor amongst the folks was the wise thing to expose me to. Of course such a course of action would be unheard of this day, but then it was I suspect a way for a growing young man to see what the real world was like.

So up at 4 AM, by bus to the depot, and in a large garage filled with exhaust I assembled with fifty other young men, yet for all the others this was their real life, for me I saw it as some form of punishment, but one never questioned father or Brother Richard. One just got there and pitched in. Out into the streets, not having boots and long underwear, I wanted to look cool, I set about my tasks, shovel in hand, with my nice rabbit lined gloves, digging out gutters, crossings, being splashed by every vehicle, through sunrise, noon, sun set and back to the depot. Then home, drop, then start all over again.

Not what helicopter moms subject their kinder to but it was a learning experience. But where does this lead? Well in this environment with these lost folks whose lives would gone on this way forever I learned how to use the four letter word, f**k as a noun, verb, adjective, adverb, preposition, infinitive, prefex, I could decline and conjugate it, active and passive voice, I could use it as a subjunctive, and thank God for my Latin, Greek, and French, I had learned a new one word language, imagine that, just one word, carefully emphasized by syllable and ending and I could conduct a full conversation. I do not think either my father of the Headmaster had fully thought through this but upon my return it did help my Middle English translation of Chaucer. Thus I now had the ability to speak as any good Staten Islander, just look at Jersey Shore; they are all my successors in linguistics and rhetoric, examples par excellence of Staten Island dialects.

Now this never did me any good in Cambridge, MIT or Harvard, in fact I never recall using it, but there have been times when it can so easily fall from my lips, fluid and clear, perfect pronunciation and crisp and clear diction and well parsed word structures.

Thus reading Woodward slates tome, The Price of Politics, well worth every penny, I was reminded by the actions of the then Chief of Staff at the White House how self centered egotistic amateurs use this dialect. This may was an interloper, he had no style, part thug, part Martinette,

he would use this wonderful word just to show off, as if he had learned it the way I had, in the streets, amongst the people. But when you really learn, I mean really learn its use, you have an almost operatic flow, it requires hands, head, and eye motions, choreographed in a manner which can only be gained by shoveling slush in the New York Streets. Somehow the bonding which occurs with the slush, the splash, the sinister drivers, all blends into a manner of using this word with full grammatical correctness.

Frankly it is a shame that we have those in public service act this way, it becomes their legacy, it proves nothing than perhaps the thug like character of their very being, hollow men hiding in feigned words, and as one well versed in its usage, trained by some of the world's best semiotic professionals, understanding the full sign carrying elements, I find it undignified and harmful.
Labels: Commentary, Politics

TUESDAY, SEPTEMBER 11, 2012

REMEMBERING 9/11

On September 11, 2001 I was in Prague. After the news I had dinner alone in the Marriott and was joined by two American couples who had come to Europe for the first time. The two men had flown fighters in WWII and they were there to reminisce. As we watched the television monitor they recalled briefly their time some 48 years earlier as young men and to them this was even more striking than Pearl Harbor. As with many tragedies as this we sometimes let memory slip into the past where it is safe, we forget the intensity of the feelings of that time. But for those of us who were proximate, we lost about 50 people in our town and the surrounding towns, this was real. Each town has a piece of the buildings as a memorial in some special place. We have different presidents, different leaders, but the same intense feeling amongst most Americans of the need to protect and defend. It is a day we all remember.
Labels: Commentary

ON LINE EDUCATION AND THE ACADEMY

I have serious questions as to what this on line "stuff" really is. I had taken the first MIT course and had serious problems, and frankly still do. I am trying the others as well. But here are some of the concerns:

1. What is the objective, why are you doing it? Other than just doing it one must be careful about the classic ambiguity of expectations. You may expect A and the student Z. It results in disaffection. Trust me, it always does. Do the students just want to "learn" and if so what do they expect in obtaining the certificate. Then also how does one know who really took the exams. The certificate may go to someone who never read the book. Then why give certificate. If it is for self learning then let it be to the self alone.

2. Why are you doing it? Why is an institution doing this? Just to follow others? That is a bad idea. It means that you end up justifying it on the fly. Are you being charitable, nice but with costs rising exponentially then you may be shortchanging the students who pay, or their parents, and the alumni who donate.

3. Equity is at play. The students who pay, get vetted, attend class, and pass are clearly better than the "someone" who gets a certificate.

Now in a NY Times piece on the firing of the President of UVA one reads:

What had the board so worried? In late May, as she prepared to remove Sullivan, Dragas e-mailed a board colleague a link to a Wall Street Journal column, beneath the subject line: "Why we can't afford to wait." The article described a joint venture that offers free, open online courses. In the last year, Harvard, Stanford, M.I.T. and other elite schools have moved aggressively into this arena, drawing significant global audiences, if no actual revenue. While many veteran professors roll their eyes at predictions that online learning will transform the structure of universities, to certain segments of the donor community — the Wall Street and Aspen Institute types — higher education looks like another hidebound industry awaiting creative destruction. "If you're not talking about it," says Jeffrey Walker, a UVA fund-raiser and a former JPMorgan financier, "what's wrong with you?"

Perhaps there is not only nothing wrong with you but you may be smarter than the rest. After all MIT and Harvard plan to spend $30 million apiece out the gate to start this process. That would be a big chunk of change for UVA with there being no clear reason to do it. Afford to wait ... why not if there are so many empty questions.

There is not a single tangible piece of evidence that this will change the universities. In fact as best I can gather from my MIT colleague many of those who got As were my former students back in the late 60s and early 70s taking the course again as I did. There was no vetting of the students, no idea of their backgrounds, and apparently as best I can gather no post course review of the course takers.

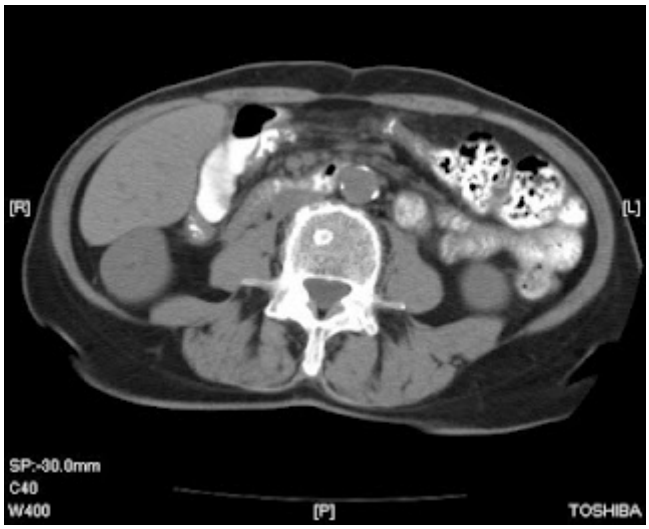
I have had this conversation with many who wanted the same fast movement and after a discussion of the type that any reasonable business person would have they changed their views drastically, and fell into the camp of "why are we doing what?".

Perhaps the same momentum do follow the lemmings was similar to what led to the financial collapse. I always remember my father's comment, prior planning prevents poor performance. So

just don't follow the lemmings unless you know why and what the consequences may be. The President was apparently quite prudent.
Labels: Academy

MONDAY, SEPTEMBER 10, 2012

THE TASK FORCE AGAIN



According to the NY Times, the USPTF has issued another dictum, namely that testing for ovarian cancer has no merit. They states:

Tests commonly recommended to screen healthy women for ovarian cancer do more harm than good and should not be performed, a panel of medical experts said on Monday.

Now this may not be exactly true, but it is mostly. There are two simple tests for ovarian cancer, CA125 in the blood and ultrasound exams of the ovaries. They are not bad, but, and here is the real problem, they do not seem to make themselves evident until too late a time. Why? Ovarian cancer grows very rapidly. Thus if one has a yearly interval, and the cells double at say a 5 day rate or even less, then at say 3.65 doubling there is 2^100 times the cell, roughly. That means a massive tumor in a ear.

Thus the question is how frequently should one scree to see a material change in survival in ovarian cancer from such screening. Again no one seems to have even thought of the correct question. But alas the USPTF seems to have this chronic ailment.

If one asks the question then I suspect based upon a back of the envelope test one should test every month or so. That is a bit expensive. But if e have a 5 day doubling time then we have 2^6 in a month, or only 64 cells. Is that enough to see or raise CA125. We do not know. How about once every 100 days, with 5 day doubling time. That is 2^20 cells or 1,000 times 1,000, and now we have a mass with CA125 effect and observable on ultrasound. But has it metastasized already? Good question.

But as with all such issues the insight is all too often in the question, not the answer. Ask the right question and you are brilliant.
Labels: Cancer, Health Care

WEDNESDAY, SEPTEMBER 5, 2012

JAMES, PRAGMATISM, AND ANTNEE SQUIRREL

I was rereading William James and Pragmatism to better understand what he meant. He says:

SOME YEARS AGO, being with a camping party in the mountains, I returned from a solitary ramble to find every one engaged in a ferocious metaphysical dispute. The corpus of the dispute was a squirrel—a live squirrel supposed to be clinging to one side of a tree-trunk; while over against the tree's opposite side a human being was imagined to stand. This human witness tries to get sight of the squirrel by moving rapidly round the tree, but no matter how fast he goes, the squirrel moves as fast in the opposite direction, and always keeps the tree between himself and the man, so that never a glimpse of him is caught.

The resultant metaphysical problem now is this: Does the man go round the squirrel or not? He goes round the tree, sure enough, and the squirrel is on the tree; but does he go round the squirrel? In the unlimited leisure of the wilderness, discussion had been worn threadbare. Everyone had taken sides, and was obstinate; and the numbers on both sides were even. Each side, when I appeared, therefore appealed to me to make it a majority! Mindful of the scholastic adage that whenever you meet a contradiction you must make a distinction, I immediately sought and found one, as follows: "Which party is right," I said, "depends on what you practically mean by 'going round' the squirrel. If you mean passing from the north of him to the east, then to the south, then to the west, and then to the north of him again, obviously the man does go round him, for he occupies these successive positions. But if on the contrary you mean being first in front of him, then on the right of him, then behind him, then on his left, and finally in front again, it is quite as obvious that the man fails to go round him, for by the compensating movements the

squirrel makes, he keeps his belly turned towards the man all the time, and his back turned away.

Make the distinction, and there is no occasion for any farther dispute. You are both right and both wrong according as you conceive the verb 'to go round' in one practical fashion or the other."

Well as I went out to check with my fried Antnee stuffing himself on the feeder and asked him what he thought he sat there a while and looked at me somewhat stunned. His first comment was:

"Was this from some Professor Sir?"

Surprised I said "Yes, Antnee."

He then replied:

"A Professor from Harvard Sir?"

I replied again, "Yes".

He then said:

"Enough said Sir."

Then he went about eating again. I guessed that was pragmatism for Antnee!
Labels: Academy, Commentary

MONDAY, SEPTEMBER 3, 2012

INDIVIDUALISM AND THE LEFT: RECONSTRUCTING INDIVIDUALISM, A REVIEW

In the book, Reconstructing Individualism, by Albrecht, one finds an interesting attempt by the left to redefine the concept. Although difficult to read, it is not well written, its portrays the mind of the left with some clarity.

Individualism as a concept suffers from a lack of consistent definition. In this book by Albrecht it is impossible to find any definition, especially of what he seems to call classic individualism. The intent of the work one gathers is to "reconstruct individualism" along the lines of Emerson, Dewey et al using a pragmatic bent most likely according to James. Strange choice to build a view of individualism upon, for at best Emerson looks at the individual in an inward sense, along the lines of being true to yourself and Dewey was in effect a Marxist in his world view, having been a member of the Defense team for Trotsky in his trial resulting with the break with Stalin. Thus even incorporating Dewey stretches the view of Individualism to an extreme, for even Dewey in his works on Individualism demonstrates at best contempt, and in his Sophist way often redefines his form in a manner disjoint from any Individualism coming from past thinkers.

The book argues that "our conceptions of individualism have remained trapped within the assumptions of classic liberalism…" The author then presents what he considers a reinterpreted individualism, called reconstructing individualism, by examining the works of Emerson, James, Dewey and Ralph Ellison. As I am familiar most with the first three, my comments shall be limited to his observations thereto.

Let me start on p. 1. The author states "America has a love-hate with individualism." From this point on I have a problem, for the author never seems to directly define what he means. Individualism has had an ever changing set of concepts and constructs. One can argue, as does the Marxist Meiksins-Wood, in Citizens to Lords p 226, that one of the first individualists was Ockham, focusing both around his arguments regarding nominalism as well as his opposition to the Avignon papacy. The Ockham school of individualism is also best explained by McGrade in the volume by Tierney and Linehan, Authority and Power; p. 149-165.

Individualism has many faces, not just the Lockean view or that of the Scottish enlightenment. The quote on the last page by de Tocqueville, wherein he criticizes individualism as he observed it was best analyzed by Schleifer in his work The Making of de Tocqueville's Democracy in America, pp 305-322. Simply the Schleifer argument therein is that de Tocqueville was reacting more to the change and threats in French society and failed to adequately understand the American view. American individualism, in the early 19th century, was note one of an isolated self-reliance but one where the associations noted by de Tocqueville managed to assist communities and individuals. It was no a society of separation but one of association and cooperation.

Thus one is somewhat amazed by the title of the first chapter, “Individualism has never been tried” since it not only was but became the very foundation of the American spirit for a long period of time.

Thus the main critique is the lack of definition, especially with any clarity, of what the author means by individualism. The argument he makes is somewhat sophist in approach by incrementally alleging elements which he then rejects.

On p 8 he speaks of Dewey’s democracy as community. Dewey was anything but an individualist. The essence of is educational philosophy was a centralized and common core of basic education. For example, Dewey was often in mortal combat with the Catholic Church in New York City since the Church had an education system disjoint from what Dewey wanted. Dewey vehemently opposed the Church’s parochial schools. Dewey in so opposing any alternative was then effectively rejecting any attempt at individualism. He sought standards, standards that he and a select few would establish, to create a homogenized America.

Before continuing, again on p 8 the author describes what he calls a broad set of assumptions common to the four individuals whose work he intends to integrate. The first is an example of the style throughout:

“A pluralistic metaphysics that analyzes human activity, truth, power, and value as emerging and existing only within and against the limitations of specific conditions.”

Now frankly I have read this several dozen times, I have even tried to diagram the sentence. It makes no sense. Give it a try. Each word is a known term but placing them in this order seems to lead to an un-interpretable collection of words.

The most telling element of the text is in Endnote 2 on p 312 where the author attempts to demonstrate the pragmatic individualism of the current president while criticizing without any comment the opposing party. The key rule in writing documents which would stand the test of time is not to put such statements in the document. One now clearly understands the intent of the author to be the justification of the administration in power at the time of the writing and thus it may readily call into question the intellectual substance in view of the blatant political nexus.

Now Chapter 1 is dealing with interpreting Emerson as a Pragmatist, an interesting interpretation. On p 26 the author provides a reasonable overview of the philosophy of Emerson. On p 31 the author constructs a nexus between Emerson and William James, the son of a family friend and the prime mover of the American pragmatism movement. The evolution in pragmatic thought and the reification of religious thought can be readily seen in the progression from Emerson to James to Dewey. Emerson was clearly a product of the growing sense of American separatism, his speech at Harvard announcing the break with Europe was in a way the temporal instant in which the split was recognized, American was to “think” and thus act on its own, relying no longer on what Europe what to proffer. Thus in a sense the break that Emerson was creating even between his Universalism, anti-Trinitarian views, and the beginning of pragmatism are patched together by the author in this chapter. On p 36 there is a telling phrase when the author states:

"Here I depart from the assessment of Charles Mitchell, who concludes that James "wanted to make use of Emerson, not make sense of him, and his method was to mine Emerson for the valuable insights…" …James did conclude that Emerson's voicing of monist and pluralist perspective revealed a lack of consistency…However … James went further … to "make sense" of the conflict between Emerson's monism and his pluralism."

The issue may very well be at the heart of Pragmatism as explored by the author, a reasonable nexus between Emerson and James.

Chapter 2 deals with the individualism of Emerson. On p 55 the authors struggles with the issue of Emerson's individualism. He states:

"Emerson's individualism reflect is attempt to articulate an ethics commensurate with a world of limitation and power."

Now as with many other statements I did have some difficulty here with what seems to be said. If this is an attempt to describe, define, delimit the "ethics" or behavior norms of society, a society which exists in a world with well-defined limits of wealth, goods, etc and a world controlled by power, namely a few who exert control over the many, then Emerson may have done so, albeit with limited success. On p 56 the author again continues this discussion as he discusses the essays of Emerson. On p 57 the author also discusses the idealism of Emerson, as a real practice of ethical and practical behavior.

On p 67 the author states:

"…Emerson contends that individuality can only be realized in a social context …. that the interaction between the individual and society must allow for the nourishment and growth of individuals most vital talents"

Classic individualism as seen in the time period would not disagree with this. Somehow the individualism used as the straw target of the author is some isolationism, a Thoreau like separatism at Walden, rather than just what was said, an ability to allow each to maximize their talents within a flexible community.

On p. 70 the author uses the classic quote from Emerson on "Self Reliance" where he compares the Harvard dandy to the New Hampshire back woodsman. The Harvard dandy fails and thus never gets the next chance but the New Hampshire lad, despite lack of a great education, through individual drive and fortitude succeeds again and again. In a close reading one sees the dandy with his large "community" of friends and advocates, suffers an early and permanent failure, but the lad from New Hampshire with no more that his own "self-reliance' never sees a failure. This is both consistent with individualism yet the author seems hard pressed to take it for what it says.

Chapter 3 begins the pragmatism of William James. Overall his presentation of James flows well as does his discussion of James' view of individualism.

Chapter 4 is on Dewey, and here one may have some concern. Dewey was a complex person who was often at odds with the institutions which he was involved with, like his departure from Chicago, as well as his somewhat alienated location at Columbia. He was a strong supporter of Marxist causes, although not an outright Communist, he also was a key player in the general attitude of gross anti-Catholicism rampant at Columbia. To even try to say Dewey was in any way and individualist would at best be a stretch. Yes, there is a nexus to James, a sense of pragmatism in his philosophy, and his approach to epistemology was reasonable for its time, his political views, and individualism is as political as it is philosophical, is nowhere like what one would accept as true individualism.

On p 192 the author states:

"…Dewey is critical for understanding how pragmatism allows, and indeed requires, us to reconceive individualism. Of all the writers considered in the current study, Dewey articulates the most comprehensive critique of classic liberal individualism, as well as the most systematic argument why a reconstructed individualism is not merely compatible with, but essential to, a democratic ideal of community."

This is truly a powerful statement and most telling. Yes indeed Dewey is a pragmatist, no one would deny that, but he is also in many ways a communitarian. The Dewey ideal of community would reject any form of individualism, it is more akin to Marxism, the individual disappears and the class remains. Nominalism would be rejected in this class based society, class as a conforming group not as a separatist set of associations. The author talks on p. 194 of a "trial by experience". Indeed, individualism as exhibited in an entrepreneurial society, one where individuals are allowed to risk and if successful obtain rewards, as individuals, would in Dewey's sense be subsumed into a group, a national pool of contributors to the whole.

On p 195 the author states:

"Dewey's transactional model of selfhood leads him to reject the tired dualism of "individual" versus "institutional" approaches to reform, insisting instead that reform requires both the remaking of social conditions so as to instill new habits of individuality and the necessary role that individual imagination and choice play in so remaking social conditions."

In a sense Dewey always saw "'society" as something moldable and the individual first fitting in that remolded society. One need just read Individualism Old and New by Dewey to fully understand his societal group think view.

Chapter 5 is about Dewey and reconstructing individualism. The bottom of p 245 has a most interesting statement:

"At the same time, the fact that an increasingly collective system of production has remained tied to an outdated system of individual property has alienated the vast majority of workers from meaningful control over and understanding the larger ends that direct their labor, thereby stripping their individuality of socially integrated meaning."

This seems to be a Marxist view; society composed of classes, workers deprived of their due, and the individual must be subsumed under the integrated working class. The individual cannot exist except in the group of a socially properly structure society. This is hardly individualism as we understand it.

Then on p. 260 he states:

"An individualism that had at its core this goal of effective liberty and equality would seek, above all, to create social conditions that would afford all persons an equal opportunity to participate in the associated activities through which individual's capacities are educated and liberated. So conceived, "individualism" describes an integral component of democracy considered as a way of life or the ideal community…"

This is total rejection of individualism and an acceptance of communitarian like systems. The author continues at length on p 261 a detailed discussion of this point. He believes society must structure the organizations to support individuals. He states:

"In an American context, be it Dewey's of the 1930s or ours of today. proposals involving a significant degree of socialism are in danger of being pigeonholed, dismissed or vilified."

Yes, because socialism is the very antithesis of individualism, of entrepreneurial societies, allowing free and open creative opportunities. I believe that here the author takes a clear and unambiguous position.

Chapter 6 deals with Ellison which I shall leave to the reader since I have no insight to him at all.

Now if one desires to understand individualism one need read many works which are available including Hayek, to name one. This book is in reality a socialist's view of what they would like individualism to become; it in no way describes individualism.
Labels: Books, Individualism

SUNDAY, SEPTEMBER 2, 2012

A WELL POSED OBSERVATION

There are times when those outside the US may have a better understanding of that this election is all about. In the Telegraph the author states:

Whatever the outcome of the American presidential election, one thing is certain: the fighting of it will be the most significant political event of the decade. Last week's Republican national convention sharpened what had been until then only a vague, inchoate theme: this campaign is going to consist of the debate that all Western democratic countries should be engaging in, but which only the United States has the nerve to undertake. ***The question that will demand an answer lies at the heart of the economic crisis from which the West seems unable to recover.*** *It is so profoundly threatening to the governing consensus of Britain and Europe as to be virtually unutterable here, so we shall have to rely on the robustness of the US political class to make the*

running.

What is being challenged is nothing less than the most basic premise of the politics of the centre ground: that you can have free market economics and a democratic socialist welfare system at the same time. The magic formula in which the wealth produced by the market economy is redistributed by the state – from those who produce it to those whom the government believes deserve it – has gone bust. ***The crash of 2008 exposed a devastating truth that went much deeper than the discovery of a generation of delinquent bankers, or a transitory property bubble. It has become apparent to anyone with a grip on economic reality that free markets simply cannot produce enough wealth to support the sort of universal entitlement programmes which the populations of democratic countries have been led to expect.***

Free markets have certain dimensions that basically reward success and punish failure. When Government intervenes to prevent failure for a few, albeit allegedly to prevent failure to the many, and extends to the many more than just a safety net, then we are doomed as a society. The alternative has not been thought through. There is no viable alternative to a free market, some have been tried and abandoned. The germ of a free market is the individual entrepreneur, and the death of that entity shall result in the death of the market, with as one says no Plan B available to take over.

From the illogical arrogance of Ms Warren the Harvard Professor, what else one may ask, to the Rasputin like control of some in our political system, we are faced with a clear choice, one which we may not be able to put off without facing oblivion.
Labels: Political Analysis

SATURDAY, SEPTEMBER 1, 2012

CHEATING OR COOPERATION

There was an interesting piece today in the NY Times regarding a "cheating" scandal at Harvard. The article leads with:

Harvard students suspected in a major cheating scandal said on Friday that many of the accusations are based on innocent — or at least tolerated — collaboration among students, and with help from graduate-student teachers who sometimes gave them answers to test questions.

Harvard University revealed on Wednesday that nearly half of the undergraduates in the spring class were under investigation for suspected cheating, for working together or for plagiarizing on a take-home final exam. Jay Harris, the dean of undergraduate education, called the episode "unprecedented in its scope and magnitude."

Now my recent experience in my local Community College taking Organic Chemistry let me see this first hand. Back in the 50s and early 60s at MIT students did their own Problem Sets and on Take Home Exams it was assumed that you did the work yourself. In fact the competition was so severe you would not trust others work, and they would not trust you. Independence was essential.

But today, there is a culture of "sharing". Before each class where there was a homework due the students gathered together and compared assignments, made changes as necessary and converged to an answer. It was accepted. No, I did not participate, I was the "old guy", they were all young students. But in a Facebook generation this sharing is de rigueur, commonplace. It is the way they work. They had been taught such team work in their education process all along their young lives. It is the way we are taught today, no individual performance, we all are told to work in a group, to share. It is a cultural norm, yet life does not work quite that way.

Harvard is getting a lesson in what their liberal professors have been preaching, the loss of individualism and the ascent of groupism. Is it good or bad. Grammar schools no longer give out grades, class ranking is no longer accepted, and sharing is accepted as the way to go.

Perhaps the chickens are just coming home to roost.
Labels: Academy

FRIDAY, AUGUST 31, 2012

VARMINTS?

This is Bushie. He is one of almost a dozen chipmunks on our daylily farm in New Hampshire. We really liked Bushie. Now I read that they are Varmints! At least NPR in NH says so.They state:

Summer may be winding down, but for many gardeners in New Hampshire, the season's not quite over. There are still tomatoes and beans to be gathered. And rich fall squashes are just emerging. This summer's gardening season has been a challenging one. Mainly because of a few creatures that have enjoyed her plants....Ralph Waldo Emerson wrote: "I have no hostility to nature, but a child's love to it. I expand and live in the warm day like corn and melons."

Now we have never seen them do anything harmful. We fed them, the love blueberries, and they are wonderful friends. Neighbors do not like them, for reasons I really do not understand. We have dozens here in New Jersey, never a problem. But there are cranky old folks who seem to hate the little creatures. Perhaps it is more a reflection of how they see themselves. Emerson was right, you must love and respect nature, you learn from it, the good and the bad, but it is a wonderful teacher.

So perhaps one could share with the little folks. Deer and groundhogs are another issue, as well as raccoons. They are just big lugs who will munch everything. But for the little guys, they are just friends in the garden, so let them be.

I see more of what is in a person by how they deal with the other creatures they share this planet with. It speaks of their soul. I wish we could get Bushie back, but alas he was taken away by a mean mean man!

So for the folks in NPRNH, enjoy the creatures, they will not take it all.
Labels: Commentary

MORE ON DE TOCQUEVILLE

I am continually amazed as to the intellectual shallowness of some of our academics. Now I used to be one but upon entering business I had to deal with facts, for not dealing with them resulted in disaster. The same is the case in medicine. You cannot ignore sepsis, it will kill the patient, often despite your best efforts. But shallowness is unforgivable, and especially to justify a political point.

Now from Schleifer's work on de Tocqueville we have on p. 315 the following:

Tocqueville also realized that, at the same time, the suffocating effects of a centralized and omnipresent government in turn further discouraged any private efforts. If unchecked, this relentless cycle of reinforcement would ultimately end in total "individual servitude,"[52[1]] the hallmark of the New Despotism. So the final portion of his book would serve primarily to express his concern for the survival of independance individuelle in democratic times[53[2]]. "To lay down extensive but distinct and settled limits to the action of the government; to confer certain rights on private persons, and to secure to them the undisputed enjoyment of those rights; to enable individual man to maintain whatever independence, strength, and original power he still possesses; to raise him by the side of society at large, and uphold him in that position; these appear to me the main objects of legislators in the ages upon which we are now entering."

52[1] Democracy (Mayer), pp. 676, 679.

53[2] Tocqueville frequently used independance individuelle and similar terms; see especially ibid., pp. 679, 681, 688, 691-92, 695-96, 699-700,701-2, 703-4.

Now this is clear and unambiguous. The New Despotism is the result of the suffocating effects of a centralized government, as we all too often see in France, and now in this country as well. We fear losing our citizenship and becoming subjects, for that is the way we are often treated by Washington.

Labels: Commentary, Political Analysis

FRIDAY, AUGUST 31, 2012

INDIVIDUALISM AND THE ACADEMY

In 1944 my mother and I moved to Berkeley. My father's ship, DD-649, was stationed out of Treasure Island. We lived up by the University. It was foggy, damp, cold, inhospitable a place. But as my father sailed out to what was to become the biggest naval battle of the War his major fear was that I was to become influenced by the Communists at the University. Strange that this was his greatest worry. Yet as I read the piece by one of it current economics faculty member I can now see the true basis for his terror. He feared the Japanese but little, the faculty at Berkeley a great deal.

This, in my opinion, somewhat rotund appearing instructor tells us

When the French politician and moral philosopher Alexis de Tocqueville published the first volume of his Democracy in America in 1835, he did so because he thought that France was in big trouble and could learn much from America. So one can only wonder what he would have made of the Republican National Convention in Tampa, Florida.

Perhaps the author also means 1840 as well. de Tocqueville spent much time writing both volumes, often abridged and missing key points, and often poorly translated. The French is still somewhat dated and makes for less than direct interpretation. One must also consider a possible Skinnerian approach of the Cambridge School of seeing de Tocqueville in the context of those commentators about him as well as those who influenced his writing. I will comment more on that later. He continues:

For Tocqueville, the grab for centralized power by the absolutist Bourbon monarchs, followed by the French Revolution and Napoleon's Empire, had destroyed the good with the bad in France's neo-feudal order. Decades later, the new order was still in flux.

In Tocqueville's imagination, at least, the old order's subjects had been eager to protect their particular liberties and jealous of their spheres of independence. They understood that they were embedded in a web of obligations, powers, responsibilities, and privileges that was as large as France itself. Among the French of 1835, however, "the doctrine of self-interest" had produced "egotism…no less blind." Having "destroyed an aristocracy," the French were "inclined to survey its ruins with complacency." … Tocqueville noted that "Americans are fond of

explaining…[how] regard for themselves constantly prompts them to assist each other, and inclines them willingly to sacrifice a portion of their time and property to the general welfare." The French, by contrast, faced a future in which "it is difficult to foresee to what pitch of stupid excesses their egotism may lead them," and "into what disgrace and wretchedness they would plunge themselves, lest they should have to sacrifice something of their own well-being to the prosperity of their fellow-creatures."

All of this was in the context of the individual and individualism and the free creation of associations for helping. This was a common thread in America, especially the frontier, and frankly still is. It is at the core of religious institutions and social institutions, why the Americans contribute more to charity than any other country. Americans are unique in their ability to see distress and to reach out a hand. This has not changed. But it was always voluntary; it was demanded of them from a moral level, not mandated by Government who took their place.

For Tocqueville, France's sickness in 1835 stemmed from its Bourbon patrimony of a top-down, command-and-control government, whereas America's health consisted in its bottom-up, grassroots-democratic government. Give the local community enough control over its own affairs, Tocqueville argued, and one "will see at a glance…the close tie which unites private to general interest." It was "local freedom which leads a great number of citizens to value the affection of their neighbors and of their kindred, perpetually brings men together, and forces them to help one another, in spite of the propensities which sever them."

Nearly two centuries have passed since Tocqueville wrote his masterpiece. The connection between the general interest and the private interest of individual Americans has, if anything, become much stronger, even if their private interest is tied to a post office box in the Cayman Islands. Indeed, no private-equity fortunes were made over the past generation without investing in or trading with the prosperous North Atlantic industrial core of the world economy.
But the mechanisms that individuals can use to join with their immediate neighbors in political action that makes a difference in their lives have become much weaker. If, say, 25% of the 1,000 households in the 30-block Brookside "fiberhood" in Kansas City, Missouri, pre-subscribe, Google will provide all 1,000 with the opportunity to get very cheap, very fast Internet service very soon. But that is the proverbial exception that proves the rule.

The above Google comments is somewhat placed askance in his argument. What is he trying to say? Google wants customers and it will do whatever it can to get them. This is a sales gimmick not a commentary on social mores!

And the Republicans gathered in Tampa to celebrate the rule – to say that the America that Tocqueville saw no longer exists: Americans no longer believe that the wealth of the rich rests on the prosperity of the rest. Rather, the rich owe their wealth solely to their own luck and effort. The rich – and only the rich – "built" what they have. The willingness to sacrifice some part of their private interest to support the public interest damages the souls and portfolios of the 1%.

I truly do not understand this diatribe. The "wealth" of those who took risks to create businesses that may have endowed them with some wealth was and is of their making. It was their risk taking, their delayed satisfaction that made it happen. Frankly the employees who were hired by

entrepreneurs took little if any risk. They entered the open market placed and took a “job” at a competitive salary. They did not put their homes and lives at risk; they just took one of many possible paths with defined compensation. Not so for the entrepreneur. My salary was always less than any one’s else, and often for years no salary. People got paid before I received a penny. My money was at risk, my children helped without compensation. This economist clearly shows not a single inkling of how entrepreneurs work.

Perhaps the moral and intellectual tide will be reversed, and America will remain exceptional for the reasons that Tocqueville identified two centuries ago. Otherwise, Tocqueville would surely say of Americans today what he said of the French then. The main difference is that it has become all too easy “to foresee to what pitch of stupid excesses their egotism may lead them” and “into what disgrace and wretchedness they would plunge themselves.”

de Tocqueville had truly mixed views of America; he was after al a Frenchman of the First Estate and was concerned deeply about democracy and specifically democracy as perceived in the French Revolution.

Now any true and capable intellectual, or even a reasonable person, would examine de Tocqueville a bit deeper. One does no more than read the work of Schleifer[2]. The author of the above seems not to have done so.

As Schleifer states:

Curiously, in the United States (and to a lesser degree in England) the term would have a heavily positive connotation quite at odds with the typically pejorative use of indvidualisme *Tocqueville and most other Frenchmen. To Americans, especially as the nineteenth century progressed, the word would conjure up images of extensive political and economic freedoms. Tocqueville's own diary remarks about the "fundamental social principles" in the United States of self-reliance and of individual independence and responsibility had captured something of what Americans would later mean by "individualism."*[5] *But Tocqueville's own understanding of the term would consistently be quite different.*

In 1840 Tocqueville would begin his explanation by attempting carefully to distinguish egoisme *and* individualisme.

“Egoisme is a passionate and exaggerated love of self which leads a man to think of all things in terms of him and to prefer himself to all.

Individualisme is a calm and considered feeling which disposes each citizen to isolate himself from the mass of his fellows and withdraw into the circle of family and friends; with this little society formed to his taste, he gladly leaves the greater society to look after itself.

Egoisme springs from a blind instinct; individualisme is based on misguided judgment rather than depraved feeling. It is due more to an inadequate understanding than to perversity of heart.

Egoisme sterilizes the seeds of every virtue; individualisme at first only dams the spring of public virtue, but in the long run it attacks and destroys all the others too and finally merges in egoisme.

Egoisme is a vice as old as the world. It is not peculiar to one form of society more than another.

Individualisme is of democratic origin and threatens to grow as conditions get more equal."

Key elements in this definition were the peaceful and reflective nature of individualism and Tocqueville's insistence that, despite apparent prudence, individualism arose from short-sighted and erroneous judgments.

Thus the individualism of de Tocqueville was an outward looking self-reliance as compared to egoism which is inward looking self-acclaim. The latter, egoism, was rampant in the French Courts. Individualism was rampant in the American frontier. It was not however in such places as Boston and the large plantations of the South. For it was at this time that the Bostonian, Alexander Wendell Holmes' father, declared themselves the new intellectuals, called the "Boston Brahmins", the intellectual elite of the New World, the first set of what we today would call the Public Intellectual. This self-anointed clan still exists despite the massive changes in society over the past two centuries.

Now back to de Tocqueville, he saw and despised the individualism. The main reason one could surmise was the rejection of the family lineage. American individualism was no respecter of one's ancestors, any American had equal opportunity, and yes to do it themselves.

The conclusion is that we often see these self-acclaimed Public Intellectuals opine on things which they seem less than capable of understanding. There are many authors who have attempted to use de Tocqueville but again have misinterpreted him. Albrecht has espoused an extreme left wing version of individualism in a Sophist manner and then critiqued it[3]. Similarly one should read Manent on de Tocqueville as it provides perhaps a more even tuned approach[4].

54[2] Schleifer, J., The Making of Tocqueville's Democracy in America, 2nd Ed, Liberty Fund Press (Indianapolis, IN), 2000.
55[3] Albrecht, J., Restructuring Individualism, Fordham Press (NY) 2012.

56[4] Manent, P., An Intellectual History of Liberalism, Princeton (Princeton) 1995, and Manent, P., Tocqueville and the Nature of Democracy, Rowman and Littlefield (Lanham, MD) 1996.
Labels: Academy, Commentary, Political Analysis

WEDNESDAY, AUGUST 29, 2012

RAND PAUL AND INDIVIDUALISM

Just heard Rand Paul speak at the RNC event. Frankly this was one of the best descriptions of American Individualism I have heard, not a push on Libertarian but clear American Individualism. Hope some folks saw it. The last phrase is spot on:

To overcome the current crisis, we must appreciate and applaud American success. We must step forward, unabashedly and proclaim: You did build that. You earned that. You worked hard. You studied. You labored. You did build that. And you deserve America's undying gratitude. For you, the individual, are the engine of America's greatness.

Labels: Commentary

SUNDAY, AUGUST 26, 2012

INDIVIDUALISM: ITS MEANING AND ITS CONFUSION

Individualism is a massive threat to the progressives, and it appears to become ever so much more for reasons which are oftimes hard to explain. But what do we mean by Individualism? There are frankly a plethora of meanings. At one extreme it is the Emersonian view of knowing yourself, being your own person. At another extreme are that of Hayek, and then the original construct of de Tocqueville.

As we shall see, Emerson is one of self-identity, Hayek and refutation of communism, and de Tocqueville the personal crisis of French society and the pending loss of social identity. Frankly none truly provide a sense of current day Individualism. It should be contrasted to the Libertarian view especially the Rand world-view of extreme selfish apartness.

To set our view in context, Individualism is a belief in the sanctity of the individual, and that Government has the limited role of protection of person and property. Individuals are free to form associations, to transact trade and to communicate in an unencumbered manner in any fashion. Individuals are equal before the law and each other and that Government and Society shall in no way construct barriers for individual development or expression. This is a simple expression of Individualism. As we shall see it contrasts with many other views.

1. Emerson

We first begin with Emerson. Emerson was a Transcendentalist, an inhabitant of Concord, MA. Things have changed little in Concord since Emerson in that it is a habitat of academics and left wing thinkers. In many ways its inhabitants often think of themselves as a step above others intellectually as well as socially. I came to best understand that having resided in the adjacent town of Acton, considered in many ways the down casts of the Concord suburbs.

Thus Emerson was a voice of both Concord and Harvard elites of the 19th century. His view of Individualism was a view of expanding the individual's spirit, less a view of the rights and responsibilities, than of the concept of self-enlightenment. For example we have from Emerson[57[1]]:

If our young men miscarry in their first enterprises, they lose all heart. If the young merchant fails, men say he is ruined. If the finest genius studies at one of our colleges, and is not installed in an office within one year afterwards in the cities or suburbs of Boston or New York, it seems to his friends and to himself that he is right in being disheartened, and in complaining the rest of his life.

A sturdy lad from New Hampshire or Vermont, who in turn tries all the professions, who teams it, farms it, peddles, keeps a school, preaches, edits a newspaper, goes to Congress, buys a township, and so forth, in successive years, and always, like a cat, falls on his feet, is worth a hundred of these city dolls. He walks abreast with his days, and feels no shame in not `studying a profession,' for he does not postpone his life, but lives already. He has not one chance, but a hundred chances.

Let a Stoic open the resources of man, and tell men they are not leaning willows, but can and must detach themselves; that with the exercise of self-trust, new powers shall appear; that a man is the word made flesh, born to shed healing to the nations, that he should be ashamed of our compassion, and that the moment he acts from himself, tossing the laws, the books, idolatries, and customs out of the window, we pity him no more, but thank and revere him, —and that teacher shall restore the life of man to splendor, and make his name dear to all history.

It is easy to see that a greater self-reliance must work a revolution in all the offices and relations of men; in their religion; in their education; in their pursuits; their modes of living; their association; in their property; in their speculative views.

Here we have the Emersonian Individualism or self-reliance. There is a feeling of self-trust and the ability to strike out on his own. This is one view, and one which prevailed for many generations, the sense of the individual taking their own future into their own hands. The Emersonian view is thus not the Individualism that we see today, nor that of the settlers of Tennessee in the same period.

2. Ockham

Then there is the Ockham view of Individualism. Ockham was one of the first in the 14th century to express a sense of the individual, not of the subject, one who claimed the Pope was a heretic, John XXII, the pope in Avignon. In a sense Ockham was preceded by Columbanus who in a similar fashion took on Gregory I on many matters. To understand the Ockham Individualism we examine some of his logical structures. Let us examine a statement, subject and predicate, in a manner akin to Ockham.

57[1] ESSAY II: *Self-Reliance* , http://en.wikisource.org/wiki/Essays:_First_Series/Self-Reliance

Namely we perform a nominalist statement. That is we deny universals and believe only in each and every example.

We might say:

“All coneflowers are blue.”

Now what we may really mean is:

This coneflower and this coneflower and that coneflower etc. to describe the subject. Namely we look at each and every coneflower that we can.

But many nominalists may stop there. I would continue expending with the predicate as well:

This blue, this blue or that blue.

Namely we may ask what specific blue we mean. I can see many blue colors. If one were to examine the spectrum of each flower for its blueness one would see different spectra. In fact each cell has a different spectrum of blue. Blue as a universal does not exist, blue as a specific expression of anthocyanins does.

Thus the nominalist sees only individuals, individual subjects and individual predicates. Thus for Ockham only the individual exists, the idea of an ideal such as a group is merely the temporal expression of individuals assembling together.

3. Hayek

Then there is the Individualism of the polis, of how man and his Government relate. The best example here is to examine Hayek.

Now Hayek states[58][2]:

No political term has suffered worse in this respect than "individualism." It not only has been distorted by its opponents into an unrecognizable caricature-and we should always remember that the political concepts which are today out of fashion are known to most of our contemporaries only through the picture drawn of them by their enemies-but has been used to describe several attitudes toward society which have as little in common among themselves as they have with those traditionally regarded as their opposites. Indeed, when in the preparation of this paper I examined some of the standard descriptions of "individualism,"

Indeed as Hayek states, the use of the term by those opposed is often in a Sophist like manner of a Protagoras or Gorgias defined by them in a manner to be rejected. Hayek clearly understood this issue. This is the key point when dealing with Individualism, not to accept the definition of the opponent but to seek truth.

I almost began to regret that I had ever connected the ideals in which I believe with a term which has been so abused and so misunderstood. Yet, whatever else "individualism" may have come to mean in addition to these ideals, there are two good reasons for retaining the term for the view I mean to defend: this view has always been known by that term, whatever else it may also have meant at different times, and the term has the distinction that the word "socialism" was deliberately coined to express its opposition to individualism. It is with the system which forms the alternative to socialism that I shall be concerned[59][3].

I can give no better illustration of the prevailing confusion about the meaning of individualism than the fact that the man who to me seems to be one of the greatest representatives of true individualism, Edmund Burke, is commonly (and rightly) represented as the main opponent of the so-called "individualism" of Rousseau, whose theories he feared would rapidly dissolve the commonwealth "into the dust and powder of individuality," and that the term "individualism" itself was first introduced into the English language through the translation of one of the works of another of the great representatives of true individualism, De Tocqueville, who uses it in his Democracy in America to describe an attitude which he deplores and rejects. Yet there can no doubt that both Burke and De Tocqueville stand in all essentials close to Adam Smith, to whom nobody will deny the title of individualist, and that the "individualism" to which they are opposed is something altogether different from that of Smith.

Again as Hayek states, even de Tocqueville uses Individualism in a manner which expresses his own fears in France rather than the actuality he observed in America.

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[58][2] http://mises.org/books/individualismandeconomicorder.pdf

[59][3] Hayek also states: “Both the term "individualism" and the term "socialism" are originally the creation of the Saint-Simonians, the founders of modern socialism. They first coined the term "individualism" to describe the competitive society to which they were opposed and
then invented the word "socialism" to describe the centrally planned society in which all activity was directed on the same principle that applied within a single factory.”

I cannot better illustrate the contrast in which Cartesian or rationalistic "individualism" stands to this view than by quoting a famous passage from Part II of the Discourse on Method. Descartes argues that "there is seldom so much perfection in works composed of many separate parts, upon which different hands had been employed, as in those completed by a single master." He then goes on to suggest (after, significantly, quoting the instance of the engineer drawing up his plans) that "those nations which, starting from a semi-barbarous state and advancing to civilization by slow degrees, have had their laws successively determined, and, as it were, forced upon them simply by experience of the hurtfulness of particular crimes and disputes, would by this process come to be possessed of less perfect institutions than those which, from the commencement of their association as communities, have followed the appointment of some wise legislator." To drive this point home, Descartes adds that in his opinion "the past pre-eminence of Sparta was due not to the pre-eminence of each of its laws in particular ... but to the circumstance that, originated by a single individual, they all tended to a single end."

True individualism is, of course, not anarchism, which is but another product of the rationalistic pseudo-individualism to which it is opposed. It does not deny the necessity of coercive power but wishes to limit it-to limit it to those fields where it is indispensable to prevent coercion by others and in order to reduce the total of coercion to a minimum. While all the individualist philosophers are probably agreed on this general formula, it must be admitted that they are not always very informative on its application in specific cases.

Neither the much abused and much misunderstood phrase of "laissez faire" nor the still older formula of "the protection of life, liberty, and property" are of much help. In fact, in so far as both tend to suggest that we can just leave things as they are, they may be worse than no answer; they certainly do not tell us what are and what are not desirable or necessary fields of government activity. Yet the decision whether individualist philosophy can serve us as a practical guide must ultimately depend on whether it will enable us to distinguish between the agenda and the nonagenda of government.

Hayek's discussion is as close as we may come to Individualism in the polis. Hayek takes the issue of Government control to task and it becomes the heart of his description.

4. de Tocqueville

The earliest popularizer of the term Individualism was de Tocqueville in his Democracy in America. He was clearly not a fan of the concept. In fact he saw it as a threat. But as a Frenchman, having understood the consequences of the mob, to him it meant uncontrolled anarchy. Many have used de Tocqueville's observations as a basis for rejecting Individualism. I would argue, however, that it is more an expression of his fear of loss of French culture than a true rejection of what he observed.

de Tocqueville had stated[60[4]]:

[60[4]] De Tocqueville, Democracy in America, Part II, Chapter 2, pp 482-484 in Mansfield and Winthrop.

I HAVE shown how it is that in ages of equality every man seeks for his opinions within himself; I am now to show how it is that in the same ages all his feelings are turned towards himself alone. Individualism is a novel expression, to which a novel idea has given birth. Our fathers were only acquainted with egoisme (selfishness). Selfishness is a passionate and exaggerated love of self, which leads a man to connect everything with himself and to prefer himself to everything in the world. Individualism is a mature and calm feeling, which disposes each member of the community to sever himself from the mass of his fellows and to draw apart with his family and his friends, so that after he has thus formed a little circle of his own, he willingly leaves society at large to itself. Selfishness originates in blind instinct; individualism proceeds from erroneous judgment more than from depraved feelings; it originates as much in deficiencies of mind as in perversity of heart.

Selfishness blights the germ of all virtue; individualism, at first, only saps the virtues of public life; but in the long run it attacks and destroys all others and is at length absorbed in downright selfishness. Selfishness is a vice as old as the world, which does not belong to one form of society more than to another; individualism is of democratic origin, and it threatens to spread in the same ratio as the equality of condition.

Among aristocratic nations, as families remain for centuries in the same condition, often on the same spot, all generations become, as it were, contemporaneous. A man almost always knows his forefathers and respects them; he thinks he already sees his remote descendants and he loves them. He willingly imposes duties on himself towards the former and the latter, and he will frequently sacrifice his personal gratifications to those who went before and to those who will come after him. Aristocratic institutions, moreover, have the effect of closely binding every man to several of his fellow citizens. As the classes of an aristocratic people are strongly marked and permanent, each of them is regarded by its own members as a sort of lesser country, more tangible and more cherished than the country at large. As in aristocratic communities all the citizens occupy fixed positions, one above another, the result is that each of them always sees a man above himself whose patronage is necessary to him, and below himself another man whose co-operation he may claim.

Men living in aristocratic ages are therefore almost always closely attached to something placed out of their own sphere, and they are often disposed to forget themselves. It is true that in these ages the notion of human fellowship is faint and that men seldom think of sacrificing themselves for mankind; but they often sacrifice themselves for other men. In democratic times, on the contrary, when the duties of each individual to the race are much more clear, devoted service to any one man becomes more rare; the bond of human affection is extended, but it is relaxed.

Among democratic nations new families are constantly springing up, others are constantly falling away, and all that remain change their condition; the woof of time is every instant broken and the track of generations effaced. Those who went before are soon forgotten; of those who will come after, no one has any idea: the interest of man is confined to those in close propinquity to himself. As each class gradually approaches others and mingles with them, its members

become undifferentiated and lose their class identity for each other. Aristocracy had made a chain of all the members of the community, from the peasant to the king; democracy breaks that chain and severs every link of it.

As social conditions become more equal, the number of persons increases who, although they are neither rich nor powerful enough to exercise any great influence over their fellows, have nevertheless acquired or retained sufficient education and fortune to satisfy their own wants. They owe nothing to any man, they expect nothing from any man; they acquire the habit of always considering themselves as standing alone, and they are apt to imagine that their whole destiny is in their own hands.

Thus not only does democracy make every man forget his ancestors, but it hides his descendants and separates his contemporaries from him; it throws him back forever upon himself alone and threatens in the end to confine him entirely within the solitude of his own heart.

In many ways this was less an observation of Individualism than a response by de Tocqueville towards the classless and open society he found himself in. Brogan presents an excellent summary of this in his biography of the author[61][5]. de Tocqueville, especially in the last sentence reveals his bias to a society where all are equal. He still saw merit and need for a society where the right people intermingled.

5. American Leftist

Now having briefly discussed these concepts I come to a recent article in the NY Times. From the NY Times[62][6] in an article ironically entitled "Deluded Individualism" what appears in my opinion to be some junior faculty member at an art school opined on the nature of what he thinks individualism is. Specifically he states:

In Chisago County, Minn., The Times's reporters spoke with residents who supported the Tea Party and its proposed cuts to federal spending, even while they admitted they could not get by without government support. Tea Party aficionados, and many on the extreme right of the Republican party for that matter, are typically characterized as self-sufficient middle class folk, angry about sustaining the idle poor with their tax dollars. Chisago County revealed a different aspect of this anger: economically struggling Americans professing a robust individualism and self-determination, frustrated with their failures to achieve that ideal.

One sees the typical and needless setting the political stage. One need read no further to see where this "argument" is to go.

Why the stubborn insistence on self-determination, in spite of the facts? One might say there is something profoundly American in this. It's our fierce individualism shining through. Residents of Chisago County are clinging to notions of past self-reliance before the recession, before the

[61][5] Brogan, H., Alexis de Tocqueville, Yale (New Haven) 2006, pp 355-356.

[62][6] http://opinionator.blogs.nytimes.com/2012/08/18/deluded-individualism/

welfare state. It's admirable in a way. Alternately, it evokes the delusional autonomy of Freud's poor ego.

Freud notwithstanding, the Individualism is the freeing of the individual to maximize their potential. There are times when individuals need help, Individualism does not negate, deny, decry, or prevent that, indeed the ability of individuals to associate for purposes of assistance is the heart of Individualism.

These people, like many across the nation, rely on government assistance, but pretend they don't. They even resent the government for their reliance. If they looked closely though, they'd see that we are all thoroughly saturated with government assistance in this country: farm subsidies that lower food prices for us all, mortgage interest deductions that disproportionately favor the rich, federal mortgage guarantees that keep interest rates low, a bloated Department of Defense that sustains entire sectors of the economy and puts hundreds of thousands of people to work. We can hardly fathom the depth of our dependence on government, and pretend we are bold individualists instead.

The above stretches the point. Mortgage deductions are limited, and that is not how the rich defer taxes, it is through capital gains, and that deferment typically goes back into rational investments, not like the Government waste in failed companies. Yes, in many ways the Defense Department is bloated, but so too are the ambitions to become policeman for the world. We do not depend on Government; we all too often are burdened by Government. Farm subsidies distort prices, and Medicare often distorts medical waste and fraud to the extreme. Yes, those who can afford Medicare should pay more, and in addition Medicare should be an insurance policy for extremes not for day to day costs.

Thanks to a decades-long safety net, we have forgotten the trials of living without it. This is why, the historian Tony Judt argued, it's easy for some to speak fondly of a world without government: we can't fully imagine or recall what it's like. We can't really appreciate the horrors Upton Sinclair witnessed in the Chicago slaughterhouses before regulation, or the burden of living without Social Security and Medicare to look forward to. Thus, we can entertain nostalgia for a time when everyone pulled his own weight, bore his own risk, and was the master of his destiny. That time was a myth. But the notion of self-reliance is also a fallacy.

The slaughter houses are examples of Pigou versus Coase. We establish Government tax burdens and then infrastructures rather than facilitating direct punishment for doing harm, Pigou versus Coase. If bad meat caused harm, and if we had an efficient system of remedies, then those harmed could readily seek restitution and punishment on those rendering the harm. For example, bankers causing a bank failure should face the most severe of punishments, the most severe. Instead they become contributors to the current Administration.

Spinoza greatly influenced Freud, and he adds a compelling insight we would do well to reckon with. Spinoza also questioned the human pretense to autonomy. Men believe themselves free, he said, merely because they are conscious of their volitions and appetites, but they are wholly determined.

We are not speaking of the mind. We are speaking of the reality of day to day life. We make decisions, often constrained ones, but it is the individual who sees ways around that, the entrepreneur, who creates the ultimate value in our society. Spinoza was the prototypical individual, rejecting his community and setting himself apart.

In fact, Spinoza claimed - to the horror of his contemporaries -that we are all just modes of one substance, "God or Nature" he called it, which is really the same thing. Individual actions are no such thing at all; they are expressions of another entity altogether, which acts through us unwittingly. To be human, according to Spinoza, is to be party to a confounding existential illusion - that human individuals are independent agents - which exacts a heavy emotional and political toll on us. It is the source of anxiety, envy, anger - all the passions that torment our psyche - and the violence that ensues. If we should come to see our nature as it truly is, if we should see that no "individuals" properly speaking exist at all, Spinoza maintained, it would greatly benefit humankind.

We are to degree independent agents, but as I stated we have substantial constraints that we manage from time to time to work around as a goal seeking creature. The author perhaps has never met or spoken to an entrepreneur. When going into Korea, Thailand, Russia, Turkey, Poland, etc I saw no constraints, just obstacles that I found ways around through associations, working with other individuals, and relying not one iota on Government or society in the sense of the author. I was not alone, there are many such entrepreneurs.

There is no such thing as a discrete individual, Spinoza points out. This is a fiction. The boundaries of 'me' are fluid and blurred. We are all profoundly linked in countless ways we can hardly perceive. My decisions, choices, actions are inspired and motivated by others to no small extent.

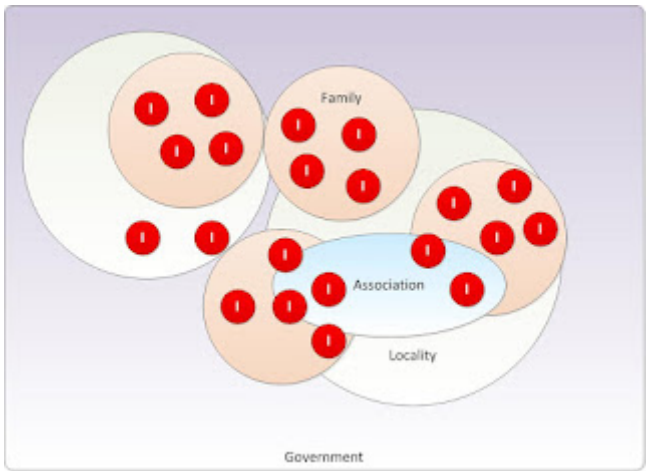
One would tend to disagree if one were an Ockhamist. A nominalist clearly sees nothing but individuals, and society is at best a collection of specific associations, transient as that may be.

The passions, Spinoza argued, derive from seeing people as autonomous individuals responsible for all the objectionable actions that issue from them. Understanding the interrelated nature of everyone and everything is the key to diminishing the passions and the havoc they wreak.

Let me respond to this view. First, Spinoza was a bit more than the writer contends, but that is a text unto itself. Second this is a Sophist argument, taking a definition of Individualism to prove a point, a definition devoid of much of what we have presented above.

6. A Canonical Model

Let me now attempt in a simple fashion to assemble all of these elements. We commence by defining certain units. It is always useful to do so because so many authors in a Sophist like manner attack a position of the other side and for which the other side never took such a position.



Individual: The individual was just that, the singular person. Although the individual oftimes had a sense of extreme personal responsibility, such was enabled and supported by family, associations, and localities.

Family: Like associations, family is a key aggregating element. Unlike de Tocqueville who sees family as position in society, American families often extend relationships, establish associations, and provide support.

Associations: The Associations are what de Tocqueville recognized when he saw the America of the first half of the 19th century. They were freely formed and ever changing relationship between individuals and focused on specific purposes. They may have been for trade, for banking, for farming, or for whatever purpose. They were flexible, often open, and frequently highly mobile. They were developed with some goal in mind, some agenda, real and objective. In a sense the church was just another association.

Locality: This is a collection of local, to some broad extent, of one's neighbors and associates. One need just look at a New England Town meeting for a typical example of locality. Not an association as such, but an amalgam of individuals. As one moves from New England one sees less of the individual influence. In New Jersey the town gatherings are often "managed" by heavy handed politician who often have personal gain at stake.

Society: Society is a Platonic ideal. It is nothing more than the amalgam of individuals, associations, families and localities. What we see as a society in New Hampshire we see differently in California. Yet we use the same name.

Government: This is the complex issue. Government for the Individualist is a minimalist form, protect person and property and allow remediation in a Coasean manner. However for the Progressive the Government is the sine qua non of existence, the arbiter of all life and the decider of the individual's fate. Just read between the lines of the Times piece and one get the understanding.

We do not deny Government and its function. We do not deny the existence of Society and the need to interact with it. We do see its role as limited, necessary, indeed, but not to the extent of

delimiting the potential of the individual.

Labels: Academy, Commentary

SUNDAY, AUGUST 26, 2012

INTERNET REVIEWS

Does anyone read five star reviews? I never do. I always go to the one star review first, truth often lies there. Especially if the one star review has many negative votes. It means that the review is both spot on and that there is some robo rating system trying to push it to oblivion.

Thus the NY Times has a piece on such reviews at the five star level, pushing a product. The Times makes two interesting statements:

The Federal Trade Commission has issued guidelines stating that all online endorsements need to make clear when there is a financial relationship, but enforcement has been minimal and there has been a lot of confusion in the blogosphere over how this affects traditional book reviews.

The tale of GettingBookReviews.com, which commissioned 4,531 reviews in its brief existence, is a story of a vast but hidden corner of the Internet, where Potemkin villages bursting with ardor arise overnight. At the same time, it shows how the book world is being transformed by the surging popularity of electronic self-publishing.

First the legality issue. I had been asked to review a couple of works and I wrote the fact in my review. Both got good grades. I typically give from 5 down to 1 stars, depending, and I also use my own name and allow contacts. Any review with a made up name is useless. If there is a 5 star review then I check out the reviewer, and still look at 1 star reviews.

Are reviews useful? Yes they often are, especially for some out of the way books, you get someone who may really know something and then lead you on to other sources.

So what of review services? Monetizing one's work can now be readily accomplished. I may even try it some day. My current approach is to post it free on my web sites and somehow people find it. I had a technical work on Obesity and Type 2 Diabetes up for a couple of years and there were over 10,000 downloads! How did these people even find it? I have had one on Melanoma Genomics up now for a month with 100 downloads. Even more so, how did they find it? With that one I have had the opportunity to discuss it with some who I never thought of with highly positive results. Are these self publishable, I doubt it, they are draft, works in progress, and subject to change and error corrections. But for many they represent a good first step.

But reviews are a double edged sword. As I had indicated, 1 star reviews always contain something, either about the product or the reviewer. The same for the 5 star review.
Labels: Internet

UNIVERSAL SERVICE, THE FCC, AND A RIP OFF

The FCC has issued an NRPM for re-arranging and expanding the Universal Service Tax to now cover Internet Broadband Services. For wireless and land lines services it is almost $15.00 per line per month now! And where does the money go? Much of it goes to rural telcos who charge low rates but get exorbitant profits! This process distorts the market and should not only not be expanded but should be eliminated.

In 1997 I published a paper arguing for the elimination of Universal Service. It had some legs but given the entrenched interests making money off of this and the general lack of independence of the FCC it went no where. But now with the current Administration this becomes a backdoor tax to pay back friends. We will now be taxing Internet purchases as well as Internet access. This tax will result in further market distortions.

It is a shame that we have so poor a group of folks at the FCC but perhaps it is the White House issuing orders.
Labels: Telecom

ROBOTS AND UEMPLOYMENT

I am always amazed as to the sudden realization that there has been a systemic change to our workforce. After all it was no surprise. It also is a continuing trend of history. Just go through New England mill towns, and what do you see, old mill factories which 100 years or so ago made fabrics, then became abandoned and then became high tech start-ups and now house health care establishments! The trend is just read by the signs on the buildings (see Lowell, MA for example). But that trend is frightening.

Robots replace manual labor and for a while entrepreneurs came in, then they left and are replaced by Health Care, namely innovation replaced by overhead! That should be the concern. We are not getting healthier, we are just spending more.

Now Friedman of the NY Times seems always to bring his new insights to the table. Frankly I never seen any true insights but alas he is what the masses of the left have to rely upon. They would be better off driving about I 495 in Boston and reading signs. From Friedman today in the Times we have[1]:

WHEN you hear the insane notion of "legitimate rape" being aired by a Republican congressman — a member of the House science committee no less — it makes you wonder some days how we became the world's richest, most powerful country, and, more important, how we're going to stay there. The short answer is that, thank God, there's still a bunch of people across America — innovators and entrepreneurs — who just didn't get the word. They didn't get the word that Germany will eat our breakfast or that China will eat our lunch. They didn't get the word that we're in a recession and heading for a fiscal cliff. They're not interested in politics at all. Instead, they just go out and invent stuff and fix stuff and collaborate on stuff. They are our saving grace, and whenever I need a pick-me-up, I drop in on one of them.

I did just that last week, visiting the design workshop of Rethink Robotics, near Boston's airport, where I did something I've never done before: I programmed a robot to perform the simple task of moving widgets from one place to another. Yup, I trained the robot's arms using a very friendly screen interface and memory built into its mechanical limbs. …

The Rethink design team includes …, the product manager of the Apple LaserWriter — as well as 75 other experts from Russia, Georgia, Venezuela, Egypt, Australia, India, Israel, Portugal, Britain, Sri Lanka, the United States and China. "It is all made in America," …, but by "the best talent" gathered "from around the world."

This is the company of the future. Forget about "outsourcing." In today's hyperconnected world, there is no "in" and no "out." There's only "good, better and best," and if you don't assemble the best team you can from everywhere, your competitor will. …

The Rethink robot will be unveiled in weeks. I was just given a sneak peek — on the condition that I did not mention its "disruptive" price point and some other unique features.

This is the march of progress. It eliminates bad jobs, empowers good jobs, but always demands more skill and creativity and always enables fewer people to do more things. We went through the same megashift when our agricultural economy was replaced by the industrial economy in the late 19th and early 20th centuries. Therefore, what this election should be about is how we spawn thousands of Rethinks that create new industries, new jobs and productivity tools. Alas, it isn't. So I'm just grateful these folks here in Boston didn't get the word.

Sarcasm as required starts his "insights" but he seems to have not read history and moreover has not truly thought through what he opines upon. Robots replace humans; it is akin to the plow, the tractor, and the changes in farms a hundred or so years ago. But now there are no big cities to go to. Furthermore these robots have been around for ages and there is no secret sauce that gives the US any sustainable advantage.

Now in reality the message was originally sent by Norbert Wiener. In 1947 he wrote his first warnings about this change and in 1961 he repeated it. From **Wiener, Cybernetics, 2nd Edition**, we have:

Long before Nagasaki and the public awareness of the atomic bomb, it had occurred to me that we were here in the presence of another social potentiality of unheard-of importance for good and for evil. The automatic factory and the assembly line without human agents are only so far ahead of us as is limited by our willingness to put such a degree of effort into their engineering as was spent, for example, in the development of the technique of radar in the Second World War.[2]

I have said that this new development has unbounded possibilities for good and for evil. For one thing, it makes the metaphorical dominance of the machines, as imagined by Samuel Butler, a most immediate and non-metaphorical problem. It gives the human race a new and most effective collection of mechanical slaves to perform its labor. Such mechanical labor has most of

the economic properties of slave labor, although, unlike slave labor, it does not involve the direct demoralizing effects of human cruelty. However, any labor that accepts the conditions of competition with slave labor accepts the conditions of slave labor, and is essentially slave labor. The key word of this statement is competition.

It may very well be a good thing for humanity to have the machine remove from it the need of menial and disagreeable tasks, or it may not. I do not know. It cannot be good for these new potentialities to be assessed in the terms of the market, of the money they save; and it is precisely the terms of the open market, the "fifth freedom," that have become the shibboleth of the sector of American opinion represented by the National Association of Manufacturers and the Saturday Evening Post. I say American opinion, for as an American, I know it best, but the hucksters recognize no national boundary.

Perhaps I may clarify the historical background of the present situation if I say that the first industrial revolution, the revolution of the "dark satanic mills," was the devaluation of the human arm by the competition of machinery. There is no rate of pay at which a United States pick-and-shovel laborer can live which is low enough to compete with the work of a steam shovel as an excavator. The modern industrial revolution is similarly bound to devalue the human brain, at least in its simpler and more routine decisions.

Of course, just as the skilled carpenter, the skilled mechanic, the skilled dressmaker have in some degree survived the first industrial revolution, so the skilled scientist and the skilled administrator may survive the second. However, taking the second revolution as accomplished, the average human being of mediocre attainments or less has nothing to sell that it is worth anyone's money to buy.

The answer, of course, is to have a society based on human values other than buying or selling. To arrive at this society, we need a good deal of planning and a good deal of struggle, which, if the best comes to the best, may be on the plane of ideas, and otherwise—who knows? I thus felt it my duty to pass on my information and understanding of the position to those who have an active interest in the conditions and the future of labor, that is, to the labor unions. I did manage to make contact with one or two persons high up in the C.I.O., and from them I received a very intelligent and sympathetic hearing. Further than these individuals, neither I nor any of them was able to go.

It was their opinion, as it had been my previous observation and information, both in the United States and in England, that the labor unions and the labor movement are in the hands of a highly limited personnel, thoroughly well trained in the specialized problems of shop stewardship and disputes concerning wages and conditions of work, and totally unprepared to enter into the larger political, technical, sociological, and economic questions which concern the very existence of labor.

The reasons for this are easy enough to see: the labor union official generally comes from the exacting life of a workman into the exacting life of an administrator without any opportunity for a broader training; and for those who have this training, a union career is not generally inviting; nor, quite naturally, are the unions receptive to such people.

Those of us who have contributed to the new science of cybernetics thus stand in a moral position which is, to say the least, not very comfortable. We have contributed to the initiation of a new science which, as I have said, embraces technical developments with great possibilities for good and for evil. We can only hand it over into the world that exists about us, and this is the world of Belsen and Hiroshima.

We do not even have the choice of suppressing these new technical developments. They belong to the age, and the most any of us can do by suppression is to put the development of the subject into the hands of the most irresponsible and most venal of our engineers. The best we can do is to see that a large public understands the trend and the bearing of the present work, and to confine our personal efforts to those fields, such as physiology and psychology, most remote from war and exploitation.

Wiener was ages ahead of Friedman. Wiener was not only the visionary but the oracle of what was to happen, and in addition the one who started the whole process. Perhaps Friedman should read more of Wiener and add that to his insight.

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[1] http://www.nytimes.com/2012/08/26/opinion/sunday/i-made-the-robot-do-it.html?hp

[2] Fortune, 32, 139-147 (October); 163-169 (November, 1945).

Labels: Economy

SATURDAY, AUGUST 25, 2012

HIRE THAT BOY

Frances Woolley has a post on Worthwhile Canadian Initiatives. I read the post upon returning from vacation and my first remark was to "Hire that Boy!". This is a clear example of creative

individualism, no caps please. The question was regarding capitalization, and he gave the answer. Apparently the teacher demanded the useless task of rewriting each sentence. Why? The test was on capitalization, not penmanship. Who writes anymore anyhow!

I scanned through the replies and not one of my friendly Canadian Economists caught on. This "Boy" is exactly the type of person I want for a start up. Solve the problem in the most efficient manner. You asked for capitalizations and you got it. If he were one of my students I would have given him an A+++. He got the idea.

Frankly this depicts the general backwardness of our Grammar School teachers. ask a question and you get an answer, the answer to what you asked. Ask another question and you will get another answer. And yes it was a boy. This is the type of person who has insight and initiative. You must reward that, but first you must recognize it.

Just in case some may have misse3d the point, the boy had keen insight into the obvious. That is a rare insight, most people plod along and never question. It is the few who see through the process, and go directly to than answer without the overhead that we seek to praise, not condemn.

Furthermore the teacher was guilty of the classic human flaw, ambiguity of expectations. She apparently had her way or no way. Yet the question posed was answered, and still she apparently rejected the obvious. Is this student demonstrating classic pragmatism at work?
Labels: Commentary

THURSDAY, AUGUST 16, 2012

MELANOMA, ZEBRA FISH, AND ALAN TURING

We have previously alluded to the use of the Turing model for demonstrating the propagation of melanoma in humans. We have further demonstrated a model of metastatic propagation and the interaction of ligand and receptors in a spatial manner similar to that of Turing. We have further demonstrated that from the recent literature that benign normal cell can actually then be used to reinforce the growth of the metastatic malignant cells. This then leads us to seek experimental evidence to this effect. To that end we look at the zebra fish and melanoma related to that model.

In a recent paper by Ceol et al they authors state[63[1]]:

The most common mutation in human melanoma, BRAF(V600E), activates the serine/threonine kinase BRAF and causes excessive activity in the mitogen-activated protein kinase pathway BRAF(V600E) mutations are also present in benign melanocytic naevi, highlighting the importance of additional genetic alterations in the genesis of malignant tumours. Such changes include recurrent copy number variations that result in the amplification of oncogenes. For

[63[1]] Ceol, et al, The histone methyltransferase SETDB1 is recurrently amplified in melanoma and accelerates its onset, Nature, 71, 513–517, (24 March 2011) ,http://www.nature.com/nature/journal/v471/n7339/full/nature09806.html

certain amplifications, the large number of genes in the interval has precluded an understanding of the cooperating oncogenic events.

Here we have used a zebrafish melanoma model to test genes in a recurrently amplified region of chromosome 1 for the ability to cooperate with BRAF(V600E) and accelerate melanoma. SETDB1, an enzyme that methylates histone H3 on lysine 9 (H3K9), was found to accelerate melanoma formation significantly in zebrafish. Chromatin immunoprecipitation coupled with massively parallel DNA sequencing and gene expression analyses uncovered genes, including HOX genes, that are transcriptionally dysregulated in response to increased levels of SETDB1. Our studies establish SETDB1 as an oncogene in melanoma and underscore the role of chromatin factors in regulating tumorigenesis.

In a more details general write up, Science Daily states[64[2]]:

Craig Ceol, PhD, assistant professor of molecular medicine at the University of Massachusetts Medical School, and collaborators at several institutions, used zebrafish to identify a new gene responsible for promoting melanoma. In a paper featured on the cover of the March 24 issue of Nature, *Dr. Ceol and colleagues describe the melanoma-promoting gene SETDB1.*

"We've known for some time that there are a number of genes that are responsible for the promotion and growth of melanoma," said Ceol, who completed the research while a postdoctoral fellow in the lab of Howard Hughes Medical Institute investigator Leonard Zon, MD, at Children's Hospital Boston. "With existing methods, it had been difficult to identify what those genes are. By developing the new approach described in this paper, we were able to isolate SETDB1 as one of those genes."

Cases of melanoma, an aggressive form of skin cancer, have been on the rise in the United States: in 2009 alone, 68,000 new cases were diagnosed and 8,700 people died of the disease. Though it accounts for less than 5 percent of all skin cancers, it is responsible for the majority of deaths from skin cancers and has a poor prognosis when diagnosed in its advanced stages. Early signs of melanoma include changes to the shape or color of existing moles or the appearance of a new lump anywhere on the skin.

The article then continues as follows:

Painstakingly analyzing more than 2,100 tumors from more than 3,000 zebrafish, researchers found that in fish with the SETDB1 gene, melanoma not only appeared earlier, but grew faster and invaded more deeply into the neighboring muscle and spinal tissue. With this new information, researchers screened 100 human melanomas for the SETDB1 gene. In 70 percent of the sample tumors, SETDB1 was present at high levels, indicating that SETDB1 may be involved in the formation of a majority of human melanomas."

64[2] http://www.sciencedaily.com/releases/2011/03/110323141852.htm

Further analysis showed that SETDB1 produces an enzyme that turns other genes on or off and is overrepresented in other forms of cancer, such as ovarian, breast and liver cancer. "It's clear that SETDB1 is up-regulated and that it's altering the activity levels of other genes," said Ceol. "Because SETDB1 regulates several genes, we still don't know which of its targets promote melanoma."

Thus another gene is identified in the melanoma chain. The last comment as to what specifically is regulated is concerning yet progress is being made.

Now how does this relate to Turing? In a more recent paper by Eom et al[65[3]] the authors state:

Remarkably, these interactions meet the predictions of Turing models of pattern formation that rely on dynamics driven by processes of reaction diffusion with lateral inhibition. Nevertheless, the molecular mechanisms that drive cellular behaviors during stripe formation have remained obscure.

Namely connecting these two we have further evidence that melanoma, using a zebra fish model, can follow the Turing approach we discussed several years ago.

We believe that this is a significant nexus between models and reality and is worthy of additional effort.

Labels: Cancer

MEDICARE AND LEFT WING ECONOMISTS

Economics is not a science, it is a form of political speech. I have spent the last four years trying to justify it. Astrology has more basis in reality than macroeconomics. In my opinion, one of the mouths of the movement on the left states:

..... Affordable Care Act cuts payments to Medicare providers by $716 billion in total over the next ten years and redirects the money to cover seniors' prescription drugs, public health, and to pay for coverage for the currently uninsured. Ryan's plan cuts payments to Medicare providers by $716 billion in total over the next ten years, uses the savings to fund tax cuts for rich, and then cuts payments to Medicare beneficiaries by $3 trillion in years 11 through 20.

Not quite, in fact not even close.

If you spent a modicum of time dealing with facts and numbers, not something these folks seem to do, one would see the current Administration's plan would drive Medicare reimbursements to

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[65[3]] Eom, D., et al, Melanophore Migration and Survival during Zebrafish Adult Pigment Stripe Development Require the Immunoglobulin Superfamily Adhesion Molecule Igsf11, PLoS Genet 8(8): e1002899. doi:10.1371/journal.pgen.1002899, http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1002899

the level of Medicaid. That means no physician could afford to treat the patient, they would lose money on every one, not that they make anything on the current reimbursements.

In fact Medicare and Medicaid created the bizarre markets we see in Health Care all by themselves! In fact the Ryan proposal may really allow markets and market prices to function. One must look a bit more but what is clear is that a $716B cut, reallocating the funds elsewhere, will result in a reduction of care, not of price.

The real problem is we allow as a society these people to teach in our state funded schools. Perhaps that is why California is a disaster!
Labels: Health Care

WEDNESDAY, AUGUST 15, 2012

WHAT BUSINESS ARE YOU IN

When Google bought Motorola's mobile handset business I wondered what business they thought they were in. MIT Technology Review, in my opinion the industry rag from Cambridge, no longer an alumni publication, has a short piece speaking of their approach.

They state:

According to the Times report, Woodside plans to reduce the number of devices Motorola makes from the 27 it introduced last year down to just a few, and wants those devices to have super-long battery life, improved cameras, and possibly even new features such as voice recognition technology that can recognize people chatting in a room. Dugan is reportedly hiring metal scientists, acoustics engineers, and artificial intelligence experts, too.

But whether the DARPA research model can work in the fast-evolving world of smartphones is unclear, says Chetan Sharma, a wireless analyst in Seattle. "Regina does bring in outside perspective specially related to projects that are leaps, versus incremental steps," he says. "However, this will need to be executed under the constraints of competition, time, and money."
....

Sharma says a big task will be convincing other handset makers that use Android that Google won't give Motorola preferential treatment. "The biggest challenge for them is to keep the Android ecosystem together while launching their own Google branded devices," Sharma says. "It is a tough battle to attract the ecosystem and effectively compete against them at the same time."

The strategy seems to be:

1. Buy the company.

2. Get the IP

3. Try to make money on what is left.

4. Play with the technology.

I am again reminded of a conversation I had with Bob Galvin the then CEO of Motorola in 1985. He wanted to expand Motorola into the service business from its then position in the hardware business. The business was then then Digital Radio Network. Namely providing brick sized data handsets working on a wireless band and selling the service to companies. I assembled a team, sold several companies on the idea but soon saw that the Motorola types were hardware types, the DNA was fixed. They had no idea what a service was.

Thus when I see Google which is a simple service business spend time and money on a product company then I assume that someone has a grand service strategy or this is a really big mistake. The Android cannibalism is a real concern. The culture is different. And with all due respect, DARPA is no Huawei.

Frankly the biggest challenge is culture. The key to success is focus. I remember what happened when the RBOCS, Bell Atlantic et al, were let loose, they spent hundreds of millions on things they had no idea about. I spent a couple of years getting rid of them too. Why some brilliant minds in them also wanted to get into the movies, and lost over $100 million or so. My time at Warner made me just chuckle. Thus it will be interesting to see how this plays out. Hubris, read the Greek plays folks, the gods always have strange tricks afoot!
Labels: Commentary, Wireless

QALY AND PROSTATE CANCER

NEJM published a Dutch study on Prostate cancer and the QALY. Now they conclude, if that be what we call it:

The benefit of PSA screening was diminished by loss of QALYs owing to postdiagnosis long-term effects. Longer follow-up data from both the ERSPC and quality-of-life analyses are essential before universal recommendations regarding screening can be made.

I have written a few years ago about the QALY, an oftentimes Brit concept to justify rationing. Carefully read the conclusion, if such be the case. It is not a conclusion but an opinion. They continue:

We predicted the number of quality-adjusted lifeyears (QALYs) associated with screening using utility estimates for various health states. The utility estimates were obtained from the Cost-Effectiveness Analysis Registry16 and additional studies 17-33 and ranged from 0 (death or worst imaginable health) to 1 (full health). In addition, we analyzed data from ERSPC on treatment-related complications, such as urinary incontinence, bowel dysfunction, and erectile dysfunction. Favorable and unfavorable values were assigned according to the minimum and maximum values in the cited references. A utility estimate of 0.99 was used for the screening phase...

Now a QALY is a rigged value which is oftimes the selection of the "researcher". If one has a

choice between erectile dysfunction and death, perhaps death for some is a better alternative. But allowing one to assume that all fear such an outcome as compared to bone met induced death is rather extreme. Yet we must remember that the Dutch do allow and support euthanasia.

They conclude:

In conclusion, this study quantifies how much of the benefit of the overall reduction in prostate cancer mortality in the ERSPC must be adjusted when the harms are taken into consideration. It is essential to await longer follow-up data from the ERSPC, as well as longer-term data on how treatment and active surveillance affect long-term quality of life, before more general recommendations can be made regarding mass PSA screening.

What harms. It is as if death has no value but being unable to chase the little ladies around the old age home is of more value! I am continuously amazed by the sophistry, in my opinion, of such studies. Having seen terminal PCa patients with bone mets I am amazed that anyone would consider loss of a night in the hay and a moral alternative.
Labels: Cancer, Health Care

CNV AND PROSTATE CANCER

Each day we see more relationships between genes, SNPs, miRNA, and now CNVs to some form of cancer. There is a recent paper in The American Journal of Pathology which relates CNVs to prostate cancer, PCa, and the prognosis of the disease.

We start with a brief discussion of a CNV. It is defined as follows:

Copy number variant (CNV): A duplication or deletion event involving >1 kb of DNA.

Simply a CNV may be the addition of one or more copies of a gene or part thereof in a chromosome. It simply adds to the chromosome. They are quite common and thus are seen frequently. Some are related to certain genetically inherited disorders. In the paper at point they are used to ascertain potentially prognostic data.

From the paper by Yu et al[66[1]]:

[66[1]] Yu, Y., et al, Genome Abnormalities Precede Prostate Cancer and Predict Clinical Relapse, The American Journal of Pathology - June 2012 (Vol. 180, Issue 6, Pages 2240-2248, DOI: 10.1016/j.ajpath.2012.03.008).
http://www.journals.elsevierhealth.com/periodicals/ajpa/article/S0002-9440%2812%2900241-6/abstract

[66[2]] Freeman, J., Copy number variation: New insights in genome diversity, Published in Advance June 29, 2006, doi: 10.1101/gr.3677206 *Genome Res.* 2006. *16: 949-961* http://genome.cshlp.org/content/16/8/949.full.html#ref-list-1

The prediction of prostate cancer clinical outcome remains a major challenge after the diagnosis, even with improved early detection by prostate-specific antigen (PSA) monitoring.

To evaluate whether copy number variation (CNV) of the genomes in prostate cancer tumor, in benign prostate tissues adjacent to the tumor (AT), and in the blood of patients with prostate cancer predicts biochemical (PSA) relapse and the kinetics of relapse, 241 samples (104 tumor, 49 matched AT, 85 matched blood, and 3 cell lines) were analyzed ...

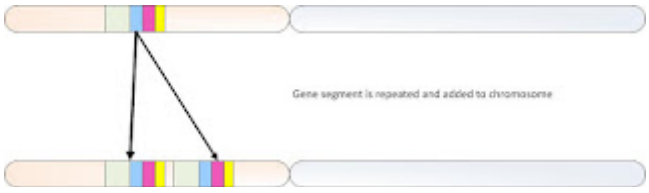
By using gene-specific CNV from tumor, the genome model correctly predicted 73% (receiver operating characteristic P = 0.003) cases for relapse and 75% (P < 0.001) cases for short PSA doubling time (PSADT, <4 0.="0.">

By using median-sized CNV from tumor, the genome model correctly predicted 75% (P < 0.001) cases for relapse and 80% (P < 0.001) cases for short PSADT. For the first time, our analysis indicates that genomic abnormalities in either benign or malignant tissues are predictive of the clinical outcome of a malignancy.

We briefly examine the CNV in general. In the work of Freeman et al we have[67[2]]:

DNA copy number variation has long been associated with specific chromosomal rearrangements and genomic disorders, but its ubiquity in mammalian genomes was not fully realized until recently. Although our understanding of the extent of this variation is still developing, it seems likely that, at least in humans, copy number variants (CNVs) account for a substantial amount of genetic variation. Since many CNVs include genes that result in differential levels of gene expression, CNVs may account for a significant proportion of normal phenotypic variation. Current efforts are directed toward a more comprehensive cataloging and characterization of CNVs that will provide the basis for determining how genomic diversity impacts biological function, evolution, and common human diseases.

We show an example of a CNV below graphically.



Here we have depicted a gene, the multicolor object in a chromosome and we have shown a CNV with an identical copy of the gene in the same chromosome. The authors continue:

CNVs often occur in regions reported to contain, or be flanked by, large homologous repeats or segmental duplications. Segmental duplications could arise by tandem repetition of a DNA segment followed by subsequent rearrangements that place the duplicated copies at different chromosomal loci. Alternatively, segmental duplications could arise via a duplicative

transposition-like process: copying a genomic fragment while transposing it from one location to another

It must be noted that these are identical duplications of the genes, or segments thereof. If of a gene the segment can be transcribed as easily as the original. This raises the question that the resulting translated protein is at a potential multiple level of concentration, although this may not necessarily be the case. They continue:

Large duplications and deletions have been known for some time to be related to the presentation of specific genetic disorders, presumably as a result of copy number changes involving dosage-sensitive developmental genes. This has led to the establishment of genetic diagnostic tests for certain, well-characterized microdeletion and microduplication syndromes (e.g., Angelman syndrome, DiGeorge syndrome, Charcot-Marie-Tooth disease, etc.).

If a de novo chromosomal aberration is recognized in a patient with a constitutional genetic abnormality (i.e., follow-up studies fail to reveal a similar chromosomal aberration in either of the two parents, and non-paternity has been excluded) and the aberration is not one of the dozen or so well-known common chromosomal polymorphisms (e.g., inversion on chromosome 9), the aberration is assumed to be the cause of the clinically recognized abnormal phenotype.

Finally the CNVs are not necessarily related to disorders. Some have CNV but many CNV are not noticeable. They thus state:

CNVs that do not directly result in early onset, highly penetrant genomic disorders may consequently be considered to be neutral in function, but afterward shown to play a role in later onset genomic disorders or common diseases. Analyses of the functional attributes of currently known CNVs reveal a remarkable enrichment for genes that are relevant to molecular–environmental interactions and influence our response to specific environmental stimuli.

These include, but are not limited to, processes involving drug detoxification (e.g., glutathione-S-transferase, cytochrome P450 genes, and carboxylesterase gene families), immune response and inflammation (e.g., leukocyte immunoglobulin-like receptor, defensin, and APOBEC gene families), surface integrity (e.g., late epidermal cornified envelope and mucin gene families), and surface antigens (e.g., galectin, melanoma antigen gene, and rhesus blood group gene families). Likewise, some CNVs encompass genes that may contribute to interindividual variation in drug responses, as well as in immune defense and disease resistance/susceptibility among humans.

From the Thorne and District Gazette[68][3]:

This study was appropriately designed to see whether patients who have different outcomes have differences in copy number variation. However, before this technique can be used as a test, it will have to be trialled on a much larger cohort of people, so that researchers can get a clearer picture of its use in clinical settings. For example, researchers will need to know how often the

[68][3] http://www.thornegazette.co.uk/news/health/behind-the-headlines/dna-blood-test-for-prostate-cancer-1-4606100

test might miss patients that are likely to relapse, and also how often the test incorrectly suggests a person's cancer is likely to relapse, which could lead them to have unnecessary further treatment. Also, as the authors note, the techniques used in this study need high-quality DNA, so may be difficult and expensive to perform…

The article then states regarding the outcomes:

1. *Approximately one-third of the patients had a relapse soon after surgery, with a median time to progression of 1.9 months.*
2. *One-third had a relapse but much more slowly, with a median time to progression of 47.4 months.*
3. *One-third of patients in the cohort were free of cancer for at least five years.*

Based on the associations they found, the researchers developed an algorithm for predicting whether a patient would relapse, and how quickly they would relapse. This was based on whether the genetic code at specific locations was repeated or deleted, or on the size of copy number variation found across a person's genome. They then tested their prediction model on an additional 25 samples.

They then conclude:

The researchers found that the prostate cancer samples had a large number of genetic abnormalities. (i) Deletions of specific regions occurred at high frequency, and amplification (abnormal repetitions) of other regions occurred in a subset of samples. (ii) Healthy tissue adjacent to a tumour also had similar amplification and deletion patterns. (iii) The blood of patients with prostate cancer also contained copy number variations, and some of these variations occurred in the same locations within the DNA as they had in the prostate cancer samples.

The researchers then developed a tool to predict whether a cancer would relapse based on DNA regions that had a significant proportion of amplification or deletion in prostate tissue samples from patients who relapsed, but not in patients who did not relapse. The prediction model looking at cancer tissue samples could predict a relapse correctly 73% of the time. (i) It had a 75% accuracy for predicting rapid relapse. (ii) The prediction model based on examining healthy tissue samples could predict a relapse 67% of the time. (iii) It had a 77% accuracy for predicting rapid relapse. (iv) This blood-based prediction model had an accuracy of 81% for predicting relapse, and a 69% accuracy for predicting rapid relapse. (v) The cancer tissue analysis tool had an accuracy of 70% for predicting relapse, and 80% for rapid relapse. (vi) The healthy tissue sample tool had an accuracy of 70% for relapse and rapid relapse, and (vii) the blood sample tool had an accuracy of 100% for relapse and 80% for rapid relapse.

This is but another way to examine PCa cells. It does pose several questions:

1. Pathways: Is there also a set of pathway malfunctions that one sees in PCa also present here?

2. Is the CNV an artifact or causative. If causative then what is the specific process and how does it relate to known pathways.

3. This is a complex cellular measurement of genes. Is this cost effective?

4. The classic issue of stem cells again is raised. What chromosomes do we look at? Is this specific only to the PCa cells, the PCa stem cells, and all cells?

Definitions from Freeman et al:

1. **Structural variant**: A genomic alteration (e.g., a CNV, an inversion) that involves segments of DNA >1 kb.

2. **Copy number variant (CNV)**; A duplication or deletion event involving >1 kb of DNA.

3. **Duplicon** :A duplicated genomic segment >1 kb in length with >90% similarity between copies

4. **Indel:** Variation from insertion or deletion event involving <1 span="span" style="letter-spacing: .4pt;"> kb of DNA.

5. **Intermediate-sized structural variant (ISV):** A structural variant that is ~8 kb to 40 kb in size. This can refer to a CNV or a balanced structural rearrangement (e.g., an inversion).

6. **Low copy repeat (LCR)**: Similar to segmental duplication.

7. **Multisite variant (MSV):** Complex polymorphic variation that is neither a PSV nor a SNP.

8. **Paralogous sequence variant (PSV):** Sequence difference between duplicated copies (paralogs.)

9. Segmental duplication: Duplicated region ranging from 1 kb upward with a sequence identity of >90%. (Interchromosomal: Duplications distributed among nonhomologous chromosomes and Intrachromosomal: Duplications restricted to a single chromosome)

10. S**ingle nucleotide polymorphism (SNP):** Base substitution involving only a single nucleotide;~10 million are thought to be present in the human genome at >1%, leading to an average of one SNP differenceper1250 bases between randomly chosen individuals

Labels: Cancer

MONDAY, AUGUST 13, 2012

TEXTBOOKS

As usual, Frances Woolley has focused on an important issue in an interesting manner. Namely, the issue of textbooks and their ever exploding prices. She discusses economics texts and the ever expanding number of editions at ever increasing prices with little if any new material or insight.

Now she touches on an even more significant issue, how teaching has changed. In the 60s I was a user of chalk, and a blackboard. Large moveable boards, large chalk pieces, and lectures which were well rehearsed like that of a good, if not great, Shakespeare theatre. I always admired several professors, Dick Dudley in Math and Harry Van Trees in Engineering, who would just step up to the board and commence lecturing, chalk in hand, creating art quality presentations. In Dudley's case sans text, just one Theorem, Definition, Proof after another, it was like an opera, it flower in an errorless manner and you sat transfixed recording each and every detail, hand and brain coordinating, knowing full well that soon you would spend hours going over each page, seeing his brilliance just flow as one would see the notes on paper written by Mozart.

But alas many of those days are gone. Enter PowerPoint, the bane of many. Faculty just walk in with pre-prepared PowerPoint slide, coordinated with the large exorbitantly priced text, filled with endless pictures of no known value but justifying the costs. The faculty no longer prepares, they just pop the presentation in and "read" the teleprompter. The students then type stuff into their iPads or surf the web and wait till the exam. Does anyone do problem sets anymore?

Last year I decided to re-take Organic Chemistry after some 50 years duration. Did it change? Yes, the text by Smith is highly readable and the question and answer book is quite useful. It helped me better understand details which I had long forgotten, if ever I had learned them in the first place. The book was much better now than 50 years ago. Yet it was like a 3rd Grade math work book, problem after problem, so that the student was drilled. Did it help memorizing the 150 reactions, not really? Also it was at a Community College and the Instructor, good but obviously overworked, missed, in my opinion, the opportunity to convey the élan of the material. The text and work book were, at market, in excess of $300! That was more than my tuition! Was the book worth that amount, clearly the author did a massive job, and remuneration was well worth the effort. But really, that is a lot of money.

Now, to examine macro-economics. Macroeconomics is fundamentally two things; first, it is understanding the tautological collection of numbers we measure as an economy, namely GDP and its components, and the players who try to effect changes. Second, and most importantly, it is a part of political science, not really a science but a catch phrase for how people view the economy and what we hold near and dear. Conservatives versus Liberals, Individualists versus Progressives. They are belief sets, and each side attempts to use equations to explain them, nay, to justify their positions. Yet the justification falls all too short. Just look at Romer and her unemployment projections. Her projections never even got close to reality. She espoused a political theory which seems at best to have failed and at worst may cause the collapse of our

society. Yet we all too often fail to have students understand the philosophy, the mindset, and the anthropological underpinnings of macroeconomics.

Thus the challenge of macroeconomics is unlike many others. Consider Skinner versus Wood, the latter a self-proclaimed Marxist, each have their view of the development of a political world, and in turn an economic one as well. How do we deal with these world views ab initio, rather than go into a Samuelson, not understanding that much of what he espouses is as political in viewpoint as any politician. That the “truth” he espouses is itself a point of view. My first economics text was I believe a second edition of Samuelson. It was very light on math and just as light on his descriptive curves. However when I read his classic text, Foundations of Economic Analysis, I was at first impressed. Yet after a while I caught on to the trick. His economic models were created to fit the solutions to differential equations models we had done for real systems in Electrical Engineering. Thus unlike the engineer who modeled reality and then analyzed it, the economist often finds a model which he can analyze and fits reality to that model.

Now to books. A good course in macroeconomics should consist of a selection of readings, many of them from classics and many culled from the many existing texts out there on the used market. If we need something new then it is never too early for the student to access the primary sources, yes the journals or even better the draft writings which are still works in progress. After all that is what we do later in our careers. The professor should list out the topics and suggested readings and the student should find out how to access them.

Now why does this not happen. Money. Plain and simple. At a 15% sales commission, then for each $200 book the Professor gets $30. Sell 1,000, get $30,000, sell 5,000, and get $150,000. It pays for that house on the Vineyard, that trip to Bali. It also is a massive “takings” from the students, and placing the economy further in debt. It is not cost effective; it is punitive, and nonproductive. Part of any macroeconomics course should be the understanding of this takings process.

Now frankly it gets even worse in say physics and math. Calculus has not changed in almost 300 some years. I can use a text from 100 years ago and do as well as if I used a recent version. Same with physics, same with Latin, French. Etc.

Now Frances bemoans the whole process saying:

Professors generally assign readings by chapter, for example, "Week 2: chapter 4, consumer theory." But chapter 3 in the current edition might be chapter 2 or chapter 4 in the old edition. Professors often require students to complete end-of-chapter problems, and problem numbering or wording may differ across editions. When a professor says "Study Figure 3.4 carefully, I'll be asking a question about it in the final exam", the student with an older edition of the text, where Figure 3.4 is labelled 2.4, may end up studying the wrong thing.

It's just like software upgrades - an old version of Microsoft Word might do everything the user needs, but if Microsoft introduces a new .docx file format, old versions are rendered useless, because they are unable to read files generated by other users.

The whole process disgusts me. New editions destroy value, by making old editions worth less. They hurt students, who face high prices for texts. Any pedagogical benefit from having a slightly more updated text is more than offset by the increase in the number of students who decide to save money by reading Wikipedia instead of a textbook. Ultimately, it is a colossal waste of resources - all the effort that goes into producing a new edition that differs little from the old one; all of the perfectly good older textbooks that end in the recycling bin.
But what is the alternative? One possibility is banning new editions - or limiting publishers to one every six years.

I never assigned Chapters. I assigned topics, and that was in the Dark Ages before on-line systems. Use the Library, it worked. But now it is even easier. The ease and ability to gain access should change the way we teach, it should free us from text books totally. Assigning topics, not chapters, allowing students to learn the topics via what is available, it is essential. When I studied under Dudley, I amassed a library of texts on analysis; I even wrote my first book to know the material better. Perhaps a new path, sans texts, is not only possible but better.

Yet there is another option regarding books, namely the Internet and electronic versions. In my first two books published by Wiley, I spent months perfecting the drafts, the galleys, and the final proofs, so that almost 75% of my time was on process, and correcting introduced errors. In the past several years I have posted 10 draft books, all of which I modify as I discuss them with others. I have one on Obesity and Type 2 Diabetes which download over 100 per week and well over 5,000 per year. Yes it is free, yes it is not peer reviewed, yes I change it from time to time, and yes I get comments. But somehow there is great consumption, knowing it is draft, knowing it may contain errors, and knowing it is subject to change. Why then cannot academics do the same? It appears that it is less ego and more greed, getting students to pay outlandish prices so that they can enrich their pockets. This is a prime example of what is wrong with the Academy. Unless managed it will result in a bubble like collapse.
Labels: Academy, Commentary

LUDUS NUMQUAM FINIT

The family motto, "the fun never ends", and often meant with at best offhand humor. Fun often entails looking back and asking why we ever did this. Well the NY Times has a "fun" tale, building a scaffolding arounf the statue of Columbus on 59th Street.

They state:

“I like it,” he said recently. “I think it’s fun.” The fun is just beginning, with the scaffolding rising for the piece, by the Japanese artist Tatzu Nishi, who plans to furnish the living room with couches, lamps and a coffee table for visitors, who will be able to commune face to face in homey comfort with the 13-foot tall explorer as he pokes up into the space from atop his lofty pedestal.

Yes the fun is just beginning. More crowds, more traffic and some "artists" view of greatness. Why not ust leave things alone and let us have "fun" with what we have. Why add more "fun" to the mess.

Labels: Commentary

SUNDAY, AUGUST 12, 2012

EHR PROGRESS?

The EHR systems are still provider centric. Frankly this is one of the biggest mistakes ever. They require providers to transfer data, often in an unusable manner. Now we are seeing the 3rd generation coming.

As HealthCare states:

For Stage 3, the Health IT Policy Committee's Meaningful Use Workgroup wants physicians and hospitals to increase their use of clinical decision support; computerized physician order entry (CPOE); structured, machine-readable data; and medication reconciliation (the process of comparing a patient's medication orders to all the meds he or she has actually been taking). The plan also ramps up requirements for patient engagement.

In a plan recently unveiled in Washington, D.C., the workgroup made its preliminary recommendations for Stage 3.

New for Stage 3 would be requiring providers to enable at least 10% of their patients to submit their medical history electronically, to accept readings from home medical devices, and to update and correct information in EHRs. Providers also would need to supply electronic care plans to other providers and care sites when patients are referred or moved, and the referring site would be required to send a small percentage of results back,

One need just look at what is proposed and the workload is increasing exponentially. Patient Care plans are like Grammar School Class Teacher Plans, they will become some off the shelf piece of pdf and that is NOT the way medicine is practiced. This appears to be a techy's dream of how complex to make something. What will this do to the practice of medicine. Already many physicians have hired another person to enter and keep the EHR, and many physicians may never look at or even know how to examine an EHR.

In addition the need to integrate with billing and authorization is totally lacking. The data is not patient centric and it fails to adequately deal with displaying data for chronic disease management. This is a total nightmare and will just explode the costs of health care with no positive benefit.

Labels: Electronic Medical Records, Health Care

SUNDAY, AUGUST 12, 2012

TYPE 2 DIABETES, GENES, AND TOO MUCH DATA

The number of genes now associated with Type 2 Diabetes has begun to explode. In a recent piece in Medical Press they state:

Ten more DNA regions linked to type 2 diabetes have been discovered by an international team of researchers, bringing the total to over 60....

Their findings are published in the journal Nature Genetics. 'The ten gene regions we have shown to be associated with type 2 diabetes are taking us nearer a biological understanding of the disease,' says principal investigator Professor Mark McCarthy of the Wellcome Trust Centre for Human Genetics at the University of Oxford. 'It is hard to come up with new drugs for diabetes without first having an understanding of which biological processes in the body to target. This work is taking us closer to that goal.'....

The researchers analysed DNA from almost 35,000 people with type 2 diabetes and approximately 115,000 people without, identifying 10 new gene regions where DNA changes could be reliably linked to risk of the disease. Two of these showed different effects in men and women, one linked to greater diabetes risk in men and the other in women....

With over 60 genes and gene regions now linked to type 2 diabetes, the researchers were able to find patterns in the types of genes implicated in the disease. Although each individual gene variant has only a small influence on people's overall risk of diabetes, the types of genes involved are giving new insight into the biology behind diabetes.Ten more DNA regions linked to type 2 diabetes have been discovered by an international team of researchers, bringing the total to over 60.

The problem of course is that this represents a correlation not a causation. There is no underlying model for the disease at the pathway level. The genes may very well have been affected as a result of the existing Type 2 Diabetes inflammation. That frankly is all too often the case and the cause for subsequent sequallae.

It will be essential to understand the pathway breakdown, and the underlying pathway dynamics, not simply finding more genes than less.

In my opinion one of the worst things is the ability to find all of these genes as if they mean something. One must recall that clinically so great a percentage of Type 2 patients are obese, and it is that one to one relationship which dominates. Unlike cancer, we all too often can "cure" Type 2 Diabetes and prevent the sequellae by reducing obesity. Get the BMI below 22.5 and it can become a success.

However the search for genes without causation and just correlation can in my opinion just muddy the water. It gets lots of papers but misses the issue.
more at: http://medicalxpress.com/news/2012-08-ten-diabetes-gene-links-picture.html#jCp

Ten more DNA regions linked to type 2 diabetes have been discovered by an international team of researchers, bringing the total to over 60.

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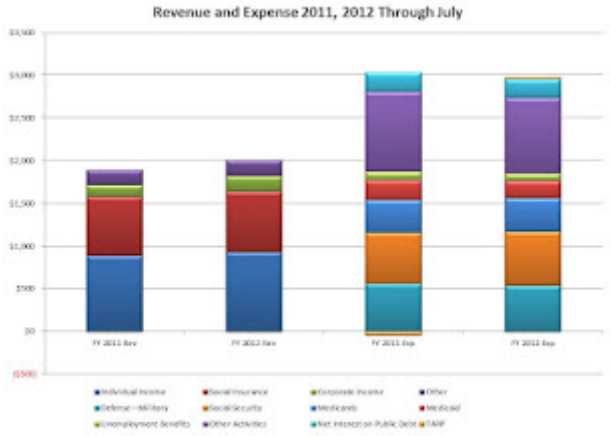
Read more at: http://medicalxpress.com/news/2012-08-ten-diabetes-gene-links-picture.html#jCp
Labels: Diabetes, Genetics, Health Care

TUESDAY, AUGUST 7, 2012

BUDGET DEFICIT JULY 2012

The CBO reports in the 2012 and 2011 Budget deficits for the nine months of each year, through July.



Note that we have had a small improvement at best. The CBO states:

CBO estimates that the Treasury Department will report a deficit of $975 billion for the first 10 months of fiscal year 2012, $125 billion less than the $1.1 trillion deficit incurred through July 2011. Through the end of July, revenues were about 6 percent higher this year than at the same point last year; outlays were about the same in both years. Because October 1, 2011, occurred on a Saturday, roughly $31 billion in payments that would have been made in 2012 were made in 2011. In the absence of that shift, the deficit so far this year would have been about $93 billion smaller than last year's figure.

Frankly things are just not getting any better. Medicare is up very slightly, amazing given more subscribers and price inflation, SSI is up 5.8% which is more people collecting. Unemployment is down, but likely to increase. Between Defense and Other we have $1.5T or half of the budget.

Labels: Economy

MASSACHUSETTS ON OVERDRIVE

The Commonwealth of Massachusetts just enacted an even more restrictive Health Care Plan than the ACA or so it appears. In a Press Release today they state:

The new law will:

Achieve Billions in Savings: *Sets a first-in-the-nation target for controlling the growth of health care costs. The law holds the annual increase in total health care spending to the rate of growth of the state's Gross State Product (GSP) for the first five years, through 2017, and then even lower for the next five years, to half a percentage point below the economy's growth rate, and then back to GSP.Results in nearly $200 billion in health care cost savings over the next 15 years, which will lead to up to $10,000 in additional take-home pay, per worker, over 15 years.The average family will see an estimated savings of $40,000 on their health care premiums over 15 years.*

Move to Alternative Payments: *To control costs and improve quality of care, the law requires government agencies like MassHealth, the GIC and the Connector to use global and other alternative payments to achieve savings for taxpayers. Encourages alternative delivery systems across health care fields to deliver additional savings for patients, business owners and working families.*

Increase Transparency: *The law also gives consumers better information about the price of procedures and health care services by requiring health insurers to provide a toll-free number and website that enables consumers to request and obtain price information.*

Address Market Power: *To monitor and address the market power and price disparities that can lead to higher costs, the law allows a Health Policy Commission to conduct a cost and market impact review of any provider organization to ensure that they can justify price variations. The law identifies triggers for when a provider or provider organization will be referred to the attorney general for investigation. An independent Center for Health Information and Analysis will conduct data collection and reporting functions.*

Promote Wellness: *The law creates a Wellness Fund of $60 million administered by the Massachusetts Department of Public Health for competitive grants to community-based organizations, health care providers and regional planning organizations.*

Enact Malpractice Reform: *The law includes malpractice provisions proposed by Governor Patrick, requiring a "cooling-off" period before a party may initiate a suit, while making providers' apologies inadmissible as evidence. Many studies show that an apology can prevent a lawsuit but due to the threat of litigation, providers have oftentimes remained silent.*

Support Health Information Technology *Massachusetts is already a national leader in adopting electronic health records and health IT efforts. The law complements these efforts, by advancing several health information technology programs, including the Executive Office of Health and Human Services' work with the Obama Administration to build and operate the statewide health information exchange.*

It appears however that what was enacted was a price cap mechanism on the provision of services. What also seems confusing is that if we have ACA then what is the State doing with regard to this? This has thus become a confusing nightmare for Massachusetts hospitals as well as physicians. They now see conflicting legislation and almost instantaneous reimbursement reductions, with a similar reduction on Medicare as well.

The Teaching Hospitals it appears will suffer the most. It will be interesting to see what happens in the long term. Medical education may become what we now see in Teacher education. A disaster!
Labels: Health Care

MONDAY, AUGUST 6, 2012

OPEN ACCESS AND PUBLISHING

Believe it or not the world is changing, all the time even. And that include the publishing of professional papers and documents. The very term publishing is making a change. I have been through the process for over fifty years almost and at times it is frustrating. At first you scramble, then with a reputation you are asked to submit almost anything. Thus the clan of reviewers are often keepers of the "truth" as they see it. The Internet has blow that asunder and Open Access publishing is but one dimension of that.

The Scientist has an interesting piece worth a read. The state:

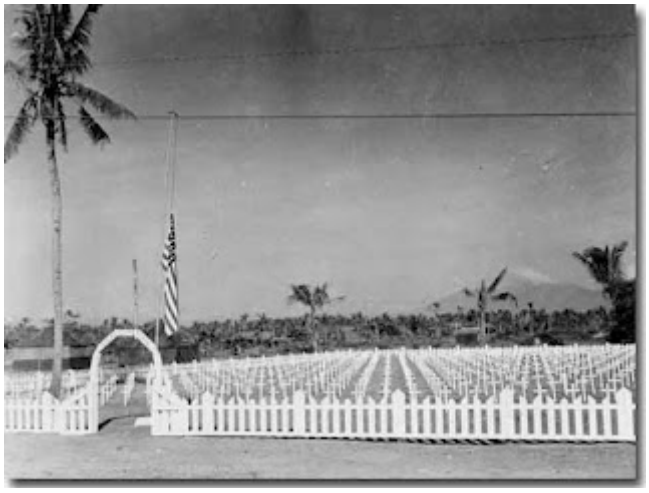
While poor quality publishers are proliferating, often creating hundreds of cookie-cutter journals, they tend to publish relatively few articles. On the other hand, PLoS recently published its 50,000th article. We reanalyzed data from a study we recently published in the Journal of the American Society for Information Science and Technology that characterized the APCs of journals charging them. We found that two thirds of the approximately 106,000 articles published in 2010 in these journals, listed in the Directory of Open Access Journals, were in publications listed by the 2010 Journal Citation Report (JCR) and another 11 percent were listed in the Scopus abstract and citation database but not in the JCR. The publishers of these indexes screen the journals they list for quality including ensuring that they are properly peer-reviewed. This suggests that the majority of scientists publishing in OA journals that charge APCs are savvy enough to avoid low quality publishers. It appears that they care about the quality of the journals in which they publish, as do the promotion and tenure committees that evaluate researchers. Beall and others have pointed out a legitimate concern with predatory publishing, but it is important to keep that concern in perspective.

I suspect Journals like PLoS will become accepted on a par with those which charge extreme amounts per article. I personally use PLoS and have subscriptions to some old standards, NEJM, Science, etc, but PLoS and other on line available sources exceed now by orders of magnitude my subscription access.

I believe this will change the velocity of dissemination and will be a tremendous benefit to science.

Labels: Academy

REMEMBERING AUGUST 6TH

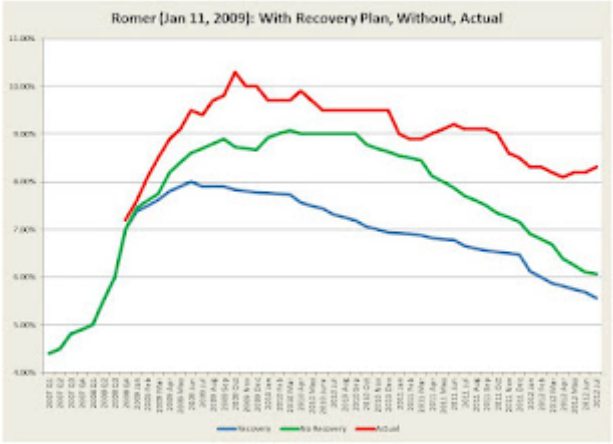


The Mount Hood Cemetery on Manus in December 1944. There would be another 8 months of bloodshed, Iwo Jima and Okinawa, but for the men buried here it would be rest. August 6, 1945 despite the death led to resolution, a resolution which was inevitable even in late 1944.
Labels: Commentary

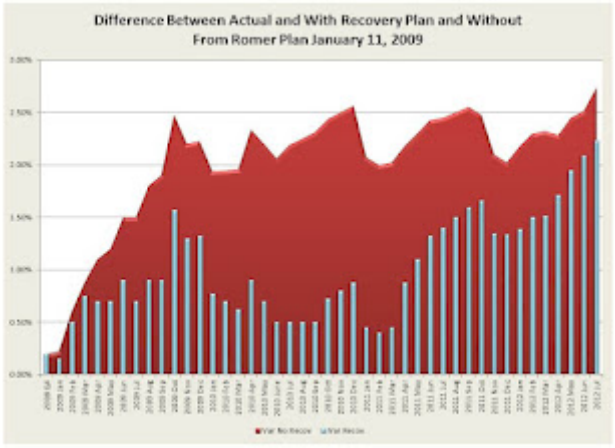
FRIDAY, AUGUST 3, 2012

EMPLOYMENT JULY 2012

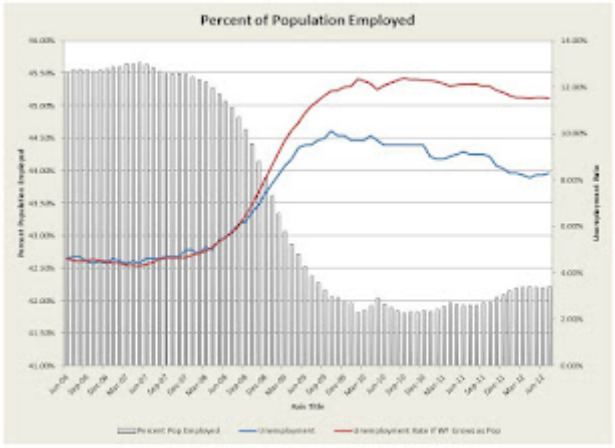
Things just do not seem to be getting better. This month we hit 8.3% unemployment but as usual the details matter. Let us review them.



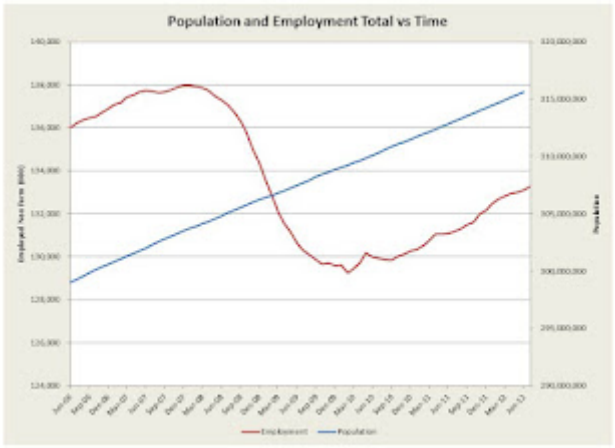
First the above is the Romer Curve. Remember that on Saturday January 11, 2009 she released from the new Administration web site what their efforts would do. We continue to be amazed as to the variance from reality. Again so much for economists! They must be the same people who did estimates for the Big Dig in Boston, $2B versus $40B actual!



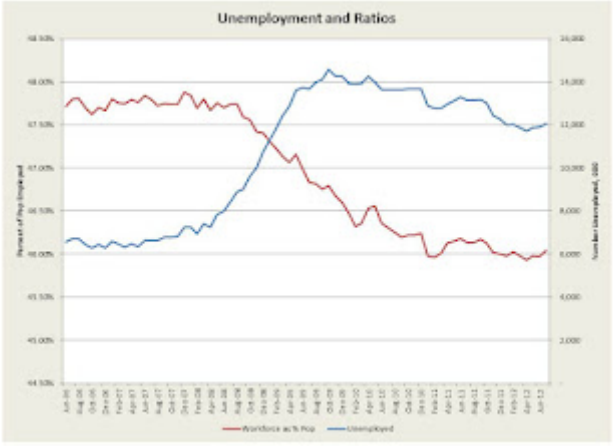
The above shows the variance and it is clearly growing in a never ending manner. Confusion, uncertainty, more costs, all add up to no growth. And the Administration has no clue!



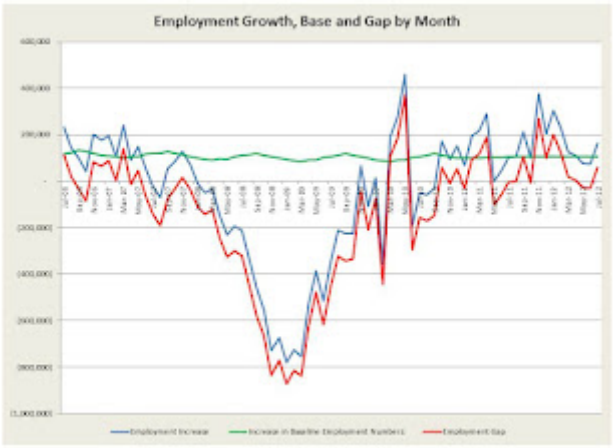
The above shows a glimmer of hope. The percent employed is still ate the same level as the past few months. Yet the unemployment increases but the base unemployment has dropped a bit. We may just be looking at noise however at this stage. Stagnation is at play.



The above shows the gap which we need to fill. It is that 8-10 million people permanently unemployed and no hope in sight.



The above shows the actual unemployed increasing which is a serious concern. It is not two years from the alleged summer of recovery.



Finally another glimpse of good news, the net jobs did keep the increase in employable at work, thus only 8.3%

We see a return of the Recession late this Fall and this just assures that now.
Labels: Economy

WEDNESDAY, AUGUST 1, 2012

THE PSA DEBATE CONTINUES

Well the PSA debate continues. My readers know what side I am on and here is a piece supporting my work. It is by Dr. Messing of Rochester Medical Center.

The article in Cell states:

The objective of this study was to estimate the total number of patients who would be expected to present with metastatic (M1) prostate cancer (PC) in the modern US population in a given year if the age-specific and race-specific annual incidence rates of M1 PC were the same as the rates in the era before prostate-specific antigen (PSA) testing .... If the pre-PSA era rates were present in the modern US population, then the total number of men presenting with M1 PC would be approximately 3 times greater than the number actually observed.

Simply stated the evidence demonstrates that the use of PSA has reduced the number of M1 cases of PCa by a factor of 3. Messing as a clinician has obviously seen first hand the results of not mitigating against this deadly disease. The bone mets, collapse of the spinal cord, the DIC results to name a few. Bone pain is excruciating. Thus anything that can be done to mitigate this is essential.

On the NIH web site they have a compelling article describing the work.

The article states:

"PSA testing, for all its pluses and minuses and all that . . . permits you to catch the disease earlier," said lead researcher Dr. Edward Messing, chair of urology at the University of Rochester Medical Center in Rochester, N.Y. "These people are all going to die, they are going to die incredibly expensively and die miserably," he said, referring to the many men whose diagnoses would be delayed by not testing. "I don't know that all these people could be saved with PSA testing," but many could, he added. The report was published online July 30 in the journal Cancer.

Messing said the annual number of prostate cancer deaths dropped from about 42,000 in the 1990s to 28,000 now. "The only thing that can explain that is PSA early detection and treatment," he said.
Many cases of prostate cancer are not life-threatening, which is why testing is controversial. The U.S. Preventive Services Task Force (USPSTF) in May recommended against routine PSA screening, saying too many non-lethal cancers were being treated aggressively, exposing men who didn't need treatment to serious side effects such as impotence and urinary incontinence. But Messing disagreed with that advice. Condemning PSA testing "wasn't a brilliant conclusion," he said.

For the new study, Messing's team compared information from the U.S. Surveillance, Epidemiology, and End Results database for the years 1983 to 1985 -- immediately before widespread PSA testing started --- to data from 2006 through 2008. In the 2008 data, 8,000 cases of prostate cancer were diagnosed after the malignancy had spread to other parts of the body. Using these cases as a base, the researchers constructed a model that used data of advanced cancer diagnosed in the 1980s and predicted how many cases of advanced cancer would have been diagnosed in 2008 if PSA testing was not done. Their model showed instead of 8,000 actual cases in 2008, about 25,000 cases would have been diagnosed.

This is consistent with our arguments as well. This is telling especially today since HHS also announced all the "free" stuff for women while the USPSTF denies men equal protection. As I

have said again and again, there will be some morbidly obese GS9 controlling the destiny and death of men. Welcome to the world of the ACA.
Labels: Cancer, Health Care

NEW MEANING TO FREE

HHS has just announced a list of several "Free" health care services mandated by the ACA. Specifically they state:

For the first time ever, women will have access to even more life-saving preventive care free of charge.....

1. *Well-woman visits.*
2. *Gestational diabetes screening that helps protect pregnant women from one of the most serious pregnancy-related diseases.*
3. *Domestic and interpersonal violence screening and counseling.*
4. *FDA-approved contraceptive methods, and contraceptive education and counseling.*
5. *Breastfeeding support, supplies, and counseling.*
6. *HPV DNA testing, for women 30 or older.*
7. *Sexually transmitted infections counseling for sexually-active women.*
8. *HIV screening and counseling for sexually-active women.*

Now "Free" is a rather powerful word. Since all of these cost someone, take contraceptives and even more so HPV DNA tests, then someone must pay unless the providers are donating their services, in which case they are paying, unless the workers are donating their services, and the link goes on. Remember that there is "no free lunch" and that applies to the above as well.

Now for the phrase "first time ever" one should note that all of the above have been available before just that there was some cost sharing. Cost sharing with the user. Now the user is spreading their costs over everyone, namely the 50% or so of men are paying for what was a cost sharing part before. Yet this is the same ACA which wants to stop PSAs and refuse surgery to men with prostate cancer allowing many to die a painful bone met death.

There are several issue here worth noting:

1. Nothing is free, and when we say it is free we open the door for abuse.

2. The tests mentioned above were always available to anyone, paying or clinic patient. By mandating them it is suspected to up the utilization , increase costs, yes there are costs, and yet not really improve any patient care.

3. HPV and HIV are sexually transmitted diseases. One causes cancer and the other lots of real nasty stuff. The problem is for a sexually active person, protection of some sort is sine qua non, yet testing could become a chronic problem being done periodically and at a significant cost.

4. Gestational diabetes is always a concern in pregnancy and the Oby will or should always be on

the look out. Also the expecting mother should be made aware of the signs and respond accordingly. The difference here one supposes is that now it is mandated to be paid for 100% by the insurer.

5. Frankly the real question is what does free mean. Free means that the woman does not pay, but pay what? If the Government or Insurer will pay a physician a fixed amount for ll of the mandated service then will the woman be denied service by a physician because the "free" service payment is less than the costs?

To see what could happen just look at yesterday's CBO release on Medicare. They state:

Medicare's payment rates for physicians' services are scheduled to be reduced by 27 percent in 2013, CBO estimates, under the provisions of law known as Medicare's Sustainable Growth Rate (SGR) mechanism. The SGR mechanism consists of expenditure targets, which are established by applying a growth rate (calculated by formula) to spending for physicians' services and certain related services in a base period, and annual adjustments to the payment rates, which are designed to bring spending in line with the expenditure targets over time. In each of the past several years, legislation has been enacted to override the SGR and to either maintain or increase those payment rates when they were otherwise scheduled to decrease.

The Medicare payments are estimated to drop by 27% in January 2013. That means that almost all Medicare physicians will be compensated well below costs. Just think of all those additional staff to handle the Electronic Healthcare Record systems. Who will now be paying for them. Mandates for free are increasing while allowed payments decrease.

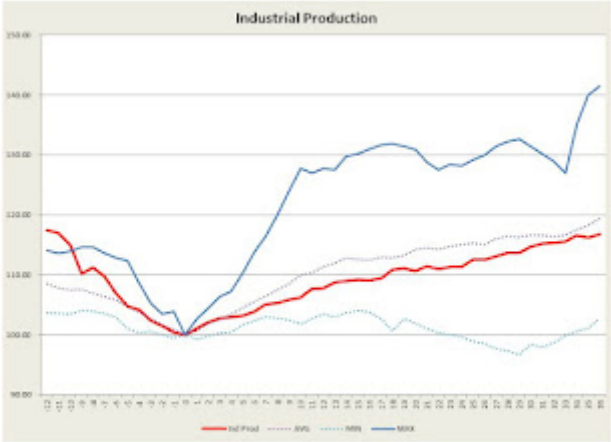
Frightfully one could see in a generation that medicine will turn into what Public School Teachers are today, overpaid and under-educated. It would then be better to go off to another country, like Canada even!
Labels: Health Care

TUESDAY, JULY 31, 2012

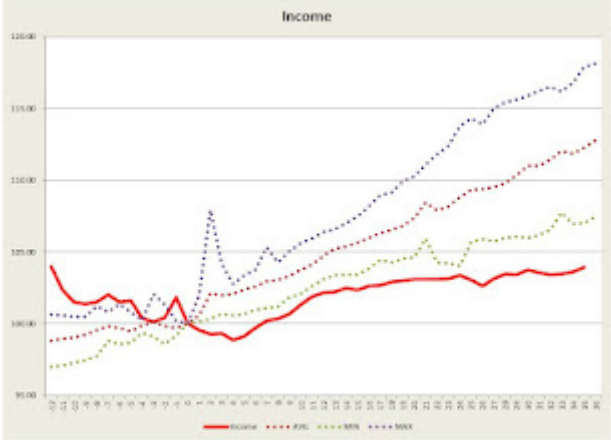
RECESSION STATISTICS Q2 2012

We have examined and comment here on the St Louis Fed's Recession Statistics. We have been tracking them quarterly since the beginning of the collapse and frankly they are appearing to get worse. Given what we see and other data we have reported upon there is a strong possibility of a second recession this Fall.

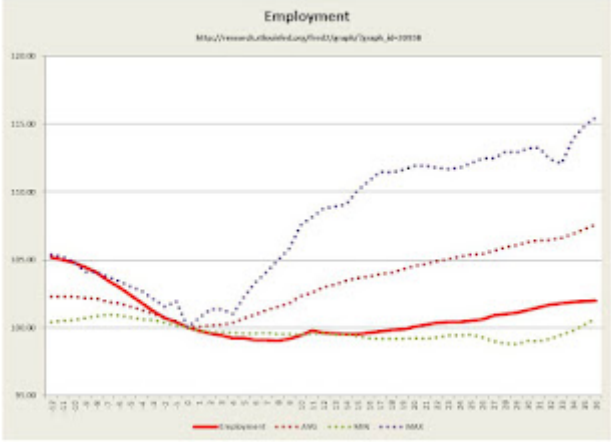
Let us examine the data.



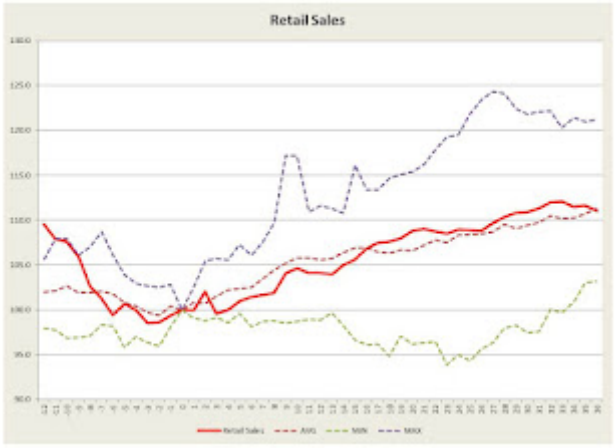
Industrial Production appears on average, weak but on par. This frankly is the best metric.



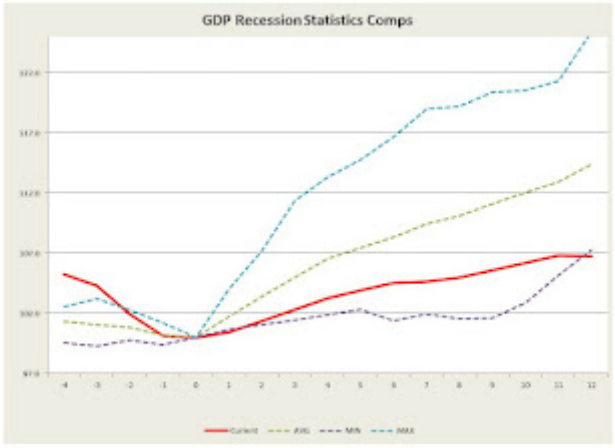
Income is below the lowest. Income is just not recovering and in fact it will be the driver for the next dip. Despite Production, if there are no customers then we will see that drop also.



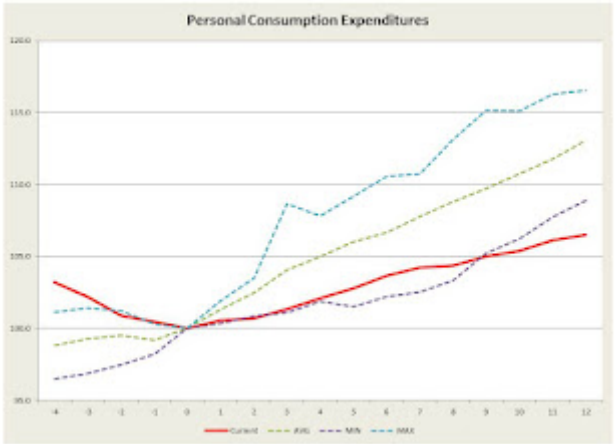
Employment is very weak. Not the worst yet but getting there. It shows no sign of any improvement and this will drag on well into 2014.



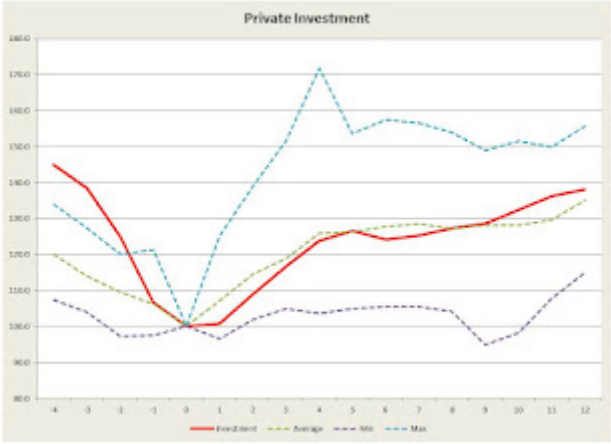
Retail Sales seems to be keeping up but I suspect that a good deal of that is credit increase as well as Government Supports; Unemployment, FICA elimination and Food Stamps. These Government Programs are non job creating and just add drag to the economy.



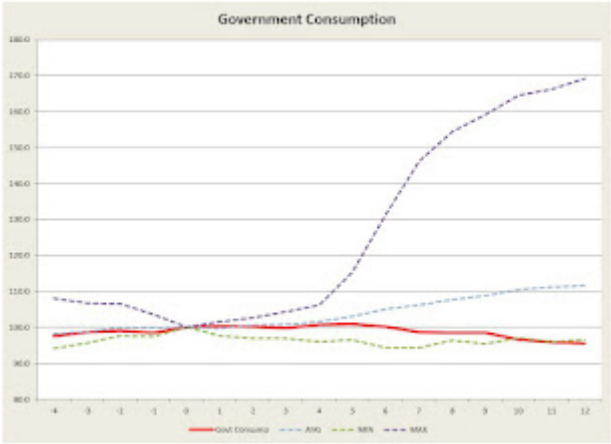
The GDP stats show we are now below the lowest. This is truly a concern. The weak growth rate will not see any improvement under the current administration.



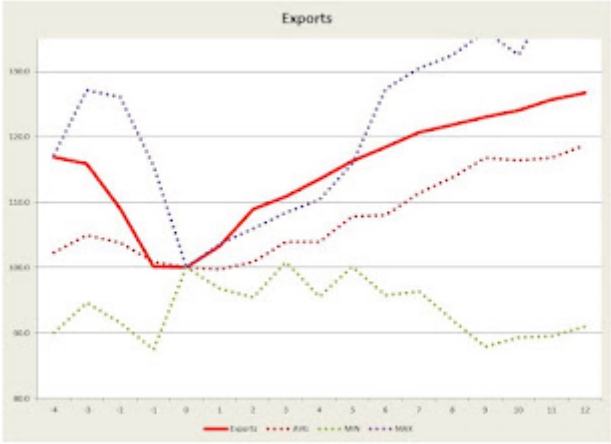
Personal Consumption, an element of the GDP, is well below the lowest. People are just not buying, not enough income and employment.



However Private Investment is above average. Money is around but the investments do not result in employment, just improvements in productivity.



Government Consumption is the lowest yet, and much of this is State and Local.



Exports are high relative...

Imports are average.

The above presents a dire forecast for 2013-2014, especially if we remain on course.
Labels: Economy, Recession Statistics

MONDAY, JULY 30, 2012

MELANOMA, SUN DAMAGE AND PATHWAYS

There is extensive epidemiological data indicating that melanoma is caused by UV radiation. Now there has been, up to this date, little information relating specific effects of UV radiation to specific causative gene changes. In a recent article in Cell by Hodis etal, the authors relate the impact of sun damage on melanocytes and the initiation of melanoma[1].This is an interesting paper and the approach is quite innovative and worth examining.

The authors summarize their work as follows:

Despite recent insights into melanoma genetics, systematic surveys for driver mutations are challenged by an abundance of passenger mutations caused by carcinogenic UV light exposure.

We developed a permutation-based framework to address this challenge, employing mutation data from intronic sequences to control for passenger mutational load on a per gene basis.

Analysis of large-scale melanoma exome data by this approach discovered six novel melanoma genes (PPP6C, RAC1, SNX31, TACC1, STK19, and ARID2), three of which—RAC1, PPP6C, and STK19—harbored recurrent and potentially targetable mutations.

[1] http://www.cell.com/retrieve/pii/S0092867412007787

Integration with chromosomal copy number data contextualized the landscape of driver mutations, providing oncogenic insights in BRAF- and NRAS-driven melanoma as well as those without known NRAS/BRAF mutations.

The landscape also clarified a mutational basis for RB and p53 pathway deregulation in this malignancy. Finally, the spectrum of driver mutations provided unequivocal genomic evidence for a direct mutagenic role of UV light in melanoma pathogenesis.

In a release from MD Anderson Cancer Center they state[2]:

By creating a method to spot the drivers in a sea of passengers, scientists at the Broad Institute of MIT and Harvard, the Dana-Farber Cancer Institute and The University of Texas MD Anderson Cancer Center have identified six genes with driving mutations in melanoma, three of which have recurrent 'hotspot' mutations as a result of damage inflicted by UV light. Their findings are reported in the July 20 issue of the journal Cell.

"Those three mutations are the first 'smoking gun' genomic evidence directly linking damage from UV light to melanoma," said co-senior author Lynda Chin, M.D., Professor and Chair of MD Anderson's Department of Genomic Medicine. "Until now, that link has been based on epidemiological evidence and experimental data."

"This study also is exciting because many of the recent large-scale genomic studies have not discovered new cancer genes with recurrent hot-spot mutations, a pattern strongly indicative of biological importance," said Chin, who also is scientific director of MD Anderson's Institute for Applied Cancer Science.

The six new melanoma genes identified by the team are all significantly mutated and provide potential targets for new treatments.

Let us first detail several of these genes.

1. RAC1

From NCI we have RAC1 located at 7p22 and described as follows[3]:

The protein encoded by this gene is a GTPase which belongs to the RAS superfamily of small GTP-binding proteins. Members of this superfamily appear to regulate a diverse array of cellular events, including the control of cell growth, cytoskeletal reorganization, and the activation of protein kinases.

[2] http://www.mdanderson.org/newsroom/news-releases/2012/scientists-discover-melanoma-driving-genetic-changes-caused-by-sun-damage.html

[3] http://www.ncbi.nlm.nih.gov/gene/5879

From the NCI Pathway database we have a complex set of pathway interactions[4]. In a similar manner we can examine the pathways from the MMMP data base[5]. In all cases of this gene and the others recenbctly elucidated, the pathways are partially informative and need additional investigation.

2. PPP6C

From NCI we have PPP6C located at 9q33.3 and described as follows[6]:

This gene encodes the catalytic subunit of protein phosphatase, a component of a signaling pathway regulating cell cycle progression. Splice variants encoding different protein isoforms exist.

3. STK19

From the NCI database this gene is located at 6q21.3 and functions as follows[7]:

This gene encodes a serine/threonine kinase which localizes predominantly to the nucleus. Its specific function is unknown; it is possible that phosphorylation of this protein is involved in transcriptional regulation. This gene localizes to the major histocompatibility complex (MHC) class III region on chromosome 6 and expresses two transcript variants

Thus the genes perform a broad and generally non-correlative set of functions. The authors have argued that the genes are targetable as say with BRAF but a more complete understanding of full pathway interactions would be essential.

Counting UV Hits

The authors discuss the fact that m UV mutations convert C (cytidine) to T (thymidine). Now as Watson et al have shown pp 204-209[8]) when cytidine is methylated as shown below the uridine product is converted to thymidine and this there is a mis-reading of the DNA. These C to T transitions are caused in the case of melanoma often by UV. We have also argued that they may

[4] http://pid.nci.nih.gov/search/pathway_landing.shtml?what=graphic&jpg=on&pathway_id=200116&source=NATURE&output-format=graphic&ppage=1&genes_a=5879

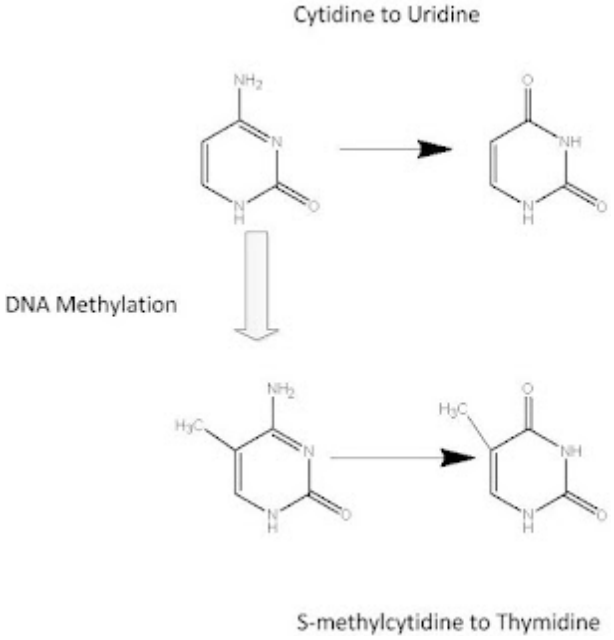
[5] http://www.mmmp.org/MMMP/public/biomap/viewBioMapImage.mmmp;jsessionid=171DFBACAC1D7843EFD1DBACB4F49593

[6] http://www.ncbi.nlm.nih.gov/gene/5537

[7] http://www.ncbi.nlm.nih.gov/gene/8859

[8] Watson, J., et al, Recombinant DNA (Fourth Ed) Freeman (New York) 2007.

equally be caused by backscatter X-rays which have enough energy to break bonds to cause a methylation as well.



Now the principle the authors employed was a presumptive one based upon the following:

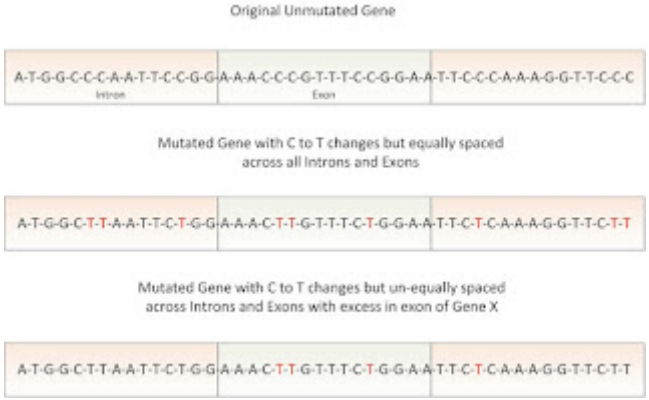
1. C to T transition is random across the DNA sequences.

2. The average number of such transitions should be the same in both Introns and Exons.

3. Exons express genes which do things.

4. If there are a statically larger number of C to T transitions in a specific Exon, i.e. a gene say Gene X, then that gene most likely is causative of the melanoma.

We demonstrate this concept in the diagram below:



Now it was through a process of this type which allowed the authors to identify a collection of twelve genes, six known to be related to melanome, and six not previously known to be related, to be presumptively causitive of the malignancy.

From an article in Science Daily they state, using a somewhat less than precise metaphor, the following[9]:

By creating a method to spot the drivers in a sea of passengers, scientists at the Broad Institute of MIT and Harvard, the Dana-Farber Cancer Institute and The University of Texas MD Anderson Cancer Center have identified six genes with driving mutations in melanoma, three of which have recurrent 'hotspot' mutations as a result of damage inflicted by UV light. Their findings are reported in the July 20 issue of the journal Cell.

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The six new melanoma genes identified by the team are all significantly mutated and provide potential targets for new treatments.

Puzzle has thousands of potential pieces, but only requires a few dozen. A number of important mutations had previously been identified as melanoma drivers. These include BRAF (V600) mutations, present in half of all melanomas, and NRAS (Q61) mutations. However, the vast majority of these mutations do not appear to be caused by direct damage from UV light exposure.

UV light causes many mutations of genes in melanocytes. The mutations occur in both introns and exons. The question is which of these mutations is significant and for example is there a level at which they become malignant. An interesting question can be asked about melanoma in situ, the early stage of melanoma where the melanocytes have enlarged nucleoli and express a loss of localization. It is well known histologically that MIS is often discovered in sun damaged areas. Thus one would suspect that at this early stage many of this methylation like changes doe to UV radiation is present.

The article continues:

[9] http://www.sciencedaily.com/releases/2012/07/120719132610.htm

To counter this effect, the researchers turned to parts of the genome that don't code for proteins, called introns, and other inactive DNA segments that flank exons. By comparing the frequency of mutations in the inactive segments to the frequency of mutations in the exons, the researchers built a framework for assessing the statistical significance of functional mutations.

Approach identifies six known cancer genes, six new ones.

The analysis identified functional mutations in the well-known cancer genes BRAF, NRAS, PTEN, TP53, CDKN2A and MAP2K1.

It also uncovered five new genes, RAC1, PPP6C, STK19, SNX31, and TACC1.

Most are associated with molecular pathways involved in cancer but had not been previously recognized as significantly mutated in melanoma. Their presence in the tumor samples ranged from 3 percent to 9 percent.

The sixth new gene tied to melanoma was ARID2, an apparent tumor-suppressor gene possessing a significant number of loss-of-function mutations found in 7% of patient samples.

"Six new melanoma genes have been picked out from thousands of mutated genes," said Eran Hodis, co-lead author who is a computational biologist in the Garraway lab at the Broad Institute and an M.D.-Ph.D. student at Harvard and MIT. "The same approach may bring clarity to genome sequencing studies of other cancers plagued by high passenger mutation rates, for example lung cancer." ...

Most exciting, three of the discovered genes possessed 'hotspot' mutations found in the exact same position in multiple patients providing another line of evidence indicating these mutations contribute to melanoma.

"We have now discovered the third most common hotspot mutation found in melanoma is present in a gene called RAC1, and unlike BRAF and NRAS mutations, this activating mutation is attributable solely to characteristic damage inflicted by sunlight exposure" said Ian R. Watson, Ph.D.,...

Observations

This is a significant contribution in my opinion. It also, in my opinion, raises some very interesting questions.

1. How many hits are required to make the change?

2. What are the pathway effects that result in malignancy?

3. How does MIS fit within this model?

4. If UV radiation can do this then we would expect that X rays would have equal effects and if so then backscatter X rays which penetrate just enough would be of significance. If that is correct how much radiation would be required?

5. If we have these putative genes and there are targets, then how easy would it be to develop anti-cancer drugs for these targets?

6. If we see BRAF failure and return of the malignancy then is it possibly from these new genes, if so which ones, and if some of them in what order of importance?

7. When performing biopsies on melanomas, should examination for these genes be a common practice?

This paper raises many more such questions.

References

Hodis, E., et al, A Landscape of Driver Mutations in Melanoma, Cell**,** Volume 150, Issue 2, 251-263, 20 July 2012.

Labels: Cancer

SUNDAY, JULY 29, 2012

MDM4 AND MELANOMA: MORE PATHWAYS

Recent efforts in managing melanoma have focused upon BRAF and a mutation of a V600 BRAF form. By targeting this mutation and the pathway related thereto one can find ways to block the mutated pathway and this in principle block the continuing metastasis. This works for a while and then the cells find ways around this. There are undoubtedly many other changes in cellular pathways that result in uncontrolled proliferation and failure of apoptosis. Namely the cells continue to grow and fail to die off.

Focus on other pathway defects is continuing and there has been recent focus on MDM4, which is a control element of p53, the product of TP53 which is a key control element of proliferation and apoptosis. In a recent paper by Gembarska et al the authors state the following[69][1]:

The inactivation of the p53 tumor suppressor pathway, which often occurs through mutations in TP53 (encoding tumor protein 53) is a common step in human cancer. However, in melanoma—a highly chemotherapy-resistant disease—TP53 mutations are rare, raising the possibility that this cancer uses alternative ways to overcome p53-mediated tumor suppression. Here we show

[69][1] http://www.nature.com/nm/journal/vaop/ncurrent/pdf/nm.2863.pdf

that Mdm4 p53 binding protein homolog (MDM4), a negative regulator of p53, is upregulated in a substantial proportion (~65%) of stage I–IV human melanomas and that melanocyte-specific Mdm4 overexpression enhanced tumorigenesis in a mouse model of melanoma induced by the oncogene Nras.

MDM4 promotes the survival of human metastatic melanoma by antagonizing p53 proapoptotic function. Notably, inhibition of the MDM4-p53 interaction restored p53 function in melanoma cells, resulting in increased sensitivity to cytotoxic chemotherapy and to inhibitors of the BRAF (V600E) oncogene. Our results identify MDM4 as a key determinant of impaired p53 function in human melanoma and designate MDM4 as a promising target for antimelanoma combination therapy.

Now MDM4, also called Mdm4 p53 binding protein homolog, is located at 1q32. It acts in a somewhat complex manner to control p53 functions. From NCI we have the following description of the gene and its product[70][2]:

This gene encodes a nuclear protein that contains a p53 binding domain at the N-terminus and a RING finger domain at the C-terminus, and shows structural similarity to p53-binding protein MDM2. Both proteins bind the p53 tumor suppressor protein and inhibit its activity, and have been shown to be overexpressed in a variety of human cancers. However, unlike MDM2 which degrades p53, this protein inhibits p53 by binding its transcriptional activation domain. This protein also interacts with MDM2 protein via the RING finger domain, and inhibits the latter's degradation. So this protein can reverse MDM2-targeted degradation of p53, while maintaining suppression of p53 transactivation and apoptotic functions.

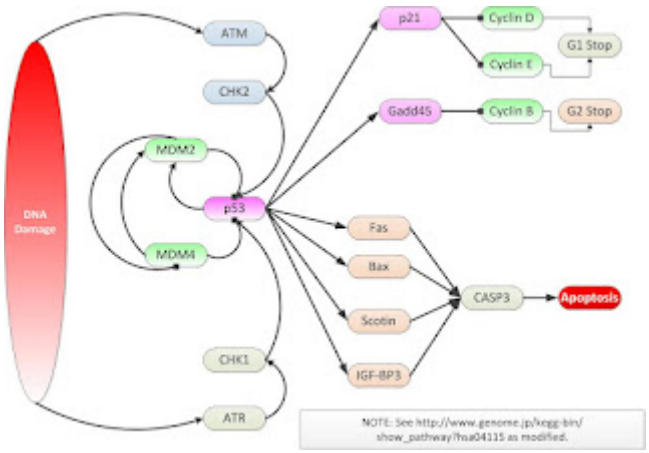
The sources for information on p53 pathway and its relation to MDM4 are extensive[71][3]. Specific details of the p53 pathway are shown in the NCI data[72][4] bases for pathways. However, we shall present a simplified description based upon KEEG pathway data. This we do below (We combine from the KEGG genome database[73][5]).

[70][2] http://www.ncbi.nlm.nih.gov/gene/4194

[71][3] http://www.mmmp.org/MMMP/public/biomap/searchBiomap.mmmp

[72][4] http://pid.nci.nih.gov/search/pathway_landing.shtml?pathway_id=200207&source=NATURE&genes_a=4194&genes_b=&what=graphic&jpg=on&ppage=1

[73][5] http://www.genome.jp/kegg-bin/show_pathway?hsa04115



Note in the above we have a complex control path between MDM2 and MDM4 with p53. The p53 is activated when DNA damage is perceived or from other factors. p53 then activates a collection of pathways which in turn block the cell cycle or initiate apoptosis. If p53 does not function then we have an uncontrolled cell. The control of p53 can be blocked by MDM4 blockage as shown above. That is the principle which the authors have presented.

Prior work by Macchiarulo et al stated the following regarding this combination[74][6]:

Alterations of p53 signalling pathway is the most frequent event in human cancers. About 50% of these, albeit showing wild-type p53, have flaws in the control mechanisms of p53 levels and activity. MDM2 and MDMX (MDM4) are the main negative regulators of p53.

The relevance of MDM2 on the regulation of p53 levels and activity has fostered the development of strategies aimed at restoring p53 functions by blocking the physical interaction between MDM2 and p53. As a consequence, a number of different small molecules and peptidomimetics have been disclosed in the last decade as inhibitors of MDM2/p53 interaction.

Recent studies, however, have thrust MDMX into the limelight as an additional chemotherapeutic target, suggesting the presence of a more complex relationship between MDM2, MDMX and p53. In this review article, we report key aspects of MDMX-mediated regulation of p53, recent advances in the structural characterization of the protein, and the progress made so far in the medicinal chemistry of MDMX ligands.

Note that MDMX is now called MDM4, to avoid confusion. The Macchiarulo paper was published a year ago (2011) and it presented the connection of MDM4 and loss of p53 control in a broader context of cancer development and spread. The Gembarska paper on the other hand has focused on melanoma. Earlier work was performed in a Doctoral Thesis in 2007 in Rotterdam, by Meulmeester who states[75][7]:

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[74][6] http://pubs.rsc.org/en/content/articlelanding/2011/md/c0md00238k/unauth

[75][7] https://openaccess.leidenuniv.nl/bitstream/handle/1887/4280/Proefschrift.pdf?sequence=1

The p53 tumor suppressor gene encodes a sequence-specific transcription factor whose activity is either disabled or attenuated in the vast majority of human cancers. Its inactivation occurs in about 50% of human tumors through mutations affecting the p53 locus directly.

p53 transcriptionally activates a vast, constantly growing number of target genes, resulting in various biological outcomes such as cell-cycle arrest and apoptosis. Several types of stress, such as oncogene activation, hypoxia and DNA damage, result in an increase in p53 levels and the subsequent activation of p53 target genes (Vogelstein et al., 2000). One of the best-characterized target genes of p53 is the mdm2 gene, which contains two promoters.

The first promoter (P1) drives mdm2 expression constitutively (Jones et al., 1996), while p53 binds two adjacent p53-responsive elements within the second promoter (P2), thereby promoting transcription of the mdm2 gene. Under normal circumstances, p53 is tightly regulated through the interaction with its negative regulator Mdm2, which counteracts p53 function in a number of ways.

The autoregulatory negative feedback loop, whereby p53 induces Mdm2 expression resulting in the repression of p53 function, most probably serves as an important mechanism to restrain p53 activity in normal cells. Therefore, uncontrolled, high expression of Mdm2 may result in improper inactivation of p53 function. It has been shown that in 5-10% of all human tumors Mdm2 is overexpressed, due to gene amplification, transcriptional- or posttranscriptional mechanisms. In most of these cases the p53 gene is wild type, presumably because Mdm2 overexpression alleviates the selective pressure for direct mutational inactivation of the p53 gene.

As regards to the pathway discussion we presented above Meulmeester remarks:

The complex web of ATM-mediated activation of the p53 pathway. ATM mediates direct and indirect phosphorylation of p53, while 14-3-3 binding to p53 is augmented by ATM-mediated de-phosphorylation of p53. Phosphorylation of Strap by ATM results in the recruitment of Strap/p300 complexes towards p53 that elevates its acetylation.

A safeguard mechanism exists to ensure proper p53 activation by inhibiting its inhibitors Mdm2 and Mdmx. Phosphorylation of Mdmx/Mdm2 attenuates their interaction with the ubiquitin protease HAUSP, resulting in the instability of Mdmx and Mdm2. Thus ATM activates p53 via a sophisticated mechanism, while it ensures proper activation by inhibition of its negative regulators .

Again note that MDMX is now MDM4. He does raise the issue of a complex feedback loop which may have some internal instabilities. Namely the loop between MDM2, MDM4, and p53 may have unstable points under certain conditions. Some have approached this via rate reaction equations but as we have discussed elsewhere the rate reaction equations require large concentrations. In a cell we have a few protein molecules with limited binding sites. This

specific low density case has particular concerns of instabilities. Thus there may not just be a mutation of MDM4 but also some instabilities in the internal dynamics.

In a paper by Mancini et al (2009), the authors state[76][8]:

MDM4 is a key regulator of p53, whose biological activities depend on both transcriptional activity and transcription independent mitochondrial functions. MDM4 binds to p53 and blocks its transcriptional activity; however, the main cytoplasmic localization of MDM4 might also imply a regulation of p53-mitochondrial function.

Here, we show that MDM4 stably localizes at the mitochondria, in which it (i) binds BCL2, (ii) facilitates mitochondrial localization of p53 phosphorylated at Ser46 (p53Ser46P) and (iii) promotes binding between p53Ser46P and BCL2, release of cytochrome C and apoptosis. In agreement with these observations, MDM4 reduction by RNA interference increases resistance to DNA-damage-induced apoptosis in a p53-dependent manner and independently of transcription.

Consistent with these findings, a significant downregulation of MDM4 expression associates with cisplatin resistance in human ovarian cancers, and MDM4 modulation affects cisplatin sensitivity of ovarian cancer cells. These data define a new localization and function of MDM4 that, by acting as a docking site for p53Ser46P to BCL2, facilitates the p53-mediated intrinsic-apoptotic pathway. Overall, our results point to MDM4 as a double-faced regulator of p53.

Thus they make the connection of control of MDM4 products as key to the ultimate functionality of p53. They also have examined the effects of cisplatin in the case of ovarian cancers. They did not examine ways to block MDM4 and its protein. The principle here is that the pathway control element such as p53 can be dysregulated by another gene MDM4. The question of course is what has happened to MDM4. We address that later.

In a discussion of the paper by Gembarska et al, Azvolinsky then states[77][9]:

While the TP53 gene, which encodes the tumor protein 53, is found mutated in the vast majority of tumors, TP53 is intact in more than 95% of melanomas. The p53 tumor suppressor pathway is important for most cancers, preventing neoplastic growth, and inactivation of the pathway is a common driver mutation for cancer.

Exploring alternative mechanisms of dysregulation of the p53 tumor suppressor pathway, Jean-Christophe Marine, the Center for Human Genetics in Leuven, Belgium, and colleagues show that the pathway is indeed altered in as many as 65% of human melanomas. Rather than a mutation in TP53, the researchers find that melanomas have upregulated Mdm4 p53 binding

[76][8] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711189/pdf/emboj2009154a.pdf

[77][9] http://www.cancernetwork.com/print/article/10165/2092149

protein homolog (MDM4), a negative regulator of p53. According to the authors, the results identify "MDM4 as a key determinant of impaired p53 function in human melanoma."

They continue:

"Melanomas do not harbor MDM4 mutations per se," explained Jean-Christophe Marine. "They select for mechanisms that cause MDM4 protein levels to go up." Marine and colleagues are currently investigating the mechanisms of MDM4 upregulation.

Approximately 50% of melanoma cases harbor a mutation in the BRAF gene, part of the mitogen-activating protein kinase (MAPK) pathway that results in constitutive activation of the MAPK pathway. A specific inhibitor of BRAF, vemurafenib, was approved last year for metastatic melanoma patients with the BRAF mutation and two other targeted inhibitors of the MAPK pathway, dabrafenib and trametinib, have recently completed phase III trials. While treatment with a BRAF inhibitor results in rapid tumor shrinkage and symptom relief, resistance is still a major issue and new agents and combinations are needed for sustaining prolonged responses.

"The whole field is looking for drugs that can prevent relapse," said Marine. "Awakening the p53 pathway in melanoma, by targeting MDM4, could be one way to achieve this—a possibility that has so far been completely overlooked." The p53 pathway has been majorly overlooked in melanoma because the mechanism by which p53 is inactivated in this tumor were unknown until this study.

The issue is both what happened to MDM4 and is MDM4 just another patch for some melanomas. Let us discuss this issue at some length.

Observations

p53 is a powerful gene which regulates the cell from the cell cycle point of view through apoptosis. It is an essential gene and has been found as a mutated version in many cancers. However in melanoma it appears that loss of p53 expression resulting from a mutation is not observed frequently. Thus, although p53 does not appear to do what it should do, p53 looks just fine when examined by its lonesome. Thus the authors had identified the controller of p53, namely MDM4 as a changed element and as a cause of the potential loss of cell cycle control and of apoptosis.

1. What causes the mutation of MDM4? What is it mutated to?

2. What melanoma cells contain the mutated or dysfunctional MDM4 gene?

3. Could this be a more complex issue when one looks at the complex set of pathways?

4. Are we trying to target aberrant MDM4 products and thus eliminate blockage on p53 functions. What of the instabilities in the control loop we have already discussed. Will this

function in low density environments. Also what are we targeting, sites on MDM4 products for blockage.

5. The stem cell issue always raises its head. Frankly this may very well be a stem cell only problem as compared to a BRAF issue. If the stem cell has unstable MDM4 characteristics than we would anticipate longer term survival, perhaps.

Labels: Cancer

ALGEBRA AND THE INTELLECT

$$ax^2 + 2bx + c = 0$$

The NY Times[1] in its inimitable fashion has a cover article in its weekly section, the lead so to speak, bemoaning the necessity to learn Algebra, at all, and perforce I suspect Geometry, and subsequently any other form of math higher than perhaps pushing keys on an iPhone.

The article states:

A TYPICAL American school day finds some six million high school students and two million college freshmen struggling with algebra. In both high school and college, all too many students are expected to fail. Why do we subject American students to this ordeal? I've found myself moving toward the strong view that we shouldn't.

Now, a word of history. When I first took algebra in the 9th grade, some 60 years ago or more, I frankly did not do that well. I had no idea what my tutor was saying and frankly I suspect neither did he. Geometry fared slightly better. But between reading Men of Mathematics at the end of my sophomore year and intermediate algebra I saw all the pieces come together, thus managing

[1] http://www.nytimes.com/2012/07/29/opinion/sunday/is-algebra-necessary.html?hp

to complete that and trig in some six weeks, then onto advanced algebra, calculus, probability and even solid geometry. I may have actually been the last student to take the solid geometry Regents exam in New York State.

Now that some sixty plus years later my two grandsons take algebra in the eighth grade. Now that is a year earlier, and the one in New York already has his Regents prep book.

“Struggling”, well yes if your instructor does not have a clue and you are being taught by rote. But “subject” is a rather strong word. In fact it is reflective of the arrogance of the ignorant. If you cannot do it then it must be undoable. I cannot learn Czech, no problem with Russian, and I lived in Prague, it was just that no matter how I tried it never stuck. Same for Portuguese, but no problem with Spanish. That is my problem not a reason to doing away with two countries.

The author continues:

This debate matters. Making mathematics mandatory prevents us from discovering and developing young talent. In the interest of maintaining rigor, we’re actually depleting our pool of brainpower. I say this as a writer and social scientist whose work relies heavily on the use of numbers. My aim is not to spare students from a difficult subject, but to call attention to the real problems we are causing by misdirecting precious resources.

To be educated means that one has a minimal set of skills. Making change, understanding data, taking measurements, predicting the future. So take global warming. This can be examined by a simple look at data. I have data for certain daylily species going back 30 years. The date of the first bloom is measured and then I plot that data on a graph. Now I seek to get a simple linear regression on the days from the first of the year that the first bloom occurs. I use a linear regression and plot the data. The result, warming! Voila. But that simple step assumes a de minimus level of understanding of algebra. Not much, really! But some, and if we want informed decisions rather than just religious followings then we need an educated electorate, at least some of them.

Or take ratios, for example, the cost per unit, the price per unit, etc. We then look at multiples of these ratios to get other ratios. People use these all the time. They rely on algebra.

But on the other hand many people are just dumb. Why waste any time and money at all. So we can avoid wasting resources by just not educating them at all. Then we can have a dual class society, the dumb ones without jobs, and the educated ones supporting everybody!

The write continues:

California’s two university systems, for instance, consider applications only from students who have taken three years of mathematics and in that way exclude many applicants who might excel in fields like art or history. Community college students face an equally prohibitive mathematics wall. A study of two-year schools found that fewer than a quarter of their entrants passed the algebra classes they were required to take.

It is a University, you are hopefully expected to be educated, and that means mathematics. If an eighth grader can learn this in New York and West Virginia, what is wrong with students elsewhere. Consider the draftee in WW II. The Navy had a problem, it needed students who understood math quite well. Torpedoes, 6” guns, radar, radio, fire control systems, and the like demanded algebra and geometry and trigonometry. Many draftees had it and thus it opened their career path after the War. Those who did not were just seamen, doomed to stay below petty officer rated sailors. The officers, including those with history degrees had to have even more.

As for high Math SAT scores, there is the old MIT tale, somewhat true, when the Freshman Calculus instructor states:, “Well you all got 800 in your SATs, but you still have to earn you’re A here.”. The response to this was to look around at the 100 or so students and think that all 800s were here. Then the Instructor noted, “Oh, the other 100 are at Cal Tech.”

Even jobs such as an electrician or carpenter require a modicum of algebra and geometry. The thought process is essential. Trade schools teach algebra, geometry, otherwise getting licensed to practice one's trade would be impossible. Ohms law and Pythagoras' triangle would be a sine qua non. Understanding nature is predicated on measuring and predicting, in reality. Is algebra too hard, possibly with the wrong teacher, I had one. But with the right teachers it provides insight. Perhaps the problem is our educational system.

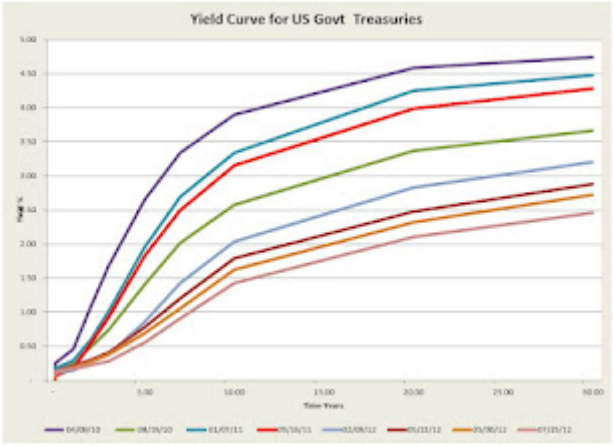
The again the world uses spreadsheets, all the time, from budgets to understanding any business structure. What is a spread sheet, a set of algebraic instructions, unless of course you use it just for entering numbers. But to learn one needs understanding of relationships. That is algebra. Word problems must become visceral, one must "feel" the system, understand the implications. If one thing gets larger does the other thing get larger or smaller, and how quickly. Judgement results.

In today’s world we would have to add all the IITs in India, and Tsing Hua in Beijing for starters. And by the way, how many historians do we really need?

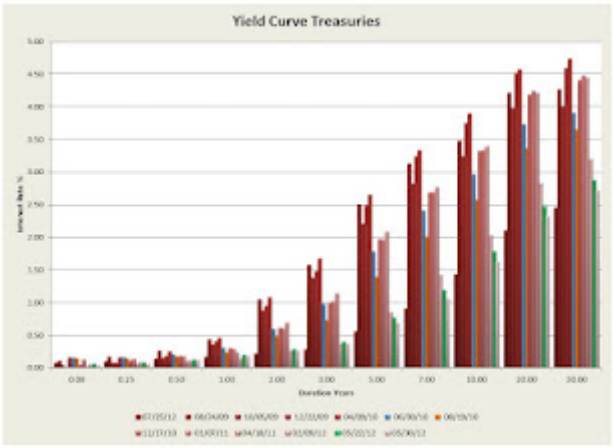
Labels: Education

WEDNESDAY, JULY 25, 2012

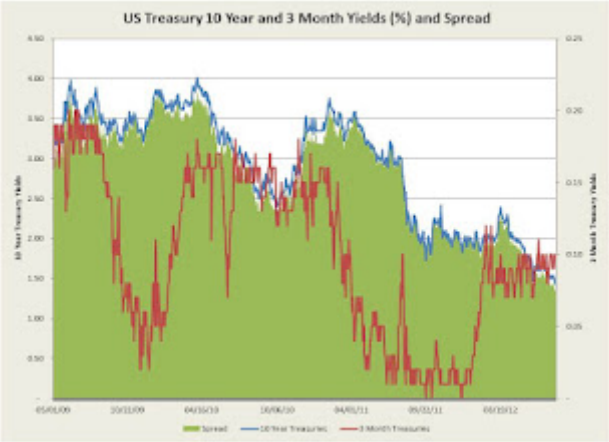
YIELD CURVE JULY 2012



First just look at the drop in the rates in the above. This is unheard of in Treasuries. Perhaps it states that we have entered the negative interest domain. Now look at the following:



This is another view, although the short term rates are de minimus, the long tern rates are collapsing. The question is how much of this is the FED propping up the Treasury. No for a final look.



Three month rates have recovered from zero but 10 year rates are collapsing below any prior level. The spread has dropped to all time lows. Yet there is no investment other than in the Government sucking up all the printed money. This will be a very deep hole if we can ever climb out of it. Frankly I do not see why the "economists" are missing this one.

Labels: Economy

MONDAY, JULY 23, 2012

CBO AND THE ACA TO WATCH

The CBO announced an upcoming release worth watching for:

CBO expects to release two reports related to the Affordable Care Act (ACA) tomorrow, July 24th, around 2 pm. One report will present updated projections of the budgetary effects of the coverage provisions of the ACA to reflect the Supreme Court's recent decision. The other report will present a cost estimate for the repeal of the ACA that passed the House of Representatives on July 11th. Both reports will be posted on CBO's website.
Labels: Health Care

SUNDAY, JULY 22, 2012

RADICAL PROSTATECTOMY AND SURVIVAL

Will et al have published a paper in NEJM which concludes that radical prostatectomy in patients with prostate cancer does little to increase survivability. One could be concerned that this paper may be used beyond what in my opinion it should be. I shall describe the details and then present my opinions as to why there may be concern.

Will et al conclude[1]:

[1] Will, T., et al, Radical Prostatectomy versus Observation for Localized Prostate Cancer, NEJM. July 19, 2012.

Patients had to be medically fit for radical prostatectomy and to have histologically confirmed, clinically localized prostate cancer (stage T1-T2NxM0 in the tumor–node–metastasis classification system according to the American Joint Committee on Cancer) of any grade diagnosed within the previous 12 months. Patients also had to have a PSA value of less than 50 ng per milliliter, an age of 75 years or less, negative results on a bone scan for metastatic disease, and a life expectancy of at least 10 years from the time of randomization. The study sites assessed eligibility on the basis of locally obtained PSA values and biopsy readings. After randomization, a central pathologist reviewed the biopsy and radical-prostatectomy specimens, and a central laboratory measured PSA.[2]…. Among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up. Absolute differences were less than 3 percentage points.

Let us first give some substance to the data and terms. This conclusion may have significant impact on many men who may very well be denied care under the ACA CCE rules if this paper stands and is interpreted without comment. Our objective is to analyze the paper to some extant but more importantly to raise an opinion which may re-interpret the results.

Let us first then define in some detail the AJCC terms[3]

- **T1**: tumor present, but not detectable clinically or with imaging
    - **T1a**: tumor was incidentally found in less than 5% of prostate tissue resected (for other reasons)
    - **T1b**: tumor was incidentally found in greater than 5% of prostate tissue resected
    - **T1c**: tumor was found in a needle biopsy performed due to an elevated serum PSA
- **T2**: the tumor can be felt (palpated) on examination, but has not spread outside the prostate
    - **T2a**: the tumor is in half or less than half of one of the prostate gland's two lobes
    - **T2b**: the tumor is in more than half of one lobe, but not both
    - **T2c**: the tumor is in both lobes

Will et al go on to describe their patients as follows:

…13,022 men with prostate cancer,

5023 were eligible for enrollment. A total of

731 men (14.6%) agreed to participate and underwent randomization to

radical prostatectomy (364 men) or

[2] Will, T., et al, Radical Prostatectomy versus Observation for Localized Prostate Cancer, NEJM. July 19, 2012.
[3] AJCC 6th Edition, 2002. Note D'Amico used the 5th Edition and thus we should be aware of a possible change. There was none.

observation (367).

The mean age was 67 years. Nearly one third of the patients were black; 85% reported full independence in activities of daily living.

The median PSA value was 7.8 ng per milliliter (mean, 10.1).

About 50% of the men had stage T1c disease (not palpable, detected by means of PSA testing), and about

25% had histologic scores of 7 or higher on the Gleason scale;

40% of the men had low-risk,

34% intermediate-risk, and

21% high-risk prostate cancer (about 5% had missing data).

On the basis of central pathological review, 48% of the patients had histologic scores of 7 or higher on the Gleason scale, and 66% had tumors in the intermediate-risk or high-risk categories.

D'Amico tumor risk score is used to differentiate in the above segmentation (low, intermediate, or high), which was based on tumor stage, the histologic score assigned by the local study site, and the PSA level[4]. As D'Amico states:

In order to have the multivariable analysis results of the Cox proportional hazards regression model be applicable in the clinical setting for an individual patient, risk groups were defined. These risk groups were established from a review of the literature and were based on the known prognostic factors:

1. *PSA level,*
2. *biopsy Gleason score, and*
3. *1992 AJCC T stage.*

Patients with AJCC clinical T stage T1c, T2a and PSA level of 10 ng/mL or less and biopsy Gleason score of 6 or less have been identified to be at low risk (<25% at 5 years) for posttherapy PSA failure.

[4] D'Amico et al, JAMA Network | JAMA: The Journal of the American Medical Association | Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer, 1998.

Conversely, patients with AJCC stage T2c disease or a PSA level of more than 20 ng/mL or a biopsy Gleason score of 8 or more have a risk higher than 50% at 5 years of posttherapy PSA failure.

The remaining patients with PSA levels higher than 10 and 20 ng/mL or lower, a biopsy Gleason score of 7, or AJCC clinical stage T2b have been found to have an intermediate risk (25%-50% at 5 years of posttherapy PSA failure).

Patients with AJCC clinical stage T1a, T1b were not managed using implant therapy because of the significant rate or urinary incontinence noted[17] using this approach in patients with a history of a transurethral resection of the prostate. Therefore, patients with AJCC clinical stage T1a, T1b disease managed with RP or RT were excluded from the study to ensure statistically valid comparisons.

We summarize these categories below:

Factor/Category	*Stage*	*PSA*	*Gleason*
Low	T1c or T2a	PSA Less Than 10	6
Intermediate	T2b	10-20<psa<20< p=""> </psa<20<>	7
High	T2c	PSA More Than 20	8 or greater

Furthermore from D'Amico et al we have the following:

Specifically, patients with biopsy Gleason score of 2 through 6 had no statistical difference in their estimates of PSA failure-free survival across all the treatment modalities evaluated in this study.

First, the comparison of PSA outcome for expectant management vs treatment is lacking. This comparison would be particularly relevant in the low-risk patients where 5-year PSA-progression rates numerically approximate the 10-year clinical-progression rates noted from expectant management series

Now returning to Till et al who concludes:

Among men with clinically localized prostate cancer that had been diagnosed after PSA testing came into practice, our study showed that radical prostatectomy did not reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up.

The effect of radical prostatectomy on mortality did not vary according to age, race, self-reported performance status, or coexisting conditions, but our findings suggest that it may vary according to PSA value and possibly tumor risk.

Positive results were from multiple subgroup comparisons; the tests of interaction typically approached but did not reach significance and may therefore be due to chance.

Among men with PSA levels of 10 ng per milliliter or less, all-cause mortality was slightly lower at 12 years in the observation group than in the radical-prostatectomy group; prostate-cancer mortality in the observation group was 6%, with a nonsignificant absolute reduction of less than 1.0 percentage point in the radical-prostatectomy group.

Among men with low-risk disease, observation was associated with a nonsignificant reduction in all-cause and prostate cancer mortality, with no significant between-group difference in bone metastases.

Among men with a PSA value that was greater than 10 ng per milliliter and possibly among those with intermediate-risk or high-risk prostate cancer (as determined according to the PSA value, local histologic findings, and stage), ***absolute reductions in all-cause mortality with radical prostatectomy ranged from 6.7 to 13.2 percentage points.***

Thus there appears to be a reduction in survival. But what does that say? In high risk there very well may already be a metastasis, especially with such a high Gleason score.

Observations

Let me now make several observations. These are opinions which are subject to some further analysis but they in my opinion present several clear concerns and limitations.

1. No PSA velocity measurements are performed: Namely what if we used PSA velocity as a predictor, not just PSA. Gleason scores are ex post facto. Gleason of 8+ is a significant mortality risk. Gleason of 6- is often rare. One does not record a Gleason 1 score for example and Gleason 3-4 is also infrequent.

2. No family histories were used: This is often the sine qua non determinant. If a 1st degree relative had an aggressive PCa then there is a high chance that the presenting patient will also have such. Also this test is free. Why it was not included is a concern.

3. No genetic analyses on tumors: The aggressiveness of the tumor is often demonstrated by the genes it expresses. Given the ease to do such tests and the limited numbers of patients it should have been incumbent on the study to have performed this analysis.

4. No attempt to ascertain PCa stem cell: As with the genetic study not being done, there also was not attempt to ascertain any stem cell activity.

5. There is no attempt to define an aggressive form of PCa. One can admit the existence of indolent and aggressive. However, identifying what constitutes aggressive is questionable at this time. We have many genetic markers but there is not a bright line test. One can agree that a small percent are aggressive, and a large percent is indolent but again no test exists to determine this. Let us assume 5% are aggressive and 95% indolent. Further the 95% indolent will have no change in survival due to the PCa. However the 5% may very well have such a change. Furthermore if to get positive results from a prostatectomy with aggressive forms we must say perform it when the PSA velocity hits the 0.7 level, more than likely the patients coming to be

seen are lost to the ravages of the disease, especially since they are performing tests on PSAs of 10. Thus the sample may be contaminated by results which fail to show any efficacy. That is 5% of all 3 groups will die and thus there will be de minimis efficacy. Just as we noted in the faulty prior studies, the wrong levels may very well have been chose, and thus the wrong question asked. The question should be; what PSA/PSA velocity tuples provide significant positive survival efficacy from prostatectomy.

6. What if one used PSA velocity and biopsied when it exceeded 0.7 per year. If that were the case then what percent would have an aggressive form.

Thus it is our belief that although this paper does provide some valuable results it fails in our opinion to understand and present many key factors essential for understanding and treating such a prevalent and deadly disease. Furthermore the alleged conclusions may actually create in my opinion a clear and present danger for those patients with family histories and genetically prone prostate cells. Namely under the new ACA regime, this may very well be used by the Government for refusal of service and result in substantial mortality and morbidity.

Now strangely NCI reports on FDA approval of a new test using percent free PSA but not PSA velocity.[5] They state:

A PSA test score between 4 and 10 ng/mL often prompts physicians to recommend a prostate biopsy. Most biopsies from men with PSA scores in that range, however, reveal no cancer or identify cancers that likely will never pose a health risk. And biopsies themselves have risks, including the risk of life-threatening infection.

The Access Hybritech p2PSA test measures a form of PSA called [-2]proPSA in the blood. Results from the test are combined with a PSA score and a measurement of free PSA to calculate the Prostate Health Index, or phi.

FDA approval was based on a clinical study of nearly 660 men, approximately half of whom had prostate cancer. In the study, the phi *score was better able to distinguish between benign conditions and prostate cancer than the PSA score. The study also found that the probability of having prostate cancer detected following a biopsy rose as the* phi *score increased.*

One does question the “life threatening” issues since in most cases of competent biopsies with proper preparation and execution the morbidity is low.

Ultimately, as with the other studies, perhaps the issue is the question which was asked. Perhaps the question should have been:

"What, if any, PSA measurement, Free PSA %, and PSA velocity, combined in some metric, will, with radical prostatectomy, increase survival?"

[5] http://www.cancer.gov/ncicancerbulletin/071012/page8

As with any research the key is always the question, not just the result. All too often failure to pose the proper question just reinforces poor judgement.

But in NEJM there is also an interesting and revealiong editorial piece by Thompson and Tangren which states:

On the other hand, high-grade, aggressive prostate cancers usually have a lethal course if left untreated. Those of us who treat this disease are heartened to see men we treated years or decades ago for aggressive, high-grade cancer who remain cancer-free today. It is these men who are at greatest risk for death from cancer and who are most likely to benefit from therapy but whom we must treat effectively. Effective treatments often require multiple therapeutic approaches; for example, mortality is reduced among men with high-risk tumors in whom radiation therapy and surgery are augmented by androgen deprivation.

Prostate cancer is not a monolithic cancer but a spectrum of disease. The screening, detection, and treatment we provide must focus on cancers that matter, and future clinical trials must do so as well.

These authors indicate other issues with this study. We believe that valuable that this study may be there are many dimensions that need be addressed. Indeed as Thompson and Tangren state:

Those of us who treat this disease are heartened to see men we treated years or decades ago for aggressive, high-grade cancer who remain cancer-free today.

Indeed, there are the many men with PSA of 10-15 with an indolent disease who will never die from the disease. There are also those men who one year have a PSA of 4 and then next 40, and are dead in three years. It would seem clear we are no dealing with the same disease and until we can determine via defects in pathways and the like what the difference is we are like creatures from Plato trying to identify the type on the basis of shadows on the walls of our caves.

Labels: Cancer, Health Care

TUESDAY, JULY 17, 2012

POUCH CAMP

Pouch Camp lake, a Boy Scout Camp on the high point of Staten Island, was my swimming hole from some 60 years ago. On hot July days one could ride a bike up the long road, some five miles of climbing a hill, deplete of any traffic, and spend a day swimming in the large cool lake. The inner area was for beginners but one would swim out to the platform and dive into the cold spring fed waters. Missing from this photo is the rowboats and canoes which made the scene complete. Back then, before air conditioning, the cold water was great, then back on the bike and down the hill, hands off the handle bars, wind blowing cool, despite the 90+ temps. Yes this was technically New York City, but it just as well could have been Nebraska! There were no helicopter moms, no Sandusky types, just kids, Schwinn bikes, and a swimming hole.

Labels: Commentary

MARX AND THE DISSOLUTION OF THE INDIVIDUAL

Here are two quotes:

"Society does not consist of individuals, but expresses the sum of interrelations, the relations within which these individuals stand." Karl Marx, Grundrisse, 1858

"If you've got a business, you didn't build that. Somebody else made that happen." Current President 2012

Does one see some similarity? As we have argued the Individual and their ability to perform goes to the heart of any entrepreneurial culture, and its destruction will lead inevitably to that culture's destruction.
Labels: Political Analysis

MIRNA AND PROSTATE CANCER

We have written a great deal about prostate cancer, PCa, and especially microRNAs. A recent paper by Yang et al present some new interesting results:

Recognition of micro-RNA function and their contribution to the biology of disease has given a new insight into disease mechanisms, with these discoveries potentially improving clinical diagnostic and therapeutic options.

miR-125b has been identified as an important regulator in various cancers, including prostate cancer, but the mechanism of this regulation remains incompletely understood. In these studies, the effect of castration on miR-125b serum expression was evaluated in mice, simulating androgen deprivation. ...

A previously studied target of miR-125b, a regulator in the apoptotic pathway, BAK1, could not completely account for the role of miR-125b in prostate cancer. Thus, we looked for additional targets of miR-125b and found that NCOR2, which is a repressor of AR, is a direct target of miR-125b. We found that NCOR2 protein expression was blocked by mimics of miR-125b, and a luciferase binding assay confirmed that NCOR2 is a direct target of miR-125b. Our data provide novel evidence that miR-125b is an important regulator of the AR with specific ramification for the effectiveness of antiandrogens and other hormonal therapies in prostate cancer.

We have discussed the significant potential of these small 22 base pair RNAs that can interfere with well defined pathways. This is an interesting example and worth following as a model.
Labels: Cancer

TUESDAY, JULY 17, 2012

MORE ON THE FACTS

As the current President said in his speech:

There are a lot of wealthy, successful Americans who agree with me -- because they want to give something back. They know they didn't -- look, if you've been successful, you didn't get there on your own. You didn't get there on your own. I'm always struck by people who think, well, it must be because I was just so smart. There are a lot of smart people out there. It must be because I worked harder than everybody else. Let me tell you something -- there are a whole bunch of hardworking people out there. (Applause.)

If you were successful, somebody along the line gave you some help. There was a great teacher somewhere in your life. Somebody helped to create this unbelievable American system that we have that allowed you to thrive. Somebody invested in roads and bridges. ***If you've got a business -- you didn't build that.*** *Somebody else made that happen. The Internet didn't get invented on its own. Government research created the Internet so that all the companies could make money off the Internet.*

The point is, is that when we succeed, we succeed because of our individual initiative, but also because we do things together. There are some things, just like fighting fires, we don't do on our own. I mean, imagine if everybody had their own fire service. That would be a hard way to organize fighting fires.

This can stand for itself.

The entrepreneur is a somewhat unique creature. They come up with an idea, often many ideas, try one after another, isolate themselves, defer many things in life, they become Pied Pipers, gathering teams who believe in their vision, build a business, spend their own money, to the extreme, and if lucky, yes lucky not having a Government interfere, then they reap a reward. But they are just as willing to start again. They are driven by succeeding. by competing, they are not the "team players" that somehow Washington imagines. Steve Jobs was no team player, nor were any of the Silicon Valley types I have known for almost fifty years. They make investment bankers look like Mother Theresa. But that type of single-mindedness is at the core.

This type of thought is killing the American entrepreneur. The Internet frankly was abandoned in the 80s by the Government and it was Vint Cerf and Bob Kahn that kept it going, and in the mid 80s when I took over NYNEX R&D we again supported it via NYSERNET, a non Government entity. Facts can all too often be confusing. Yes it was Al Gore's office which pushed what was then NREN, not inventing anything but promoting it, not with money but with a vision. Was Gore the driver, I do not recall him to be personally, but he did take on the challenge and for that he justly deserves credit.

This lack of nuance, this belief, total and absolute, on Government, is possibly to be our downfall. Remember Rome fell, despite the Catholic hating Gibbon and his tale, from the Roman citizens reliance on Government. Come the Huns, they had not a clue on how to make their own bread, for they got bread and circus from the lord and master. Beware the hand that feeds you!
Labels: Politics

MONDAY, JULY 16, 2012

THE FACTS ABOUT BUSINESS

The current President is quoted as saying (see White House for full released statement):

"If you've got a business, you didn't build that. Somebody else made that happen."
Now I would like to correct him:

1. In Russia I worked with many partners, some were ex KGB even, and I can assure the man that I had no assistance from the US Government.

2. In The Czech Republic my partner was a former Czech Communist Party member, a fine man, who worked with me despite the US.

3. In Thailand I worked through family friends and past acquaintances. There was no Government support there either Mr President.

4. In Korea I found partners to work with despite what the US State Department did not do to help. Again Mr. President I did this on my own.

5. In Germany I worked with partners one of which had a Stasi lady friend, again no American help there.

6. In Poland I had a Polish friend jailed by the Soviets and he and I had no help from the Government.

7. Then there was Greece, Turkey, Israel, Slovak Republic, Bulgaria, Romania, and the list goes on. No help there Mr. President! Greece was even easier than the US! Believe it, especially now.

8. Then there was New Jersey. We had to leave there Mr. President because the power company was in my opinion the worst in the world, at least as I saw it.

So Mr. President, perhaps one should find the facts before they opine. I hired thousands, in over twenty countries, and at no time did I get help from any Government agency of the US. In fact such entities as the FCC would slow us down.

So Mr. President, let me be clear, I never went to a public school, never used a single tax dollar, and I still pay more in Medicare than I cost and, well taxes, they keep coming on.

The US needs entrepreneurs, and if we keep telling them they never did it on their own, well Mr. President they will go elsewhere. Money and opportunity is fungible. No Government official has ever been so antagonistic to the people who create value as those in the current administration. In my experience Mr. Putin is more accepting of entrepreneurs than some here in the US. It is truly a pity!
Labels: Politics

LOSS OF THE INDIVIDUAL

In the works by Ullmann[1] and then Morris[2], the concept of the individual is shown to come forth during the middle ages. I would argue that it was also present at the time of Columbanus, as evidenced by his correspondence with Gregory I, the "Great", wherein one sees an individual, Columbanus, communicating with a Roman head of state. Notwithstanding one sees the "individual" arise, one separate from a citizen, a subject, or some other member of a group. Even the Marxist author Meiksins-Wood states that Ockham was one of the first philosophers promoting the concept of an individual[3]. Ockham rejected the Aristotelian constructs of Universals and perforce of the thought therein came to see man as a collection of individuals, separate and distinct human beings. Thus from the 10-13th centuries we see the understanding and acceptance as people as individuals.

By the 19th century we see America as a land of individuals, and the concept of individualism developing and prospering. At the early part of the century we have de Tocqueville and his observation of the individualism of Americans, and I would argue in the famous paper by Weaver and Brandeis, the concept of privacy, and more critically the "right to be left alone", is an individual right, and the paper is essentially and essay on individualism.

Dewey's work on rejecting individualism was one of the first strong Progressive articulations of a changing view of what America should be[4]. Dewey rejected the de Tocqueville individualism of the frontier and of what had made America what it was and introduced the controlled Progressive version, his new individualism.

Lukes has written extensively on individualism and his seminal work is a core document[5]. For Lukes the key ingredients of individualism are[6]:

Respect for Human Dignity
Autonomy
Privacy
Self-Development

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[1] Ullmann, W., The Individual and Society in the Middle Ages, Hopkins Press (Baltimore) 1966.

[2] Morris, C., The Discovery of the Individual 1050-1200, Univ Toronto Press (Toronto), 1987.

[3] Meiksins-Wood, E., Citizen to Lords, Verso (New York) 2008, pp 226-227.

[4] Dewey, J., Individualism Old and New, Prometheus (Amherst, NY) 1999.

[5] Lukes, S., Individualism, Harper (New York) 1973.

[6] Lukes, ibid, p 125.

As we had already stated privacy, and more to the point, anonymity, are key to individualism; the very right to be left alone. Respect of human dignity is simple all are created equal, and that each is to be respected. Autonomy is the core as well, the ability to go off and create. That fills the same space as self-development.

Now I would argue that the current President in his recent speeches, as has Prof. Warren in her campaign addresses, take the Progressive, if not almost communist (or at least Marxist by the denial of individuals and the acceptance of classes, a nominalism of sorts), stance that no one ever did anything on their own and as such whatever one attains in life is owed to society as a whole. That is the individual may exist, but that is a mere phenomenon, not germane to our society. The society as an Aristotelian abstraction is all that exists, nominalism, if you will a total anti-Ockham world.

The danger of course is that if we allow this gross rejection of the individual, and if we demand the group as the only element of existence, we drive out creativity, we drive out freedom, and we destroy our very idea of this country. The truth is that individuals create, individuals conceive of new things, take personal risks, and the may attain great success. We want to nourish such an environment, not create one where we destroy the individual. It has taken well over a thousand years to get individualism to this point. That is one third of humanity's recorded history. Do we want to destroy it in four more years?

Labels: Political Analysis

SATURDAY, JULY 14, 2012

WE HAVE SUCH POOR ECONOMISTS

This political season has brought out why we had the crash. Bad bankers, well a bit. But really horrible economists. There are some left wing economists who teach, and who in my opinion know nothing about the economy.

They bemoan private equity. Almost every start up has received money from some form of private equity. And leveraged buy outs, if the company had been well managed then there never would have been a leveraged buy out. LBOs clear the market, they take bad companies and try to make them good. Yes good, namely profitable for the investors.

Let me reiterate something I introduced to the telephone company just after it became unregulated:

Profit Equals Revenue Less Expenses

This is a truism, a tautology, it is a definition. Why do people invest? Duh. To make money. Value is all too often based upon profit. Profit is the above. So increasing revenue and/or reducing costs is an imperative.

But somehow these economists are clueless. Perhaps their students should institute a class action suit. Economics should reflect reality, at least a little, right guys, try at least to pretend it does! That is why I like the Canadians, like Nick Rowe. He not only pretends, he often admits that he just does not know. Why I have done that a few times as well, it is good for the soul. But not these characters on the left.

We have about 4 months left. It will be interesting to see how far from reality these characters go.
Labels: Economics

HAPPY BASTILLE DAY

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

THURSDAY, JULY 12, 2012

NO MR. EINSTEIN, YOU ARE NOT TITLE IX COMPLIANT

To add to the many "you can't make this .... up" category, the White House apparently has taken its royal authority to rewrite Title IX. Now it applies to academics. Reuters states:

The White House announced new measures Wednesday to help increase the number of women in the science, math and technology fields as part of a celebration for the 40-year anniversary of a law prohibiting discrimination in education based on gender.... The new guidelines are reinforcements to the law, known as Title IX.... They include the Department of Education broadening data collection in public schools for more accurate analysis of the gender and minority gaps in enrollment, graduation rates and in science classes....New guidelines will also be issued to grant-receiving universities and colleges to help institutions comply with Title IX rules in the science, technology, engineering and math fields. ...Obama adviser Cecilia Muñoz, director of the White House Domestic Policy Council, said more work was needed to ensure equal access in academics.

If you are trying to create a highly competitive country in an ever growing global economy the worst thing you could do would have the Government dictate who gets graduate education in science and engineering. If this piece is correct it appears to do two things:

1. Exclusive of Congress it take Royal power to the extreme by using a law intended to assist sports and apply it to say qualifying exams for PhDs. Yes there are fewer women in EECS, it is hard, it is competitive, and it is at the very heart of our survival. So we want proportional representation of degrees rather the the best possible! Never before in our society has there been such a grab of power for power's sake.

2. Creating the best is a competitive event. The fastest runner is the fastest runner. The top 10% on the qualifying exams take the next step. NOT the top 10% or men, then top 10% of women. What if that second top 10% is the lower 10% overall? Darwin did have a few points to

remember. And our economic enemies work in the competitive domain, not this "social justice" domain.
Labels: Politics

TUESDAY, JULY 10, 2012

DOING AWAY WITH THE 13TH AMENDMENT

The 13th Amendment states:

Article XIII.

Section 1. Neither slavery nor involuntary servitude, except as a punishment for crime whereof the party shall have been duly convicted, shall exist within the United States, or any place subject to their jurisdiction.

Section 2. Congress shall have power to enforce this article by appropriate legislation.

Now some writer in the NY Times states:

A revived draft, including both males and females, should include three options for new conscripts coming out of high school. Some could choose 18 months of military service with low pay but excellent post-service benefits, including free college tuition. These conscripts would not be deployed but could perform tasks currently outsourced at great cost to the Pentagon: paperwork, painting barracks, mowing lawns, driving generals around, and generally doing lower-skills tasks so professional soldiers don't have to. If they want to stay, they could move into the professional force and receive weapons training, higher pay and better benefits.

Those who don't want to serve in the army could perform civilian national service for a slightly longer period and equally low pay — teaching in low-income areas, cleaning parks, rebuilding crumbling infrastructure, or aiding the elderly. After two years, they would receive similar benefits like tuition aid.

Now having gone through the Vietnam period, I got a deferment because of what I did instead, technical stuff sometimes in strange places, but that is a tale for some later time. But I saw what the draft did. It made people do strange things, and created a poor military. The Army was a mix of mostly people who did not want to be there and the result was a disaster.

Furthermore a good military should be volunteers, people committed to their work, and yes professionals. Secondly the military needs fewer and fewer people, unless there is some massive ground war and the US is under attack, in which case we are back at WW II. Third the expense, direct and indirect is massive. Indirect expense is we are taking people at their prime training and education period and putting them in the military, a place which is quite often the home for hurry up and wait.

This statement in my opinion is appalling:

The pool of cheap labor available to the federal government would broadly lower its current personnel costs and its pension obligations — especially if the law told federal managers to use the civilian service as much as possible, and wherever plausible. The government could also make this cheap labor available to states and cities. Imagine how many local parks could be cleaned and how much could be saved if a few hundred New York City school custodians were 19, energetic and making $15,000 plus room and board, instead of 50, tired and making $106,329, the top base salary for the city's public school custodians, before overtime.

Cheap labor, forced labor, and it is a violation of the 13th Amendment. This statement in and of itself in my experienced opinion demonstrates both an attitude and a gross lack of knowledge of how business works. So we force the Steve Jobs and other entrepreneurs to wast years in some Government job! Are you out of your mind!

Now the cost could be staggering. If we get a collection of 8 million 18 year olds and add another 8 million 19 year olds, that is close to 20 million. Now we "pay" them $15,000 pa, plus room and board plus management that is easily $60,000 pa. Thus we have some $1.2 Trillion a year! Are we going insane! For what! This must be the Left's idea of totally destroying the country!

And you take from the economy the very people who will build the future and waste their time for no good reason. Frankly I find this appalling! But it is after all he Times. Half baked at the very best.

As for NYC school custodian, I had a job cleaning toilets at NYC schools on weekends when in High School, my grandfather was the custodian. A licensed engineer, ran large tankers, was even US Harbor Master in NYC during WW II. But at 15 I had no idea how to bring up the boiler, how to level out the ventilation, nor did I have any license to do so. So if I read the statement correctly the author wants kids, with no licenses, no training, no experience, bring up the HVAC in our public schools. To paraphrase DeLong, oh if we only had a better press! And of course Bourdreaux responded appropriately.

Labels: Commentary

MONDAY, JULY 9, 2012

WHY THERE WERE NO ACADEMICS AT THE CONSTITUTIONAL CONVENTION

Now I have been in and out of the Academy for over fifty years. I always go back to the real world. Now to the Constitution. The NY Times had a piece on what needed to be changed in the Constitution.The respondents were all academics of some sort. Perhaps that is why the folks who wrote the Constitution had none there in Philadelphia.

One must read some of their comments. One might possibly be quite disturbed if they ever let these people loose upon humanity while implementing their ideas. There were in my opinion no Lockes, no Montisques, no Humes, not even a Burke. Perhaps that is why we have so large an

Academy. It is a place to keep them all, like say prisons. A bit more costly but they get to hang around with each other and reinforce their ideas.

The folks in the halls in Philly had jobs. They were merchants, bankers, farmers, builders. The had a modicum of understanding of what life is really like. They were not the sheltered few.

It terrifies me from time to time to see these folks opine without substance. But so far they do so only in the Times. Safe for a while.
Labels: Political Analysis

SUNDAY, JULY 8, 2012

NEWSPAPER HEADLINE, ARE WE NEXT?

2 HOSPITALS 'LETTING PATIENTS DIE TO SAVE MONEY'

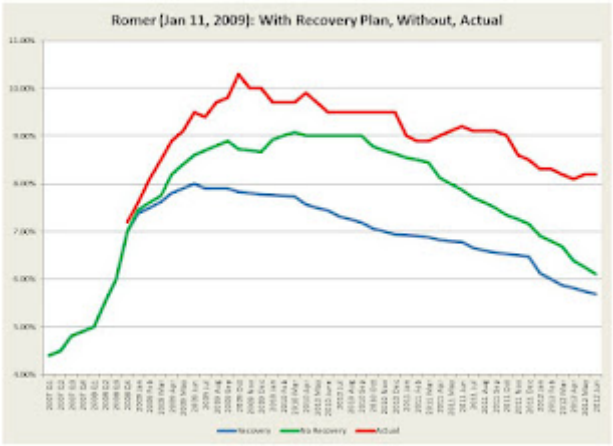
HOSPITALS MAY BE DEPRIVING ELDERLY PATIENTS OF FOOD AND DRINK TO HASTEN THEIR DEATHS AS PART OF COST-CUTTING MEASURES TO FREE UP BED SPACE, LEADING DOCTORS WARN.

Headline from Brit Telegraph newspaper. Is this the future of the ACA?
Labels: Health Care

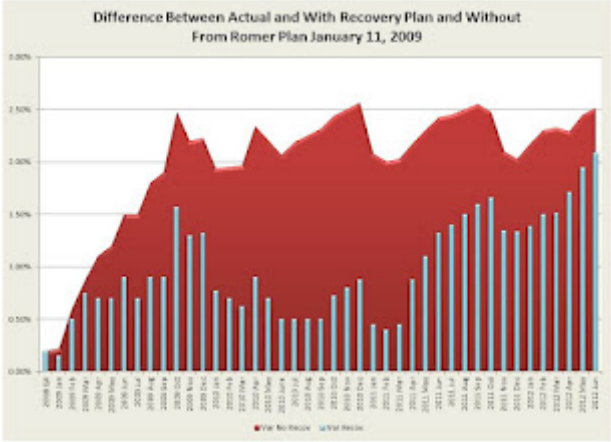
FRIDAY, JULY 6, 2012

UNEMPLOYMENT CONTINUES

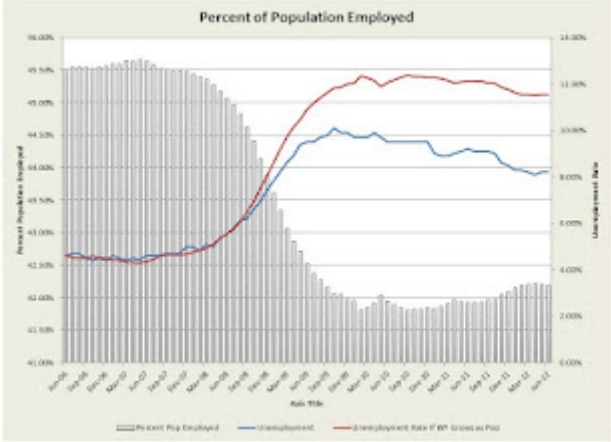
The reports again seem dire. The unemployment is still listed at 8.2% and we are entering the mid summer season. Labor Day is the semi official start of the campaign and we still have no leadership. So here we go with the data:



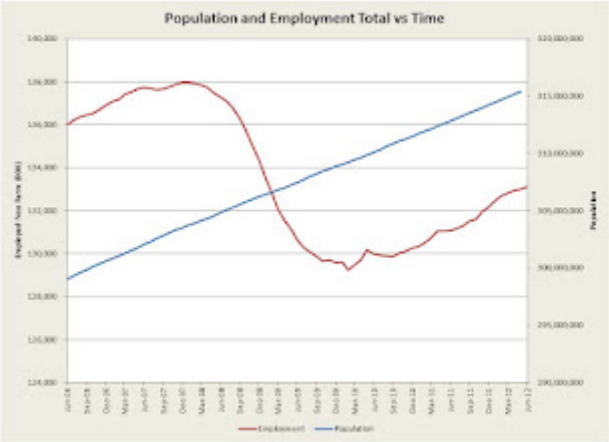
As usual we start with the Romer Curve. By now we should have had a rip roaring economy. In fact the difference between doing nothing and the Stimulus would almost begin to be negligible. But we know the truth. Clueless.



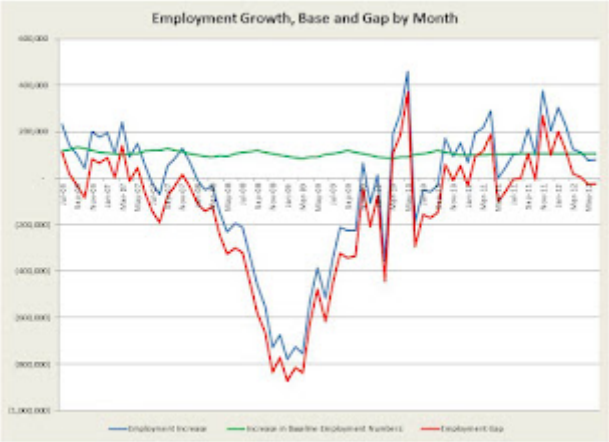
The above are her errors. One can see the ever growing disparity between reality and what she predicted. Will anyone ever admit this fact? Doubtful.



Now we have the percent of population employed as the denominator. We can see it has actually dropped a nit. Thus real unemployment has gone up! Not remained constant. namely they have taken people out of the workforce again! Otherwise we would have seen 8.4% or more.



This is the data on the gap. We are growing marginally.



But the above is the telling curve. We have a growing potential workforce based upon the green line. Namely each month new potential workers enter the potential workforce. Thus just to stand still we must add 150,000-180,000 new jobs a month. That just keeps us at 8.2%. But we are adding far fewer, thus the negative gap, the red line, shows we are negative for the past two months.

As I have said before, I believe we may have already entered another recession. The GDP will be of interest but it is for Q2 only.

Labels: Economy

STOP AND GO AND CANCER CELL PROLIFERATION

In a recent paper by Solimini et al the authors discuss the concepts of STOP and GO genes and carcinogenesis[78[1]]. The paper reports on some extensive experimental results focusing on the issue of proliferation and the loss of certain sets of gene sites, the STP and GO sites.

[78[1]] Solimini, N., et al, Recurrent Hemizygous Deletions in Cancers May Optimize Proliferative Potential, Science, 6 JULY 2012 VOL 337, p 104.

The authors begin by discussing the current concepts of changes in oncogenes and tumor suppressor genes, some of the key pathway elements that we examine in analyzing intracellular pathway dynamics. They state:

Cancer progression is directed by alterations in oncogenes and tumor suppressor genes (TSGs) that provide a competitive advantage to increase proliferation, survival, and metastasis. The cancer genome is riddled with amplifications, deletions, rearrangements, point mutations, loss of heterozygosity (LOH), and epigenetic changes that collectively result in tumorigenesis.

How these changes contribute to the disease is a central question in cancer biology. In his "two-hit hypothesis," Knudson proposed that two mutations in the same gene are required for tumorigenesis, indicating a recessive disease. In addition, there are now several examples of haploinsufficient TSGs .

Current models do not explain the recent observation that hemizygous recurrent deletions are found in most tumors. Whether multiple genes within such regions contribute to the tumorigenic phenotype remains to be elucidated…

The last sentence regarding the inability to explain the presence of hemizygous deletions under the current model is the main driver for this effort. Thus they argue and demonstrate experimentally that:

Tumors exhibit numerous recurrent hemizygous focal deletions that contain no known tumor suppressors and are poorly understood. To investigate whether these regions contribute to tumorigenesis, we searched genetically for genes with cancer-relevant properties within these hemizygous deletions.

We identified STOP and GO genes, which negatively and positively regulate proliferation, respectively.

STOP genes include many known tumor suppressors, whereas GO genes are enriched for essential genes.

Analysis of their chromosomal distribution revealed that recurring deletions preferentially over-represent STOP genes and under-represent GO genes.

*We propose a hypothesis called the **cancer gene island model**, whereby gene islands encompassing high densities of STOP genes and low densities of GO genes are hemizygously deleted to maximize proliferative fitness through cumulative haploinsufficiencies.*

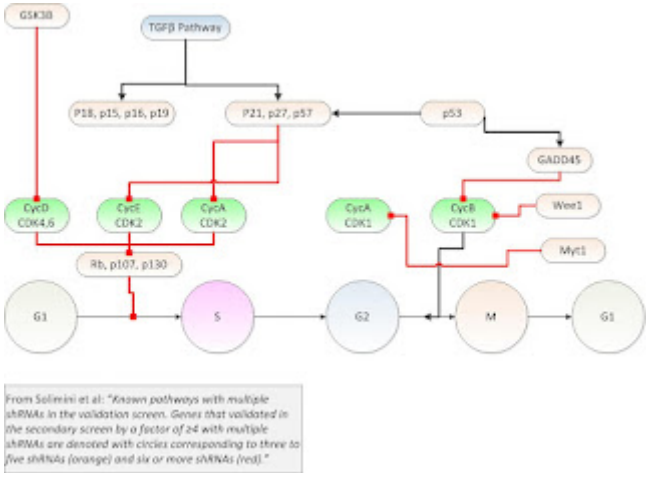
Because hundreds to thousands of genes are hemizygously deleted per tumor, this mechanism may help to drive tumorigenesis across many cancer types.

This is an intriguing hypothesis. It adds more pieces to an already complex puzzle. The Cancer Gene Island, CGI, hypothesis seems to indicate the complex changes in multiple gene sites. In particular there was a deletion of the STOP genes in preference to the GO genes. Unfortunately there did not seem to be a mechanism for these deletions, however the experimental evidence does indicate the phenomenon.

In their experimental analysis they have observed certain in vitro results which compel their hypothesis. They state:

This in silico analysis suggests that the loss of a single copy of GO genes has a negative impact on cellular fitness. To independently test this hypothesis, we turned to the other arm of our screen that identified candidate GO genes whose depletion limits proliferation and survival. Because both normal and cancer cells are dependent on these essential GO genes, we analyzed data from proliferation screens on HMECs, one normal prostate epithelial cell line, and seven breast or prostate cancer cell lines

They provide an interesting pathway model as shown below (as mofified, and also not that they have short hairpin RNAs (shRNAs)).



From Solimini et al: "Known pathways with multiple shRNAs in the validation screen. Genes that validated in the secondary screen by a factor of ≥4 with multiple shRNAs are denoted with circles corresponding to three to five shRNAs (orange) and six or more shRNAs (red)."

They conclude as follows:

The enrichment for genes localized to deletions suggests that we have identified dozens of new TSGs in recurrent deletions. We have also likely identified more TSGs outside of these regions because the STOP gene set is (i) enriched for known TSGs, many of which are not found in recurrent deletions, and (ii) enriched for genes that undergo somatic loss-of-function mutation.

Finally, this work suggests that cells possess a substantial number of genes that restrain proliferation in vitro, which could be inactivated to promote clonal expansion during tumorigenesis in addition to the traditional driver genes currently known. Given the prevalence of multiple, large, recurring hemizygous deletions encompassing skewed distributions of growth control genes in tumors, we propose that the elimination of cancer gene islands that optimize

fitness through cumulative haplo-insufficiencies may play an important role in driving tumorigenesis, with implications for the way in which we think about cancer evolution.

As with many such works this raises as many questions as it seems to answer. However the control or lack thereof of proliferation and the cell cycle is a critical issue in carcinogenesis.

Labels: Cancer

THE END OF THE DARK AGES

I read a wonderful book by Richter on the monastery at Bobbio, Lombardy, from the early Seventh to the late Eighth centuries. I present it below. But the conclusion which may be drawn is that with the wealth of documents in the Library and the growth of them one could readily deduce that the "Dark Ages" was an artifact of the Renaissance man. In fact the total lack of any comments by Gibbon in his diatribe against Catholics totally ignores this.

Bobbio, by Richter, is an exceptionally well written presentation of the history of the monastery founded by Columbanus in the early 7th century. Richter provides a history of the three hundred years, from early 600s through the late 800s and deals directly with the original sources in a smooth and accessible manner. His writing style is clear and fluid and he provides the history of Bobbio in the context of the surrounding historical settings. It is in many ways an academic tour de force. Richter takes a some what complex set of issues from the 7th through 9th centuries, using the original sources, and makes them flow and readable. As I will comment upon, having some solid secondary school Latin is always a help but not a necessity.

Bobbio was in Lombard territory when founded by Columbanus and at the time the Lombards were Arian Christians, simply they did not believe in the Trinity or the divinity of Christ. Columbanus had been "expelled" from the Merovingian territories, most likely due to his battles with Queen Brunhilda, and having left Frankish lands he settled here. It is then the tale of this monastery from the time of Columbanus that Richter so admirably tells.

The book is concise, some 188 pages, and it is structured to basically follow the history. The first three chapters present the time of Columbanus and his immediate legacy. Richter interspersed his text with excerpts from the originals in 7th century Latin (it starts on p 19 with the writ of exemption). This is actually more useful than most would expect. I found that my Latin, French, and Italian were adequate to handle the inserts but at the same time reading them does provide a sense of how the language was halfway between Cicero and the Scholastics. One can see the mild local differences and the structure is evolving but the inclusion is quite helpful.

Richter does cover the key points concerning Bobbio, especially it exemption from control by the local bishop, which I assume in the 7th century was less of an issue than in the 9th. Furthermore the text, in the first three chapters, is focused on Bobbio and much less of Columbanus. There have been several recent works on Columbanus, none as scholarly as

Richter, but it would possibly have been useful if Richter had provided a bit more background from his perspective on Columbanus.

Chapter 4 talks of the Scriptorium in the 7th century. This is a wonderful chapter and it details both the documents from that time and the ones from earlier upon which the documents were overwritten. The discussion on p 73 of the overwriting on Ulfila's Gothic translation of the Bible is intriguing. It would be interesting to hear more just of that discovery alone. The discussion here is quite complete and does set out the controversies and attempts to resolve them. What is interesting and a lingering question is that we see the strong and driving influence and competence of the Irish monks but one wonders just how they came by this. This was not a task of Richter but after reading the volume in toto is screams for an answer.

Chapter 5 speaks somewhat of the century where there were recorded abbots. The discussion on pp 92-93 is of interest in that it presents the potential lingering Irish influence. One of the questions that is not addressed to any significant degree was the openness of the abbey. The Frankish abbeys were allegedly open to lay people, and to some degree they were seen as institutions of learning, not just classic closed abbeys like those of the Benedictines. If this were the case, and given the extent of the Scriptorium in non-religious content, one may wonder.

Chapter 7 discusses the changes during the era of Charlemagne. Chapter 8 presents the economy of the monastery. There is exceptionally complete detail which is presented in a fresh and clear manner.

Chapter 9 was of most interest to me. It was the Library in detail in the 9th century. On pp 154-156 is a details presentation of the key contents and the mix of documents is intriguing. This Chapter by itself if of substantial value.

The remaining chapters provide additional detail and especially the details regarding the movement of the remains of Columbanus.

This book is superbly researched, is readable while being academically of the highest caliber. This provides a well done addition not only to the works regarding Columbanus but also to the early Middle Ages.

For anyone interested in this period, no matter where in Europe the interest may be, this is a highly recommended work.
Labels: Books

THURSDAY, JULY 5, 2012

IT'S 100F AND I JUST FEEL LIKE READING THE CANADIANS

I never met Frances Woolley but I have a student or two in her University town. But here I am in my air conditioned office trying to bang out a few more pages on pathway dynamics of melanoma and its control when I see Frances and warts. Any excuse to get away from BRAF,

MEK, p53, and PTEN. Go to warts. I am staring at the wart on my right hand, been there I think 50 years, yes Frances, they may never go away. I never found it a social stigma, but then again here I am typing this silly response.

So I guess when it gets a bit on the warm side up North they get to opine on those things that truly have meaning in life, warts. Now also having had the opportunity to have studied medicine, I know of lots of different warts. Warts in places that we never want to think of, rough warts, flat warts, itchy warts, just lots of warts. How to treat warts, first a small number may actually be a malignancy, but a very small number. Most are just, well, there. Some come and go, then there is the plantar wart on the bottom of your foot, may be uncomfortable, but is always a tough one to get rid of.

So is this a medical problem? I don't have a license so I can only speak from personal experience, not providing any medical advice, but well, it is akin to acne, do we go to a physician to get our acne fixed, well sixty years ago we did not, we just washed out faces with lye soap, probably why we look this way now!

But Frances did make my afternoon. As she says:

Sometimes, when others fail to act, private charities step in. Think, for example, of the Bill and Melinda Gates Foundation's work on malaria. Unfortunately verucca vulgaris has failed to attract charitable donations, research dollars and high profile advocates. It's harder to raise funds for ugly animals than for beautiful ones; chronic problems like poverty attract relatively fewer donations than dramatic events like tsunamis. Donors get excited about saving lives, or making dramatic improvements in people's existence. Consequently, private funds for wart research are lacking.

Or perhaps a Saturday Night Live skit on a wart charity, the Wart Foundation. Perhaps that is also why so many US comedians are from Canada. Happy summer to all! Keep it up, it is to peak 105F on the morrow! What about this global warming stuff, perhaps there may be something there as well.
Labels: Commentary

THE COST OF GETTING INFORMATION

Nick Rowe wrote a spot on piece regarding JSTOR. He clearly was using this as a metaphor for many other things so I thought I would throw in my two pieces, shilling, pence, whatever. Here goes.

1. Microsoft: If you think you have problems with JSTOR try and figure out what is wrong with your operating system if you have to go to Microsoft. The only way to find out how Microsoft works is to use Google. Does that tell you something.

2. MIT: Now I am not an economist, but I have a pile of degrees from MIT in EECS, that means computer science. Now MIT decided to put on this on line open course. I wrote about my travails, but for clarity I used to be in charge of the course many decades ago. Has not really changed much so I thought I would give it a whack. Now like Nick I have a real life, namely I do

other stuff besides trying to find out how the software works. Thus when I came upon a question which required me to enter an equation, there being no directions on how to do so, and after 5 or 6 tries, I said to myself, this is not me, it is them. I stopped, and apparently so did 119,000 other people. Tell you something? To me yes, to the MIT programmer whiz, no, it was my stupid fault. Well there went a few years of alumni donations. If Google had designed the interface then when I ran into an entry problem they would have nicely directed me to directions, example, user groups, emails, whatever. I would have solved the problem near instantly. Not MIT, too much like Microsoft. Was I ever that bad?

3. Google: Now that is the way to do things. If you make a mistake they suggest how to solve it, then they try again, it is never your fault, they try again. Now that is truly Google's future if they recognize it. Why is Google this way? The answer may be quite interesting.

4. Open Access: I just gave up peer review publications. You see when you get over seventy you keep wondering if there will be enough time to get through a review cycle. Also, the only thing you really do is make some up and coming Associate Prof happy that they got you to dot or cross something. Thus open access, open access everything. As for peer reviews, send me an email, yell, scream, even use that old device called a phone, and I have video if you insist on using facial responses.

Thus, as usual, Nick has keen insight into the obvious. I have learned that "if all else fails listen to the customer" is a powerful aphorism with a great deal of insight. Google listens, Microsoft does not, nor did MIT in its first attempt. JSTOR may be just an artifact of an older generation, like a FAX machine, just kick it once and a while Nick, it will make you happy!
Labels: Commentary

PIGOU AND CANADA

The NY Times has a piece by some academic types regarding the use of a carbon tax, yes a Pigou type tax, in Canada. They write:

ON Sunday, the best climate policy in the world got even better: British Columbia's carbon tax — a tax on the carbon content of all fossil fuels burned in the province — increased from $25 to $30 per metric ton of carbon dioxide, making it more expensive to pollute.

This was good news not only for the environment but for nearly everyone who pays taxes in British Columbia, because the carbon tax is used to reduce taxes for individuals and businesses. Thanks to this tax swap, British Columbia has lowered its corporate income tax rate to 10 percent from 12 percent, a rate that is among the lowest in the Group of 8 wealthy nations. Personal income taxes for people earning less than $119,000 per year are now the lowest in Canada, and there are targeted rebates for low-income and rural households.

Well this is not what I thought Mankiw was pushing, and I suspect ultimately Romney. They, I believe, want to just add another tax, a tax which is highly regressive, on anyone using petrol fuel. If I read this article correctly this tax is in place of an income tax. It still is a highly regressive tax not withstanding. But who ever heard of any Government lowering taxes when

they get permission to add a new one. Never happen, not in this country.

This Pigou tax is to disincent use, when there is no rational alternative. Taxing weight, carbs, whatever makes more sense and we can track the positive effects ounce by ounce.
Labels: Economics, Politics

BAD CELLS USING GOOD CELLS: METASTASIS

In the Nature article by Straussman et al, they state (also see write up by Carpenter):

Drug resistance presents a challenge to the treatment of cancer patients. Many studies have focused on cell-autonomous mechanisms of drug resistance. By contrast, we proposed that the tumour micro-environment confers innate resistance to therapy.

Carpenter states:

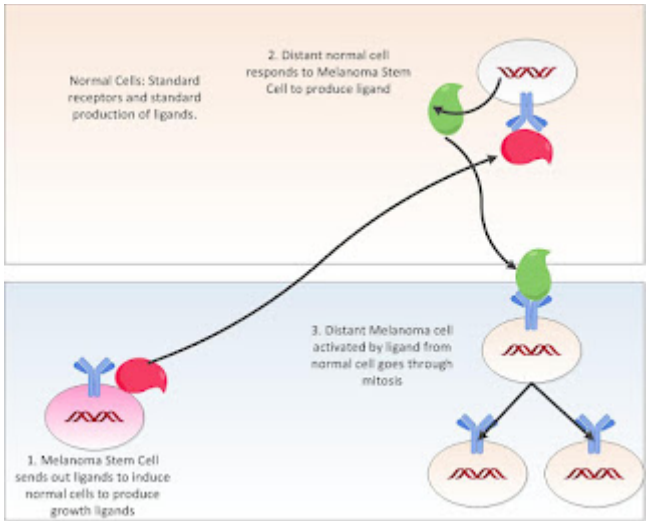
The presence of these cancer-assisting proteins in the stromal tissue that surrounds solid tumours could help to explain why targeted drug therapies rapidly lose their potency.

Targeted cancer therapies are a class of drugs tailored to a cancer's genetic make-up. They work by identifying mutations that accelerate the growth of cancer cells and selectively blocking copies of the mutated proteins. Although such treatments avoid the side effects associated with conventional chemotherapy, their effectiveness tends to be short-lived. For example, patients treated with the recently approved drug vemurafenib initially show dramatic recovery from advanced melanoma, but in most cases the cancer returns within a few months.

The Carpenter article concludes:

One of the most startling results of the teams' experiments was the discovery that a protein called hepatocyte growth factor (HGF) boosts melanoma's resistance to treatment with vemurafenib. Intrigued by this result, both teams looked at blood samples from people who had undergone treatment with vemurafenib, and found the higher a patient's HGF levels, the less likely they were to remain in remission.

We propose an alternative but what we believe to be a consistent interpretation. Consider the example below. We have conjectured based upon modeling that cancer may act as a separate entity on the human host and further that it uses the human host not only for nutrients but for communications. In fact using the results from this paper one can construct a verifiable model of a bi-system distributed environment. Here the melanoma uses a stem cell to communicate at a distance.



The above is a hypothetical example:

1. There exists a melanoma stem cell. It can produce ligands which manage to use the body's distribution system; blood or lymphatic.

2. The ligands use normal health cells which are to be activated and in turn produce at a distant site growth ligands at that site.

3.At the distant site we have Melanoma non stem cells which respond to this massive influx, an amplifier system if you will, to make the non stem melanoma cells to proliferate.

Just an interesting but possible physical interpretation.
Labels: Cancer

WEDNESDAY, JULY 4, 2012

CANCER CELLS AND THE ENVIRONMENT

There is an interesting piece on Eureka talking about how researchers now believe the environment, micro environment, can be a controller to cancer cell.

They state:

The research team has found that normal cells that reside within the tumor, part of the tumor microenvironment, may supply factors that help cancer cells grow and survive despite the presence of anti-cancer drugs. These findings appear online this week in a paper published in Nature.

"Historically, researchers would go to great lengths to pluck out tumor cells from a sample and discard the rest of the tissue," said senior author Todd Golub director of the Broad's Cancer Program and Charles A. Dana Investigator in Human Cancer Genetics at the Dana-Farber Cancer Institute. Golub is also a professor at Harvard Medical School and an investigator at

Howard Hughes Medical Institute. "But what we're finding now is that those non-tumor cells that make up the microenvironment may be an important source of drug resistance."

We have argued likewise in one of our recent White Papers. We argued that such cancers as melanoma have a compelling model for metastasis which uses both short distance micro environment control as well as long distance macro environment signalling.

Namely we have modeled melanoma metastasis as a quasi distinct organism using the human as a host and specifically using the host extracellular signalling as a means for allowing the stem cell to effect metastasis at a distance.

This laboratory effort is truly worth following.
Labels: Cancer

SOMETHING TO WATCH

PCORI is an off-shoot of the ACA. It states its mission as:

The Patient-Centered Outcomes Research Institute (PCORI) is authorized by Congress to conduct research to provide information about the best available evidence to help patients and their health care providers make more informed decisions. PCORI's research is intended to give patients a better understanding of the prevention, treatment and care options available, and the science that supports those options.

The Patient-Centered Outcomes Research Institute (PCORI) helps people make informed health care decisions, and improves health care delivery and outcomes, by producing and promoting high integrity, evidence-based information that comes from research guided by patients, caregivers and the broader health care community.
Patients and the public have the information they need to make decisions that reflect their desired health outcomes.

Now this is one of the hundreds of Federal Government Agencies, off book if you will, which have no reporting requirement to Congress, which will mandate what health care we get. Yes, in my opinion, this is where the morbidly obese GS9s will find homes and deny folks care. You can lay bets on this one.

How is it funded:

PCORI is funded through the Patient-Centered Outcomes Research Trust Fund (PCORTF), which was authorized by Congress as part of the Patient Protection and Affordable Care Act of 2010 and receives income from two funding streams: the general fund of the Treasury and a small fee assessed on Medicare, private health insurance and self-insured plans. PCORI is expected to receive an estimated $3.5 billion from the PCORTF to fund patient-centered outcomes research through September 30, 2019, the date through which the Act authorizes it to remain in operation.

Yes folks it is funded by us old folks with increased Medicare costs at in my opinion less

coverage.
Its budget is as follows:

For FY 2010, $10 million
For FY 2011, $50 million
For FY 2012, $150 million

For FY 2013, the PCORTF will receive $150 million from the general fund in appropriation plus an annual $1 fee per individual assessed on Medicare and private health insurance and self-insured plans. The combined estimated total is $320 million.

For FYs 2014-2019, the PCORTF will receive $150 million from the general fund in appropriation plus an annual $2 fee per individual assessed on Medicare and private health insurance and self-insured plans and an adjustment for increase in healthcare spending. The combined estimated total averages $650 million per year.

This will be an exploding costs base. The Government, rather than physicians and patients, will be telling us what is good for us, as I read the details. That is $650,000,000 per year as a starter for studies, yes studies. Not clinical studies, but Government funded, which in my experience means that someone has a conclusion and they seek some Beltway Bandit to confirm their view.

In Massachusetts alone the following have apparently been funded:

1. *Influence & Evidence: Understanding Consumer Choices in Preventive Care*
2. *Developing and Testing a Decision Support Tool for Primary Medication Adherence*
3. *Direct Engagement of Stakeholders in Translating CER into Clinical Guidelines*
4. *Incorporating Parent Preferences in Decision Making about Childhood Vaccines*
5. *Assessing and Reporting Heterogeneity of Treatment Effect in Clinical Trials*
6. *Developing an Analytic Tool to Assess Patient Responses*
7. *Patient Experience Recommender System for Persuasive Communication Tailoring*
8. *Decision Support for Symptom and Quality of Life Management*

These are all somewhat questionable in my opinion. Take the CER conversion into clinical guidelines. Take specifically the elimination of PSA tests by the Task Force as an example. This means that the actual lives saved will no longer be considered. The Government is writing the medical books. It does not even have a license to practice but it it now controlling how we are treated. One must and should be concerned as to what use these "studies" will be put. This will also most likely change "peer review" so that in my opinion the Government "peer review" specialists will mandate what is truth. McLuhan would have had a field day with this construct.

This is truly worth watching. They have Pilot Projects shown and this may provide some insight. But one must keep in mind that this is just one of the hundreds set up under the ACA! Watch the Deficit explode! And the care implodes! Happy 4th.
Labels: Health Care

WEDNESDAY, JULY 4, 2012

POOLS, BEACHES AND SWIMMING

The Times has an article regarding the opening of a public pool and its problems.

BILL MOHAN, FRANCIS ESPIPIO, TERRY McGARTY
Life Guards Work to Save Girl After S. I. Rescue

I started as a NYC lifeguard in 1959 and if I recall we had a beastly hot summer, 59 0r 60, at Coney Island. We had almost one million people at the beach. Yes we had some issues but lifeguards were typically 6' plus and near 200 pounds of muscle. Even more so we were the sons of Police Officers and even a few FBI agents. We all were on our way to college, had a smattering of Spanish, Puerto Rican dialects, and we walked alone down the beach watching the folks.

We never really had fights, there were no police on the beach but we walked with an oxygen tank, a heavy green thing, which I guess made us look a bit in control. We had orange and green bathing suits and tops with numbers.

The "better" life guards were assigned to the beach, second place went to pools. But we did have losses in life, some people drank a bit too much and then went in the water, then under. I recall possibly two or three losses each summer. On the other hand we had many rescues, cramps, poor swimmers, and the like.

Thus it is somewhat surprising to see these problems. We had a Chief Lifeguard, an older gentleman, Lou Lipke if I recall, who trained us on what to expect. But we had respect because we mingled with the people. One on the lifeguard chair looking an the rest of us walking amongst the crowds. It was as if we became "beat cops" knowing the people, week after week, and if I recall we never had a serious problem.

Perhaps the training has gone by the wayside, perhaps the lifeguards are different. But perhaps it

is just the newness of the situation. Hopefully it will calm down again. The pools were as important as the beaches.

But looking back we had lifeguards from the community. We knew many of the folks, and yes there were trouble makers, but they could be controlled. There were lots of us, and yes the pay was not much. But the guys were a great team.

Labels: Commentary

HAPPY 4TH

Down the road a bit from my home is the path George Washington took many times to go back and forth with his troops.

In many ways the Declaration was as a product of Jefferson reflective of Rousseau and Montesquieu a French version of individualism, not the true thing. For when de Tocqueville wrote his observations it was American individualism that most impressed him.

Thus in today's Times we are confronted with an author who states:

But then came the late 1960s, and over the next two decades American individualism was fully unleashed. A kind of tacit grand bargain was forged between the counterculture and the establishment, between the forever-young and the moneyed.

He continues:

People on the political right have blamed the late '60s for what they loathe about contemporary life — anything-goes sexuality, cultural coarseness, multiculturalism. And people on the left buy into that, seeing only the '60s legacies of freedom that they define as progress. But what the left and right respectively love and hate are mostly flip sides of the same libertarian coin minted around 1967. Thanks to the '60s, we are all shamelessly selfish.

The ideas of individualism, libertarianism, hedonism, are all mixed up in this author's mind. The Scottish Enlightenment, Locke et al, are more a source and more on point. Jefferson was a Frenchman at heart, individualism was a clear evolution from the English desire to remove class.

The Hippie world was a movement to remove responsibility. Individualism embodies duty, responsibility, while keeping that on the shoulders of the individual, not off-setting it upon the Government.

Having lived through the 60s, in Cambridge, what I saw was not individualism in any manner, but a Roman like break with that duty, by people and the Government, the Democrats in Washington especially.

Words do really mean something. The author seems in my opinion quite confused and uneducated. Words like citizen connote the meaning of being in a group. The French Revolution tried a level playing field euphemism of all being citizens. The Soviets used the term comrade. The in crowd in Rome were also citizens as were the crowd in Athens. The rights were group rights, not individual rights. Equality, level playing fields, fairness, all connote group think. The 60s was mass group think, not in any way individualism. True facilitators of mass group think.

The ultimate in individual rights was the construct of the right to be left alone, the famous paper by Warren and Brandies. It went beyond privacy, it went to the very heart of the individual and individualism. It was a right of anonymity.

The 60s were an "in your face" approach, as many of the same techniques are used today. It was Chicago politics, Saul Alinsky, and ever mayor of Chicago. These are NOT purveyors of individualism. They were destroyers of that very cherished idea.

The bottom line, what has become of our education system, our Press, with a paper of this type. Too bad we cannot wrap fish in it any longer!
Labels: Commentary

SATURDAY, JUNE 30, 2012

I TOLD YOU SO

I never have trusted cloud computing, it is akin to trusting in the kindness of strangers.

As the WSJ reports:

Large electrical storms on the east coast disrupted power for Amazon.com Inc. cloud-computing operations Friday night, causing outages for customers such as Netflix Inc. and photo-sharing service Instagram.

The Seattle-based online retailer operates data centers with servers that manage the Web operations of many other companies, a practice often called cloud computing. Power outages caused by catastrophic storms that blanketed the east coast affected Amazon's operations in Virginia.

On Saturday afternoon, Amazon was still reporting performance issues for what it calls its elastic cloud compute, relational database and elastic beanstalk services. The problems appeared to have begun appearing on the site at around 11:21 p.m. EDT on Friday.

For those old guys like me who had built global networks on their own nickle, this was always a risky business. There was just a storm, guys, not an asteroid. You should have planned for that. Secon exits, Plan B, whatever! I have seen them all...

Prior planning prevents poor performance ... my father always said that to me!
Labels: Telecom

FRIDAY, JUNE 29, 2012

KEEN INSIGHT INTO THE OBVIOUS

The ACA decision has the quote (from Mankiw sans comment) regarding economists:

To an economist, perhaps, there is no difference between activity and inactivity; both have measurable economic effects on commerce. But the distinction between doing something and doing nothing would not have been lost on the Framers, who were "practical statesmen," not metaphysical philosophers.

Brilliant! And so true.....
Labels: Health Care, Law

THURSDAY, JUNE 28, 2012

LOGIC AND ACA

Down the rabbit hole we go. A tax, no there will be no tax.

Now the Times has comments worth a comment:

In the two years since the AHCA passed, My family has saved over 2000.00. My son, 24 has remained on my policy (I had been paying 400 a month for his insurance as he began his career.) My mother's drug bill dropped by several hundred dollars.

Now I can feel comfortable that my children, both who have had earlier bouts with respiratory illness but seem fine now, will not have to be saddled with high premiums or exclusions for pre-existing conditions.

I can feel comfortable that people I come into contact with who haven't had insurance will now be able to afford it.

Perhaps this reader will tell me who is paying for this? They are apparently clueless on this issue. Health Care is not free, that is the point. When some person makes a comment like this it is clear to me that they have not a single idea that there are consequences. Even in Aristotle's day we

knew every action had a reaction, in fact for 2,000 years that was the basis of the theories of motion, not some force at a distance. Somehow or other this people have a Newtonian idea that there is some force field of zero costs that enables all of this.

Every comment the above makes has a consequence, a cost, and yet the writer is totally above reality in never recognizing them.

At the other extreme as I had said some 3+ years ago as this disaster was brewing, Government mandates must carries, services few use and many abuse, and we all pay. A sad day for America, few of us ever understand the costs side, too many live in the wonderland of Government gifts.
Labels: Health Care

ROUSSEAU AT 300

"Man is born free, and everywhere he is in chains."

I have always had mixed feelings about Rousseau. Today marks the 300th anniversary of his birth. I remeber spending quite a bit of time in Annecy on the lake in Savoy, visiting his old haunts.

Here was a man who thought we humans perfect until destroyed by society and a man who believed truly in the ideal of a social contract. He was a man also estranged from time to time from his peers but a man held up by many. In ways a counterpart of Voltaire and yet distant from him as well.

His works may seem strange to many Americans today but to the "intellectuals" of the mid 18th century they caused bells to ring.

Consider his words:

The most ancient of all societies, and the only one that is natural, is the family: and even so the children remain attached to the father only so long as they need him for their preservation. As soon as this need ceases, the natural bond is dissolved. The children, released from the obedience they owed to the father, and the father, released from the care he owed his children, return equally to independence. If they remain united, they continue so no longer naturally, but voluntarily; and the family itself is then maintained only by convention.

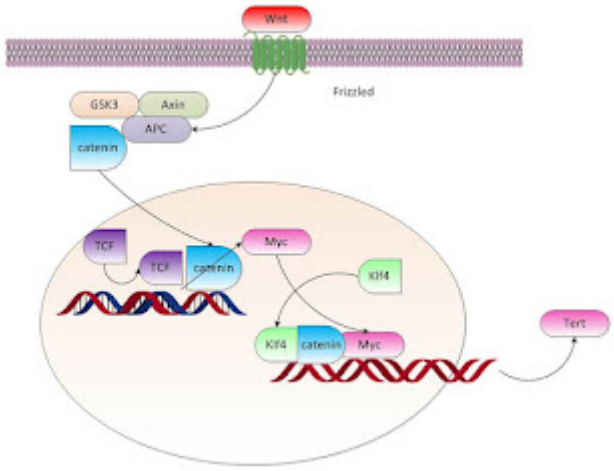
Strange is it not for he was the one who abandoned his own children. But read deeper, does he justify this action, is it not now a natural progression?

After these 300 years, one should at least reflect briefly on what this man meant to us today. On the one hand the Progressives and their view of a social contract, on the other, the Individualists and their ideal of the independence of man.
Labels: Commentary, Political Analysis

WEDNESDAY, JUNE 27, 2012

WNT AND TERT SIGNALING

Signaling pathways in the cells have been a major focus on study for the past decade or so. The focus generally has been on what protein or gene influences what other protein or gene. A recent article in Science presents some interesting work on Wnt and TERT.



Wnt is an extra cellular signaling protein and it attaches to Frizlled a receptor and sets off a cascade that moves B catenin into the nucleus and generates Myc which is a transcription protein with together with catenin and other transcription proteins generates Tert from TERT.

To quote from NCBI:

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.

As the Science article states:

Maintaining the length of telomere, the ends of chromosomes, is essential for all cells that divide many times. The enzyme telomerase lengthens these ends, counterbalancing their shortening that occurs each time chromosomes are copied. Telomerase is essential for cell viability, and loss of its function from the loss of only one of two copies of the encoding gene can lead to the failure of stem cell renewal that is seen in premature aging conditions such as dyskeratosis congenita, aplastic anemia, and pulmonary fibrosis. Conversely, telomerase activity is increased in many cancers and may be required for cancer cells to maintain their telomere length...

They continue is a rather interesting wording:

Because of the importance of telomerase expression, the signaling pathways that control TERT transcription have been extensively studied. Remarkably, many different transcription factors,

including c-Myc, Sp1, nuclear factor of activated T cells (NFAT), activating protein 2B, nuclear factor κB (NF-κB), Myb, activating transcription factor, nuclear factor 1 (NF1), and the estrogen receptor (ER), bind to the 330–base pair minimal TERT promoter and regulate transcription. In addition, a number of negative regulators bind the TERT promoter, including CTCF, elongation factor 2, p53, Ets, Mad1, Men1, and Wt1. Adding β-catenin and Klf4 to the many regulators that bind the TERT promoter is like adding one more guest to a crowded table at a dinner party.

They conclude:

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 fi nding 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.

The observation of the inter-cellular signalling with Wnt and its control over TERT and the telomere process is quite interesting. This may be an interesting way to incorporate many of the Turing models we have been discussing as well.

Labels: Cancer

MONITORING CABLE DATA

The NY Times has an article regarding the intent by cable companies to charge for usage. The state:

Here in South Texas, Time Warner Cable customers have been given the online equivalent of a scale in the bathroom, a "usage tracker" that adds up all the household's Facebooking and YouTubing. Customers who sign up for a light plan of 5 gigabytes of broadband — that's the equivalent of two high-definition movie downloads — are rewarded with a $5 discount each month if they don't go over. If they do, they pay $1 for every additional gigabyte.

then continue:

Usage-based billing is seen by some as a fairer alternative to broadband caps, a term most closely associated with Comcast, which had been enforcing a limit of 250 gigabytes per Internet customer per month. Although only a small minority of customers ever exceeded the cap, it became a lightning rod for competitors like Netflix, which accused Comcast of unfairly favoring its own services.

Now a bit of bona fides. I was COO of NYNEX Mobile, now Verizon, and SVP at Warner Cable, then Warner AMEX. I thus have some modicum of knowledge. Also as the CEO and founder of central and eastern Europe's first full fiber network I understand Internet backbone.

Unlike many of the younger generation I went thru these wars before.

My observations:

1. Billing is a total nightmare. Really. It costs more than anything you hope to recover. Really. Been there done that! Why? Because customers complain and seek remedies for calls not made, bytes not used. You have to be a complete moron, I will tell you how I really feel later, to think you will win this one. Average work here. Yes, some people use nothing, lots frankly, you win, a few are hogs, you lose. So figure out what works and you will never get a complaint, or a law suit!

2. What is the cost? Zero now, almost. It does not cost much anymore, even if you are not a Tier 1 Internet backbone carrier, which all of these guys are any how. Are you just greedy?

3. The real and only reason is to establish a barrier to entry to competitors. Yes, the cable guys want to control content, that is where the money is. This is their way to do that. It is a pre-emptive strike. Perhaps there are still anti-trust laws, like bundling and the like.

The Times missed the point. The FCC is clueless on this as is Justice. It must become a total mess before anyone acts. Just watch.

But wait, the bandwidth on wireless is exploding....

Labels: CATV

TUESDAY, JUNE 26, 2012

WHAT IS IN A NAME

I have difficulty in decoding the usage of names. Let me give several examples:

1. When back in a hospital I get called Dr. McGarty no matter what, even though I am not licensed to practice Medicine. A couple of years ago when back at the Brigham this was pandemic. For a while I thought I was in a 1950s movie of Dr Kildare.

2. In a medical specialists office I am called Dr. McGarty by the staff and depending on how well I know the specialist it is Terry or Dr McGarty.

3. In upscale professional settings such as a good law firm it is Mr. McGarty.

4. By anyone under 40 it is Terrence if they have no clue who I am. Now I never use Terrence other than in a legal context, for after all it is my first name.

5. In my local doc's office, nice local guy, his staff calls me Terrence. As if I and all the other

patients were pets, Spotty, Rover, etc. I remember my first copy of Harrison's I think the 5th edition, used, the first chapter was on how to greet patients. "Mr Jones" or "Mrs Smith", well before Gloria Steinham. One demonstrated respect, and perhaps a professional approach.

6. At a trial if one wants to denigrate a witness one calls them by their first name. Old trick.

7. But what has happened to the younger set? Answer, teachers. They were the one's who established the code of human interaction, and well they went down the drain. In an academic setting it was and may still be at better institutions Prof. McGarty etc. Yet at low level institutions, such as my local Community College, it was Terrence.

So what is in a name? It tells you the "class" of the user. Yes, class, it is like the use of "huh" or "uh" or "Um". Animal grunts, resulting from the collapse of our primary and secondary educations system. Do we have problems, yes indeed, and it begins with manners.

Labels: Commentary

SATURDAY, JUNE 23, 2012

TURING AT 100

The NY Times has a piece commemorating Turing's 100th birthday anniversary today. Despite Turing's work on computers and codes, in the long run it may be one of his last papers published in August 1952, entitled (he died June 7, 1954):

The Chemical Basis of Morphogenesis, Phil Trans Royal Society London pp 37-72, 1952

He states in the Abstract:

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system.

The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on Hydra and or whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading.

Frankly the paper has lasting insight which may surface again as we examine metastatic processes and intra/extra cellular signalling.

It should be noted that the pattern in the above Hemerocallis can be explained by Turing's work. For those who understand the wave equation with a nonlinear constraint then we see two waves of red, one in the center and one at the edge (see my paper on Turing coloring). It can likewise be argued that the flow of inter-cellular ligands in metastatic cancers follow a similar model (see my White Paper).

One can only imagine what would have happened if he had gotten further with the Watson and Crick paper, dated April 25, 1953.
Labels: Commentary

FRIDAY, JUNE 22, 2012

LKB1 AND MELANOMA

LKB1 has been demonstrated to be the underlying control element in Peutz-Jeghers syndrome, a proliferative melanocytic genetically dominant disorder. It controls certain pathways and as a result can be considered as a candidate in the development and progression of melanoma. Generally LKB1 is a gene whose protein stabilizes the growth and location of melanocytes. Understanding its impact in Peutz-Jeghers allows one to examine what happens when its function is suppressed in melanoma. Albeit not an initiator in the process, its aberration in a melanocyte argues for movement and loss of control.

In a recent paper by Liu et al the authors examine this premise and conclude that loss of LKB1 is significant especially in metastatic evolution. As Liu et al state:

Germline mutations in LKB1 (STK11) are associated with the Peutz-Jeghers syndrome (PJS), which includes aberrant mucocutaneous pigmentation, and somatic LKB1 mutations occur in 10% of cutaneous melanoma. By somatically inactivating Lkb1 with K-Ras activation (±p53 loss) in murine melanocytes, we observed variably pigmented and highly metastatic melanoma with 100% penetrance. LKB1 deficiency resulted in increased phosphorylation of the SRC family kinase (SFK) YES, increased expression of WNT target genes, and expansion of a $CD24^+$ cell population, which showed increased metastatic behavior in vitro and in vivo relative to isogenic $CD24^-$ cells. ***These results suggest that LKB1 inactivation in the context of RAS activation facilitates metastasis by inducing an SFK-dependent expansion of a prometastatic, $CD24^+$ tumor subpopulation.***

Earlier work by Zheng et al noted:

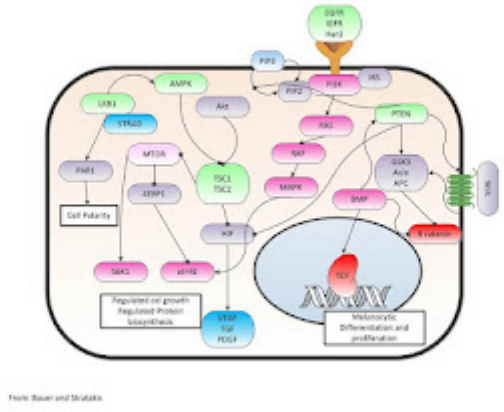
The LKB1-AMPK signaling pathway serves as a critical cellular sensor coupling energy homeostasis to cell growth, proliferation, and survival. However, how tumor cells suppress this signaling pathway to gain growth advantage under conditions of energy stress is largely unknown.

Here, we show that AMPK activation is suppressed in melanoma cells with the B-RAF V600E mutation and that downregulation of B-RAF signaling activates AMPK. We find that in these cells LKB1 is phosphorylated by ERK and Rsk, two kinases downstream of B-RAF, and that this phosphorylation compromises the ability of LKB1 to bind and activate AMPK. Furthermore, expression of a phosphorylation-deficient mutant of LKB1 allows activation of AMPK and inhibits melanoma cell proliferation and anchorage-independent cell growth.

Our findings provide a molecular linkage between the LKB1-AMPK and the RAF-MEK-ERK pathways and suggest that suppression of LKB1 function by B-RAF V600E plays an important role in B-RAF V600E-driven tumorigenesis.

Thus Zheng et al putatively identified these two pathways as sources for melanoma development. Liu et al appear to have extended this to metastasis.

Now in a paper by Bauer and Stratakis the authors provide an excellent overview of the controlling pathways. We provide a revised version of their pathway controls in a normal melanocyte below.



The LKB1 gene, also called STK11, which encodes a member of the serine/threonine kinase, regulates cell polarity and functions as a tumour suppressor. This is clearly demonstrated in the above.

Now Liu et al state regarding this pathway model:

Two independent pathways appear to be critically important in regulating cell growth in response to nutrient supply and mitogenic stimulation:

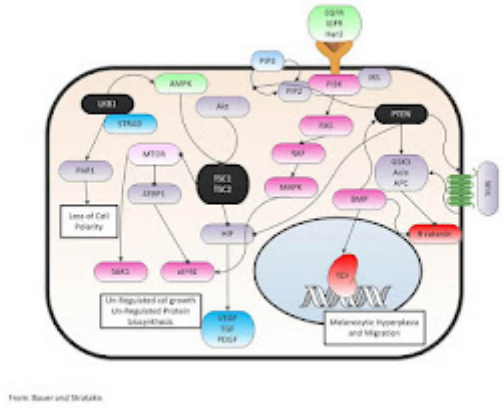
(i) the PKA/PRKAR1A-LKB1 tumour suppressor protein pathway, acting via AMPK, and

(ii) the PI3K/AKT pathway.

Recent evidence suggests that the tumour suppressor gene complex, TSC1/TSC2, orchestrates the signal from both pathways to the downstream target, mTOR, which in turn regulates the ribosomal protein S6 and 4EBP-1, a repressor of the translational initiation factor eIF4E. In this model, at times of nutrient stress LKB1/AMPK activation of the TSC1/TSC2 complex results in inhibition of mTOR and a decrease in protein synthesis. Under stimulation of mitogenic pathways, PI3K phosphorylates PIP2 to PIP3 resulting in recruitment of AKT to the membrane where it is activated by PDK1. Activated AKT inhibits the TSC1/TSC2 tumour suppressor complex leading to increased mTOR activity. In the later pathway, PTEN antagonises PIP3 action through dephosphorylation, and thus provides an ‘‘off’’ switch for regulating mitogenic pathway induced cellular growth and proliferation.

Cross talk of several other pathways appears to play important regulatory roles in the lentiginoses syndromes to include the Ras/MAPK pathway in the regulation of translation, the LKB1 pathway in cellular polarity, the AKT pathway (as well as the TSC1/TSC2 complex) in the regulation of the Wnt/GSK3b/b-Cat pathway, and the BMP pathway in the regulation of PTEN (see text for further discussion). Lastly, both PTEN and mTOR appear to have negative regulatory effects on VEGF through loss of stabilisation of the hypoxia inducible transcription factor 1 (HIF1).

When LKB1 is inactivated we have the following changes observed:



These models or Bauer and Stratakis are compelling and establish a paradigm which the work of Liu et al can be considered.

Let us go back to LKB1 and its function. From NLM database we have[1]:

LKB1 is a primary upstream kinase of adenine monophosphate-activated protein kinase (AMPK), a necessary element in cell metabolism that is required for maintaining energy homeostasis. It is now clear that LKB1 exerts its growth suppressing effects by activating a group of other ~14 kinases, comprising AMPK and AMPK-related kinases.

Activation of AMPK by LKB1 suppresses growth and proliferation when energy and nutrient levels are scarce. Activation of AMPK-related kinases by LKB1 plays vital roles maintaining cell polarity thereby inhibiting inappropriate expansion of tumour cells. A picture from current research is emerging that loss of LKB1 leads to disorganization of cell polarity and facilitates tumour growth under energetically unfavorable conditions. Also it is known as PJS; LKB1; hLKB1.

This gene, which encodes a member of the serine/threonine kinase family, regulates cell polarity and functions as a tumor suppressor. Mutations in this gene have been associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by the growth of polyps in the gastrointestinal tract, pigmented macules on the skin and mouth, and other neoplasms. Alternate transcriptional splice variants of this gene have been observed but have not been thoroughly characterized.

From the results of Shaw et al we have[2]:

[1] http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=retrieve&dopt=default&rn=1&list_uids=6794

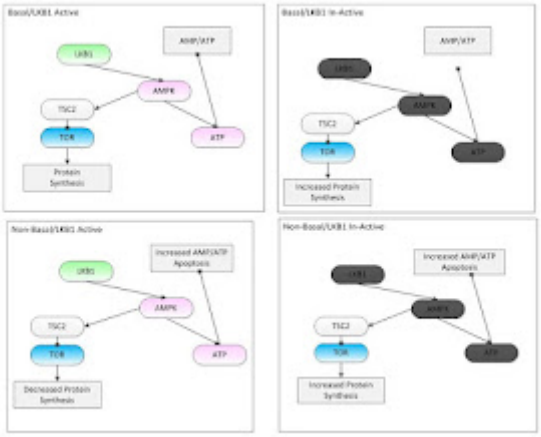
[2] http://www.ncbi.nlm.nih.gov/pubmed/14985505

AMP-activated protein kinase (AMPK) is a highly conserved sensor of cellular energy status found in all eukaryotic cells. AMPK is activated by stimuli that increase the cellular AMP/ATP ratio. Essential to activation of AMPK is its phosphorylation at Thr-172 by an upstream kinase, AMPKK, whose identity in mammalian cells has remained elusive.

Here we present biochemical and genetic evidence indicating that the LKB1 serine/threonine kinase, the gene inactivated in the Peutz-Jeghers familial cancer syndrome, is the dominant regulator of AMPK activation in several mammalian cell types. We show that LKB1 directly phosphorylates Thr-172 of AMPKalpha in vitro and activates its kinase activity.

LKB1-deficient murine embryonic fibroblasts show nearly complete loss of Thr-172 phosphorylation and downstream AMPK signaling in response to a variety of stimuli that activate AMPK. Reintroduction of WT, but not kinase-dead, LKB1 into these cells restores AMPK activity. Furthermore, we show that LKB1 plays a biologically significant role in this pathway, because LKB1-deficient cells are hypersensitive to apoptosis induced by energy stress.

On the basis of these results, we propose a model to explain the apparent paradox that LKB1 is a tumor suppressor, yet cells lacking LKB1 are resistant to cell transformation by conventional oncogenes and are sensitive to killing in response to agents that elevate AMP. The role of LKB1/AMPK in the survival of a subset of genetically defined tumor cells may provide opportunities for cancer therapeutics.
Also Shaw et al demonstrate several ways in which LKB1 can function when activated in vivo from either a basal or non-basal state. The description can be shown in the following Figure:



Shaw et al describe the above as follows:

Model for LKB1 as a sensor of low energy and negative regulator of tumorigenesis and apoptosis. Under basal conditions, LKB1 serves as a sensor of low energy, keeping ATP-consuming processes including protein synthesis in check via AMPK phosphorylation of TSC2.

In response to stresses such as low glucose, hypoxia, nutrient deprivation, or mitochondrial poisons, LKB1 phosphorylates AMPK, which shuts off ATP-consuming processes and up-regulates ATP production to offset the elevated AMP/ATP ratio. This activity prevents the cells

from going into apoptosis in response to elevated AMP. In LKB1-deficient cells, under some basal conditions, there may be increases in TOR signaling due to the lack of TSC2 phosphorylation by AMPK, resulting in increased growth or tumorigenic potential. In response to further increases in intracellular AMP, these cells have no mechanism to offset the elevated AMP and go straight into apoptosis.

However, although this is an interesting and compelling description of the metastatic driving factors, there are a multiple set of issues still outstanding:

1. Metastatic behavior implies the ability of the malignant melanocyte to migrate at will within the body. Movement of the melanocyte requires breaking of the E cadherin bonds with the adjacent keratinocytes. Thus is there a sequence of genetic changes and how does this putative mechanism relate to that of the E cadherin mechanism.

As Baas et al state:

A second prominent aspect of polarized simple epithelia is the presence of junctional complexes at the apical boundaries between neighboring cells. These junctions form an impenetrable seal between cells and provide strength to the epithelial sheet by serving as anchoring sites for cytoskeletal elements including the brush border.

We found that LS174T cells do not express junctional proteins, such as ZO-1, and are homozygous mutant for E-cadherin. By contrast, DLD-1 cells are capable of forming tight junctions and adhesion junctions when grown to confluency and appear to express most junctional components already at low-cell density.

We determined the localization of the tight junction component ZO-1 and of the adherens junction protein p120 before and after activation of LKB1 in DLD-1-W5 cells grown at very low density.

2. LKB1 is a gene related to the control from decreased nutrients. However we have the angiogenesis issue related to the increased nutrition of malignant cells. However on the counter side we have the Warburg effect as a counter to normal metabolism, namely cancer cells are anaerobic metabolic systems. What is the balance between the two?

3. Is the LKB1 mutation one of random gene mutations or is it a direct consequence of other downstream mutations? Is perhaps this loss of LKB1 a result of some induced miRNA effect in vivo?

This is an interesting result and very much worth following.

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Labels: Cancer

TYPE 2 DIABETES, WEIGHT, GENES AND CAUSES

In a recent paper by Perry et al, ***Stratifying Type 2 Diabetes Cases by BMI Identifies Genetic Risk Variants in LAMA1 and Enrichment for Risk Variants in Lean Compared to Obese Cases***, the authors have performed a genome wide study identifying genes that a prevalent in non-obese versus obese Type 2 diabetics[1] (T2). We have argued previously that the predominant number of T2 cases is driven by obesity. The authors demonstrate non obese T2 and then through a genome wide analysis, GWA, identify the putative genes.

We summarize their results and we then present several questions regarding the usefulness of the results.

The authors start by stating:

Individuals with Type 2 diabetes (T2D) can present with variable clinical characteristics. It is well known that obesity is a major risk factor for type 2 diabetes, yet patients can vary considerably—there are many lean diabetes patients and many overweight people without diabetes. We hypothesized that the genetic predisposition to the disease may be different in lean (BMI<25 Kg/m^2) compared to obese cases (BMI≥30 Kg/m^2).

[1] http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1002741

Specifically, as lean T2D patients had lower risk than obese patients, they must have been more genetically susceptible. Using genetic data from multiple genome-wide association studies, we tested genetic markers across the genome in 2,112 lean type 2 diabetes cases (BMI<25 kg/m^2), 4,123 obese cases (BMI≥30 kg/m^2), and 54,412 healthy controls. We confirmed our results in an additional 2,881 lean cases, 8,702 obese cases, and 18,957 healthy controls.

Using these data we found differences in genetic enrichment between lean and obese cases, supporting our original hypothesis. We also searched for genetic variants that may be risk factors only in lean or obese patients and found two novel gene regions not previously reported in European individuals. These findings may influence future study design for type 2 diabetes and provide further insight into the biology of the disease.

They then continue:

Genome-wide association (GWA) studies have identified ~50 independent loci robustly associated with type 2 diabetes. These studies have highlighted new candidate pathways involved in the disease, identified overlap with monogenic forms of the disease, and provided genetic links with correlated phenotypes.

The GWA studies of type 2 diabetes have not so far provided a greatly improved understanding of the clinical heterogeneity of the disease. Type 2 diabetes cases vary appreciably in their clinical characteristics, particularly age of diagnosis and body mass index (BMI). There is also a group of patients who may present with evidence of an autoimmune component to their diabetes, but who are not insulin dependent. In contrast, the identification of the genetic component to monogenic forms of diabetes has often explained the clinical heterogeneity observed.

Previous studies have provided some evidence of genetic heterogeneity between non-obese and obese type 2 diabetic cases. For example, the variant with the strongest effect on type 2 diabetes risk, in TCF7L2*, has a stronger effect in non-obese cases (odds ratio = 1.53 [0.37–1.71] compared to obese cases (OR = 1.21 [1.09–1.35]). The effect of* FTO *variation on type 2 diabetes risk depends on how cases and controls are ascertained by BMI status, but this was expected given* FTO*'s known primary effect on BMI. In the most recent GWA studies of type 2 diabetes, risk variants tended to have stronger effects in non-obese compared to obese individuals – of 30 loci examined, 23 showed stronger associations in non-obese compared to obese individuals.*

The authors conclude:

In conclusion, we report associations with the LAMA1 and HMG20A (not previously associated at genome-wide significance in Europeans) gene regions with type 2 diabetes risk. We have demonstrated that lean diabetic cases are enriched for known type 2 diabetes risk alleles compared to obese cases. This enrichment is consistent with the observation that many of the variants with the strongest effects on diabetes are associated with reduced beta cell function [1]. At the opposite end of the spectrum, obese cases presumably need fewer diabetes risk variants to push them towards diabetes, as they are already under strain from the physiological impact of

obesity and insulin resistance. These data suggest a disease model where type 2 diabetes cases lie across a continuous distribution with regards to genetic/environmental risk, and betacell dysfunction versus insulin resistance aetiologies.

The conclusion is that lean or low BMI Pt with T2 has a genetic predisposition to the disorder. This is consistent with what we have been stating in our prior analyses but it fails to demonstrate what percent of the total population has such a genetic failure.

This report raises several questions:

1. Not apparent is the percent of Type 2 patients who have low BMI, <25, and the percent who have high, >30. Namely what is the incidence and prevalence of T2 in those groups? One would suspect based on generally available data that the percent of high BMI individuals having T2 is high and those with low BMI have a low percent incidence and prevalence.

2. With the genes identified in the GWA in the low BMI group, what is their function? Namely the authors should have explored the intra-cellular and intercellular pathways and their metabolic effects. Just have a gene present does not mean causality. Causality is an essential element. Presence is at best correlative.

3. There is the issue of somatic presence versus germline presence. Namely if the Pt with low BMI and gene variants, were these somatic, namely did they have this forever and if so why did they come down with T2 at some point. If not somatic, and germline then what process caused the gene mutation. What caused the gene variant? This is a key question. Also if somatic why did it take so long to present?

4. How do we define T2? I suspect the authors do so via an HbA1c measure. They seem to allude to such by taking measurements of HbA1c as well as 2 hour glucose as one would do in a classic glucose tolerance test using a 75g glucose bolus. However, I found it difficult to identify the specific definition used in the document itself.

5. Notwithstanding, there is the annoying mass balance equation, input-output=net accumulation! How do these genes change this? Do they result in lowered metabolic expenditures? But with low BMI this is not an issue. Thus are we looking at different T2 disease states? The low BMI T2 patient has excess blood glucose due to lower uptake? lower insulin secretion? Why? What do these genes do to achieve that abnormality?

We seem left with more questions than answers. This is often the case with excess data and no paradigms to validate them.

Reference

Perry, J., et al, Stratifying Type 2 Diabetes Cases by BMI Identifies Genetic Risk Variants in LAMA1 and Enrichment for Risk Variants in Lean Compared to Obese Cases, PLOS Genetics, May 2012 | Volume 8 | Issue 5 | e1002741.

Labels: Diabetes

THURSDAY, JUNE 21, 2012

IT IS A HORSE FOR PETE'S SAKE

The New Yorker has a piece which excoriates Mrs. Romney's horse. Now I am not a big horse fan, I did clean stables in New York City, got stiffed by the owner, I believe it was in 1956, St Patrick's day to be precise. The old man owner had us clean out stables in return for payment. When all done he told us we were paid by learning how to work. This was a critical life lesson, always have a contract and never trust someone you do not know. As I later dealt with many international deals I always remembered the stiffing dealt by the old man owner, a permanent limbic valence.

I also rode a bit when in New Mexico, north of Taos, great riding, and in Virginia, all western. But I do appreciate dressage and I was personally introduced to Mrs. Romney's horse this past week.

But like any sport it does take effort, expertise, dedication. Also one should remember that Bloomberg's daughter is also in the sport.

So why the uproar, from Colbert? To those uneducated I guess it looks funny. But one should remember that sixty years ago it was dominated by the US Army! Yes soldiers were the riders and the Government frequently the owner.

You see it was the cavalry which started this and when they moved to tanks then it was moved to those who could afford it. This is not an inexpensive sport. Riders, trainers, vets, stable hands, and the list goes on. But frankly the animals are magnificent.

But the New Yorker should remember, never get between a girl and her horse.
Labels: Politics

WEDNESDAY, JUNE 20, 2012

SOME OF THE WORST ROADS

Pennsylvania has some of the worst road maintenance practices in the world. Somehow they manage to take massive Interstate roads and close them to one lane on upgrades which are

heavily traveled by trucks. I experienced 2-3 hour delays on I78 the other day as I observed these trucks in single file down to 20-30 mph and blockages some 6-10 miles long. The wasted fuel, time, costs, and when one passes the blockage there is no one doing anything but there is a sign proclaiming this a shovel ready stimulus job! Three years later!

Then there is New Jersey. Five lane highways, and they are expanding the NJ Turnpike an additional 3 lanes in each direction. Hundreds of people and moving machines. No delays, the trucks are doing 70+. And no Stimulus sign.

Why the difference? Is Pennsylvania that incompetent. New Jersey seems to have managed this through some of the most incompetent Governors, and we have had quite a few. Why the difference?

MEDICARE COSTS AGAIN

Over the past few years I have examined in detail the costs of Medicare. The conclusion was simple, yes some people benefit, while others over pay by a significant amount.

One of the many economists I have been following details his analysis, weak as it is, and he fails as do most others by not examining the details; again engineers and economists.

He states:

I get the impression that many Americans believe Medicare is financed like Social Security. They know that a portion of payroll taxes goes to Social Security and a portion goes to Medicare. So they conclude workers are paying for Medicare benefits the same way they are paying for Social Security benefits.

That isn't remotely true, as new data from the Congressional Budget Office demonstrate. In 2010, payroll taxes covered a little more than a third of Medicare's costs. Beneficiary premiums (and some other earmarked receipts) covered about a seventh. General revenues (which include borrowing) covered the remainder, slightly more than half of total Medicare costs.

Last year I published a revised version of my White Paper after a discussion in the Washington Post. Details do mater. But I want to raise another issue.

1. Suppose a couple is married and files jointly. Assume both are over 65. Assume they make jointly $350,000 of income.

2. They pay 3% of the gross for Medicare or $10,500 of their salary.

3. They pay $100 per month plus $150 in addition per month due to their salary. Thus combined they pay $500.00 per month in addition to the Medicare tax. That is $6,000 per year.

4. Combined they pay $16,500 directly for their care. Yes they had paid into Medicare for 40+

years already but we put that aside.

5. They cost the system $11,000 each or a total of $22,000 pa.

6. Net they cost $5,500 which is attributed to a Medicare Fund, which they paid into.

7. Now if they are still working they most likely are still healthy and will probably stay that way thus they really cost nothing and they are penalized $16,500 pa!

This is a strange system but after all it was invented in Washington. And it will only get worse!
Labels: Health Care

CAMBRIDGE TO FOLLOW NEW YORK

The Harvard Crimson announced that the Mayor of Cambridge will try to get the city to limit soft drinks.

They state:

At Monday evening's City Council meeting, Mayor Henrietta J. Davis proposed a resolution to investigate the possibility of limiting the size of sodas and other sugary drinks in local restaurants.
"This is motivated from a concern about health and children's health," said Davis, who has served as co-chair of the Cambridge Healthy Children Task Force since 1990.

"All this positive work can only go so far when the environment is filled with two size servings of soda," Davis said.

The resolution recommends that the Cambridge Public Health Department examine whether or not a ban on large servings of soda would help to reduce obesity. In an emailed statement, the city's Chief Public Health Officer Claude-Alix Jacob wrote that the department would have a decision ready by the fall.

Davis noted the similarities between this resolution and New York City Mayor Michael Bloomberg's initiative to limit sodas over sixteen ounces, an act that has drawn accolades from Alec Baldwin and criticism from the New York State Restaurant Association, which labeled the act the "latest in a long list of anti-restaurant initiatives."

As we have explained with our previous discussion of the Bloomberg Rule, this adds costs but in reality has no effect. One suspects it is a "feel good" approach. Instead of one large soda they get six small ones.

As usual, the law of unintended consequences will follow through.
Labels: Health Care

TUESDAY, JUNE 19, 2012

THE EHR CONUNDRUM

I have written extensively on the EHR, electronic health record conundrum, over the past few years but the best description is given in a picture by a patient in this weeks JAMA.

The author states:

No one was more surprised than the physician himself. The drawing was unmistakable. It showed the artist—a 7-year-old girl—on the examining table. Her older sister was seated nearby in a chair, as was her mother, cradling her baby sister. The doctor sat staring at the computer, his back to the patient—and everyone else. All were smiling. The picture was carefully drawn with beautiful colors and details, and you couldn't miss the message. When he saw the drawing, the physician wrote a caption for it: "The economic stimulus bill has directed $20 billion to health care information technology, largely funding electronic medical record incentives. I wonder how much this technology will really cost?"

It is really worth a view of the picture. I have seen this in various modes:

1. A good friend and superb clinician well over 40 can now be seen asking questions while typing on his screen.

2. A dermatologist friend hired an additional staff person to create her records.

3. A group of residents spend their time looking at screens rather than going to patients.

4. A gerontologist scans his patients from the nurses station, never really looking in to even see if they are alive at a nursing home.

Osler would spin over in his grave. The culture of medicine is being lost. Once we actually looked at the urine and could even identify a disorder by its smell. That is unheard of today. One even uses an electronic stethoscope to record heart beats and use AI technology to seek out beat abnormalities.

That, I fear, is the risk with the EHR.
Labels: Electronic Medical Records, Health Care

WEDNESDAY, JUNE 13, 2012

BLOOMBERG AND FAT

There is an article in TNR defending Bloomberg's soda ban. As the author states:

The truth is that there's nothing inherently wrong with paternalistic government or, in the harsher, feminized shorthand of its detractors, the "nanny state." Parents and nannies can be good or bad. No adult likes to be told how to live his life, but most of us benefit from baby authoritarianism far more than we'd like to admit. The government doesn't want me talking on the phone while I drive? I can't say I've given that vice up completely, but fear of getting ticketed makes me do it a lot less than I used to, and I may live longer as a result. The government wants me eating less salt? I don't live in New York, but, when I heard Bloomberg was tightening the noose, I reexamined my attachment to sodium chloride and found it to be fairly weak. Bloomberg didn't want Hitchens to smoke? Hitchens, who died this past December of throat cancer, went to his grave believing his vices remained none of Bloomberg's business. But after being diagnosed in 2010, he conceded unsentimentally that he had long "been taunting the Reaper into taking a free scythe in my direction." If New York City regulations persuade some of his acolytes to give up cigarettes and thereby avoid his fate, don't let's consider his legacy tarnished.

Now the interesting fact is that Bloomberg is an engineer by training, as are the major heads of the Chinese Government. Now strangely this is like Chinese paternalism, controlling family size. However it is rather un-American, we Americans just don't like being told what to do. You see the vows of poverty, chastity and obedience are truly un-American. But perhaps we are developing the seven deadly sins; sloth, gluttony, envy etc.

But the real issue is as follows:

1. Excess calories cause obesity.

2. Obesity causes Type 2 Diabetes

3. Type 2 Diabetes causes kidney failure, blindness neurological disorders, heart failure, and the list goes on.

4. The sequellae to Type 2 Diabetes can be managed, albeit at a high cost and for an extended period of time.

5. Thus calories are a straight line to massive societal costs.

The question then who pays for this? That is the key point.

1. If we want total freedom then we must insist on allowing the costs to fall where they may. If you do not want to be told what to do then we, the tax payers, will not have any duty to care for you. Like that glutton in Monty Python, one more mint, and kaboom!

2. If we demand society, namely the taxpayer foot the bill for the gluttons, then we have free riders getting a benefit, or the rest of us incurring the liability. This is clearly an unjust situation. Jut Refer to Aristotle Nicomachaen Ethics.

3. However if we demand justice then those gluttons must pay if we allow freedom, namely a non-nanny state. The question then is how to get them to pay? Bloomberg denies this alternative and he wants to stop them.

4. The Bloomberg solution has costs. There will be costs to train, costs to comply, costs to report, and costs for failures, and costs to police. And yet the proposal totally fails to address the real problem, calorie intake. For the true problem, total calories, not soda, must be addressed in some other fashion. Further he focuses on a large soda not on the very product itself. The consumer can disintermediate, get several smaller one. This is a costly and unworkable solution, it will not solve the problem. In fact it is an arrogant solution, and lacking in true recognition of the problem.

5. How to solve the problem. Two ways, both economic. Tax input or tax output and use the funds to pay for the sequallae. It work well on cigarettes, mainly because it was tobacco. But here we have carbs, and their calories. So we can tax all carbs, or tax per excess BMI. Just a simple proposal, since we already have the IRS doing health care compliance, we can have them do weight compliance as well. Thus for example, we can pass a law that requires every person to present themselves at the IRS office for a weigh in once a year. Then for every pound over their maximum we charge then an additional, say, $100 per year. If your maximum weight is say 150 pounds and you weigh 200, you must pay an additional $5000 per year. Imagine, the deficit gone in just one year or less. However one could imagine morbidly obese IRS agents, kindred TSA types, weighing in all of us taxpayers.
Labels: Health Care

SUNDAY, JUNE 10, 2012

OBESITY

Remember:

Input Less Output = Net Accumulation

that is a tautology, and a law of nature. The NY Times has a long piece on obesity. It states:

The causes of obesity are everywhere. Societal factors play a big role: the lack of safe places to play, walk or bike; sedentary jobs; less time devoted to cooking and more eating out; bigger portion sizes in packaged and prepared food; and incessant marketing of junk foods that are high in calories. Sugar-sweetened drinks accounted for at least 20 percent of the increases in weight in the United States between 1977 and 2007, according to one study cited by the institute.

The causes of obesity dear reader are in yourself! Fifty years ago we walked a mile to school, a mile home for lunch, a sandwich, a mile back and then a mile back home at days end. Then I would deliver newspapers on a ten mile route with 123 customers spread all over hell and gone. There was no school lunch, no breakfast, and never had deserts. No money.

Then when running my companies in central Europe, Czech Republic, Greece, Poland, Russia, portions were small and deserts were unheard of.

The worst offender if the Department of Agriculture and its food programs. It is food for the porcine. We should dismantle the program totally. Let kids walk, let them bring their lunch or walk home. Exercise and limited lunches are key. And breakfast at school, just look at the calories of a typical DoA breakfast, it exceeds 1200 cal! That is 70% of the daily maximum intake just there. Then lunch, another 1200. No wonder we have problems, as with so much else, it is the Government!

The Times continues:

The institute says that a major cut in obesity rates will require multiple strategies on a population-wide scale. This will be even more challenging than the fight against smoking. But there isn't any choice if we want to protect the public's health, the strength of the economy and the government budget.

Nonsense. The solution is to just control yourself. Tax weight, tax carbs, and disband the DoA!
Labels: Health Care

THE ANNOYANCE OF FACTS

Kaiser has had an interview with a former Government bureaucrat who states:

If the whole law goes down, the death rate in the United States will go up beginning in 2014. Because we know that the number of uninsured people will not go down, it will go up, and that growth in the number of uninsured people increases the number of people who die, so it's pretty straightforward as far as I can tell. We'll also have enormous chaos in the delivery system, but how that will play out exactly is hard to know.

What is the basis of that statement. People will still be served, no one will be turned away. What will be the cause of this increase. In addition since the law has not yet fully gone into effect, how

can there be an increase based on no law if no law was in existence. I may be the Abelard of Health Care but his logic is empty!

He then continues:

As best as anyone can tell, the reaction to the health law has been founded in an extraordinary amount of misinformation about what's actually in it and what it will actually do. And it seems to me there's no better way of educating the public about what the law will do and what effects it will have than just actually proceeding to implement it. I think when people begin to see exchanges offering a range of subsidized insurance products, when they begin to see some of the other things that are happening and not happening as a result of the legislation, public opinion will catch up.

No perhaps I am not "anyone" but I did read each version and the last final one three times in detail as this blog demonstrates. It is a nightmare! I have repeatedly detailed line by line. And he has the gall to say that:

And it seems to me there's no better way of educating the public about what the law will do and what effects it will have than just actually proceeding to implement it.

We saw that same arrogant attitude from Congress. It is no wonder that people are so opposed. And also if obesity causes Type 2 Diabetes and if Type 2 Diabetes is the major cost element in health care cost explosions then perhaps the man would show by example and take off the weight to reduce the risk.
Labels: Health Care

AND I HAVE A BRIDGE FOR SALE

Today in the NY Times Romer is giving out advice again. But remember it is the very same Romer whose projections on unemployment we have been tracking for almost the past four years, never even close!

I agree that we need more effective fiscal and housing policies. But neither is likely to happen, at least not before the presidential election. As a result, the Fed is the only plausible source of immediate help for the American economy. It was set up as an independent body precisely so that somebody can do what's right when politicians can't or won't.

Then she suggests:

After the Fed has pushed interest rates down to zero, its main remaining tool is communications. It can affect expectations of future growth and inflation, which can have powerful effects on consumer spending and business investment today. But to have a big impact, the monetary actions need to be bold — and pursued with gusto. In an earlier column, I discussed one of economists' favorite examples of such a policy: setting a target for the path of nominal gross domestic product.

If the Fed doesn't want to do something as drastic as adopting a new operating procedure, it could at least make any smaller actions it takes more effective. The previous rounds of quantitative easing may have done little to improve expectations because their size and duration were limited in advance. If the Fed does another round, it should leave the overall size and end date unspecified. Or, better yet, the ultimate scale and timing could be tied to the goals the Fed wants to achieve.

Frankly leadership is totally lacking, across the board. It appears that the folks in DC are totally clueless but that perhaps is not totally true. We have shown for four years that the FED has just pumped up the banks and then allowed then to continue to play with money mortgaged on our grandchildren's future. Then we also watch as Fiscal policy runs amok, again total lack of leadership.

Currently the FED is just an observer.A nice place to sit and drink coffee and watch others mess things up. But following the above somewhat vague suggestions based on her track record, please!

Labels: Economics

SATURDAY, JUNE 9, 2012

COLUMBANUS AND THE FIRST INDIVIDUALIST

Columbanus was somewhat of a unique individual amongst those at the end of Roman Empire, is such an end can be stretched to the beginning of the seventh century. He stands out for a multitude of reasons that recent authors have noted. Within the past two years three biographies of the wandering Irish monk have been written and they each have certain positive attributes. I review each accordingly. The three books are those by Tristram [[ASIN:1856076865 Columbanus: The earliest voice of Christian Ireland]], Reynolds [[ASIN:0321338898 Columbanus: Light on the Early Middle Ages (Library of World Biography Series)]] and Richards [[ASIN:1845401905 Columbanus]]. I will review each in turn but there is some commonality I shall include in each.

Reynolds has written a splendid work on Columbanus. Of all that I have read his is clearly the best. It is clear, well written, and concise, covers all the points, lacks the risky speculation of others, and fills in the gaps of the world around Columbanus.

Chapter 2 is a summary of what his youth may have been like. There is a great deal available on early Ireland in this time but unlike other areas there were no real cities or centers of humanity, the country was highly disperse and the ruling class was fluid. In addition there was often war like interactions that had been an inherent part of the Irish culture and perhaps that also contributed to the temper we see arising in Columbanus.

Chapter 4 describes his entry into the Monastery. He goes from one at Cleenish on the north end of the Shannon onto Bangor the dominant one at the time. The author makes an excellent reference to the writings of Columbanus at this time on what was to become the Three Chapters

controversy. One of the key questions would be; how did the Irish perceive these issues, which were often weighted by Platonic understanding. For example did they have access to Plotinus and they clearly must have been fluent in Greek since many of these writings were in the original Greek. The author has a good discussion on pp 34-35. On p 37 there is a brief discussion on his leaving Bangor and going to Gaul. The details are brief.

In Chapter 5 the author makes a detailed discussion of the "white martyrdom" of leaving Ireland for good. However there is the potential forced return we see later and one may ask how these relate. Chapter 6 is a superb discussion of the Merovingians. The author has done a great job in a few pages of laying out the players, the culture and the issues. However there is the knowing issue of just how well they managed to communicate. This is somewhat discussed out on pp 50-51. Namely the Irish had Latin, as did the Merovingians, but the pronunciation and localisms were significant. It is never clear if Columbanus managed to develop a proficiency in the native Frank language, itself with significant regional variants. On p. 50 when Columbanus enters the land of the Franks one wonders about the communications. Irish was not spoken in the Frank territory nor does it appear that the Irish spoke the Frankish tongue. Latin was a lingua franca but pronunciation and dialects would yet have prevailed. One need look no further than Gregory of Tours and his Latin, a highly clumsy and fragmented Latin, nowhere Ciceronian. Likewise the Latin of Gregory of Rome, the Bishop of Rome, was simple but an amalgam of Roman political style of the late sixth century.

Chapter 7 discusses the battle with the bishops. The author does a superb job in this area. The Irish were egalitarian. They were the first individualists. As such they did not see any reason to be managed by bishops. This would be an ongoing battle for Columbanus. Chapter 8 is a discussion of the miracles. Frankly the discussion of Columbanus and the bears is always delightful but these in many ways is classic for what at the time were people considered saints.

Chapter 9 is quite interesting for it brings Columbanus to the Lombards in and around Milan and to Bobbio his final monastery. Here there are many issues brought up by the author. The Lombards were Arian, namely Christ was from God the Father, not another personhood. Second Columbanus as noted on p 88 he notes "the Irish valued a man's principles more than his position" was in essence the central tenet of individualism. He was not a subject but a person. Further the author states, "Columbanus suggested disobedience if the pope were in error" is noted by the authors as a basis of what one was to see in the Reformation. One could suggest likewise it was also the individualistic nature of the Irish, again one of the only countries NOT occupied by Rome.

There are a few weaknesses, in my opinion.

First, the bibliography is written in a manner which is nearly impossible to read. All references are combined in a single paragraph. Whether this is the author, the publisher, or the editor it is truly a poor and ineffective choice.

Second and this is a question of intent, the book is almost an academic treatise, yet there are no references to sources.

Third and this is a significant issue there are no direct quotes from Columbanus. Many of his works are readily available and hearing his voice would have been useful. Perhaps a new translation would have merit here however.

Fourth, it would have been quite helpful to have contained some of the dialog between Gregory and Columbanus. I understand the problem, namely the Latin is the original, and translations are often poor, but a key point of insight would have been a better understanding of that dialog. Jonas may refer to it but it may very well be a powerful analysis on its own as a window to the new world of the individual versus the subject, the new world view versus the old world view.

As a general note amongst all of the books reviewed, the spelling of names is nowhere consistent. The problem is the multiplicity of sources. This of course is compounded when the spelling is from multiple languages as well.

Why is it useful to understand Columbanus? That in a sense is the underlying theme of each of the three books mentioned. It is especially critical to understand the period between 600-650 AD. As stated by Reynolds in his title, it was the Early Middle Ages, NOT the Dark Ages.

The reasons for better understanding Columbanus and this particular period in history are as follows:

1. Columbanus came from Ireland, and Ireland was never part of the Roman Empire. Thus his world view and that of all the free Irish at the time was not colored by Roman world views. They were never to that point a captive people, they were free and individuals. Thus they belonged to themselves and not to an Empire. Religion was personal.

2. Gregory came from Roman ruling class, a grandson of a Pope. Gregory was effectively at war with Constantinople and the Eastern Church. Gregory did not allegedly understand Greek, Columbanus did, and Gregory was in a sense the last Roman. The Empire was entrenched in Constantinople, and it looked eastward, worrying about Persia. Gregory looked westward, and saw opportunities in the Church in the tribes now living there.

3. Gregory is at odds with Columbanus and the Irish. Gregory was from a world of Groups, one belonged to Rome, one belonged to the Church, and one belonged to the Empire. One was never an individual. The clash was I believe at the heart of the battle between the two. The evidence of that is that Gregory sends an Italian, Augustine, to Canterbury to rule the Church, where logically the Church had a whole nation of educated scholars and devoted believers next door in Ireland. That act was the poke in the eye by Gregory against Columbanus and all Irish and was, in my opinion, the beginning of the battle between England and Ireland which continues to this day.

4. The Arian faith was that of a single God, devoid of the complexities placed and piled atop one another by the early Church Greek Fathers, including the Trinity. The Arians in many ways paralleled the same path seeing humanity in Jesus but not the complexity of Trinitarian Christology. In a sense there is a strong parallel between the Arian faith in a single God and the position of Christ as with the other single God beliefs that included Jesus. The relationship

therefore between Columbanus and the Lombards, his work with Theodelinda, the Lombard Queen, and the ability to build his final open monastery in Bobbio was a tribute to his ability to cross the line while maintaining his faith.

5. Columbanus thus represents the advent of the individual, in the context of both the State and the Church. Although respectful of the Bishop of Rome, he showed no humbling before him when it came to discussions of faith. He also showed no bowing before Kings and Queens, he understood how to deal with them. In many ways he was an example of a modern man. There were no national boundaries for Columbanus.

6. In conclusion, I argue that there were no Dark Ages, just a transition from a salve based Empire transitioned into a Middle Ages, which in many ways was a long progression into modern society. The Dark Ages is a term used oftentimes in ignorance. Gibbon talks of the Fall of Rome, was there also a Fall of Carthage? We do not see the Fall of Egypt, Greece, and Persia. Why just Rome? I would argue it was in tune with the British Empire and its world view. Here with Columbanus we have the Birth of the Individual, a single person who can cross lands, tribes, cultures, languages, religions, and talk to a Pope as an equal in thought.
Labels: Books

YOU CANNOT MAKE THIS UP

The Hill reports on the plan proposed by two left wing Congress people. It is akin to taking on more ballast when you have split your bottom open. Who in their right mind would ever think of this.

The Hill states:

Sen. Bernie Sanders (I-Vt.) and Rep. Elijah Cummings (D-Md.) on Thursday proposed a new tax on Wall Street trading that would raise more than $250 billion over 10 years in order to pay for a new plan to have the federal government offer dental health insurance coverage to millions of Americans.

The two members proposed legislation that would impose a "financial transactions" tax on equity trades that would collect $2.50 for every $10,000 traded, which would cover stock and bond trades. That language would reportedly raise an estimated $288 billion over 10 years, enough to cover the expected $25 billion per year cost of the new dental plan.

What frankly is basic dental care. Back in the 1950s false teeth were common. Pull out the old ones and glue in the new. Cheap, it worked. Since then we have fluoride, and caries have gone near to zero. Dentists are depending on old folks.

Are we expected to pay for implants? That can be $8,000 per tooth! Are these characters real. Why not keep spending until we are not just broke ... but well Greece, really. I remember when I took a friend from out of the US across the New Hampshire - Vermont border and told him to have passport and visa at the ready. Perhaps that was not a real joke.

This is why people look at Congress and ask if they have a clue!

Labels: Economy, Politics

THURSDAY, JUNE 7, 2012

COMMENTS BY FED CHAIRMAN

The FED Chairman spoke today regarding the economy. First the drags on the economy we all know:

However, some of the factors that have restrained the recovery persist. Notably, households and businesses still appear quite cautious about the economy. For example, according to surveys, households continue to rate their income prospects as relatively poor and do not expect economic conditions to improve significantly. Similarly, concerns about developments in Europe, U.S. fiscal policy, and the strength and sustainability of the recovery have left some firms hesitant to expand capacity.

The depressed housing market has also been an important drag on the recovery. Despite historically low mortgage rates and high levels of affordability, many prospective homebuyers cannot obtain mortgages, as lending standards have tightened and the creditworthiness of many potential borrowers has been impaired. At the same time, a large stock of vacant houses continues to limit incentives for the construction of new homes, and a substantial backlog of foreclosures will likely add further to the supply of vacant homes. However, a few encouraging signs in housing have appeared recently, including some pickup in sales and construction, improvements in homebuilder sentiment, and the apparent stabilization of home prices in some areas.

And he continued:

Even as fiscal policymakers address the urgent issue of fiscal sustainability, a second objective should be to avoid unnecessarily impeding the current economic recovery. Indeed, a severe tightening of fiscal policy at the beginning of next year that is built into current law--the so-called fiscal cliff--would, if allowed to occur, pose a significant threat to the recovery.

Moreover, uncertainty about the resolution of these fiscal issues could itself undermine business and household confidence.

Fortunately, avoiding the fiscal cliff and achieving long-term fiscal sustainability are fully compatible and mutually reinforcing objectives. Preventing a sudden and severe contraction in fiscal policy will support the transition back to full employment, which should aid long-term fiscal sustainability. At the same time, a credible fiscal plan to put the federal budget on a longer-run sustainable path could help keep longer-term interest rates low and improve household and business confidence, thereby supporting improved economic performance today.

A third objective for fiscal policy is to promote a stronger economy in the medium and long term through the careful design of tax policies and spending programs.

To the fullest extent possible, federal tax and spending policies should increase incentives to work and save, encourage investments in workforce skills, stimulate private capital formation, promote research and development, and provide necessary public infrastructure.

Although we cannot expect our economy to grow its way out of federal budget imbalances without significant adjustment in fiscal policies, a more productive economy will ease the tradeoffs faced by fiscal policymakers.

These are well known generalizations. Simply stated we are still in the tank and Congress and the current President must do something but not too much. The incentive comment is a truism. The alternative? Dis-incent this sector? There were no specifics here, no sharp end of the world warnings, and no look to what happens a la Europe.

There must be an adult somewhere who can lay down the warning that will activate the public response.
Labels: Economy

THURSDAY, JUNE 7, 2012

UNIONS

Now I came from a union family. My father and brother were in the electrical union, my uncle was a senior person in the firefighters union, all in New York. I saw many sides of unions. As The New Republic states:

No, the real underlying story is that unions are losing their institutional legitimacy in modern America. The problem isn't that most people hate unions. The problem for unions is that most people don't care about them, or think about them, at all.

In reality, truth be told, many people really do hate unions. I have seen union workers see themselves as set apart, anointed, owed, an worse. They take, do not understand from whom the take, they are often brutes, and are focused on just getting the most from the job, independent of what they do.

There clearly was once a time when unions served a purpose. But today with laws controlling every aspect of employment the need of a union is not only questionable but it has become a veritable drag on our economies.

This is especially true with public unions. I can see this especially in New Jersey where the benefits are extraordinary and the work done is often third rate at best.

The TNR continues:

When union membership peaked in the mid 1950s at about 35 percent, it was disproportionately weighted to the Northeast, the Midwest, and California. But that meant that in those regions—the most populous in the country—either a worker was in a union his/herself, had a family

member in a union, or, at least, had a friend or neighbor in a union. People, for better or worse, knew what unions did and understood them to be an almost ordinary part of the workings of democratic capitalism.

Most important, they knew, for better or worse, that unions had power. Sixty years ago, the UAW or the Mineworkers or the Steelworkers, not only deeply affected crucial sectors of an industrial economy, they also demanded respect from broader society—demands made manifest in the "political strikes" they organized, whether legally or not, to protest the issues of the day.

Yes we had family members, and if truth be told they did not benefit from the union, it was a closed shop world, it kept out competition, it drove shipping from New York, it drove the costs in Manhattan skyrocketing, it complicated everyone's life, and unions did have power. They were and are even more so today a collection of thugs.

The time of unions has come and gone. Yet they are a source of compelled funding of Democrats. Thus they like so many other remnants of the past will continue to be a drag on society.
Labels: Political Analysis

WEDNESDAY, JUNE 6, 2012

FUTURE OF HEALTH CARE

The NY Times announced a mega merger of hospitals in New York. They state:

The proposed merger would bring together NYU Langone Medical Center, a highly specialized academic medical center, and Continuum Health Partners, a network of several community-oriented hospitals, including Beth Israel and the two St. Luke's-Roosevelt campuses.
It would create one of the largest health care systems in New York City, one that would have immense market power under the new federal health care system, and put pressure on insurance companies, independent medical practices and even rival medical schools, which may have to scramble to find places to train their students.

The true challenge is to insurance companies since these mega providers can become their own insurers. Theoretically the overhead gets absorbed into the institution and again putatively it should be more efficient. But we know what happens with oligopolies, less efficiencies and more mega mergers.
Labels: Health Care

FACEBOOK AND VALUE

In an interesting piece by Steve Coll of New America states:

Facebook has made jarring mistakes as its leaders have learned what it means to run a profit-motivated political and public forum. In 2009, for example, the corporation exposed Iranian dissidents to danger by unilaterally changing privacy rules that allowed the Iranian authorities

to see the identities of activists' online friends. The error was corrected quickly, but in general, Facebook has encouraged its users to accept greater and greater losses of privacy. Zuckerberg believes the world will be better off if it adopts "radical transparency," as the journalist David Kirkpatrick put it in his book, "The Facebook Effect."

Zuckerberg's business model requires the trust and loyalty of his users so that he can make money from their participation, yet he must simultaneously stretch that trust by driving the site to maximize profits, including by selling users' personal information. The I.P.O. last week will exacerbate this tension: Facebook's huge valuation now puts pressure on the company's strategists to increase its revenue-per-user. That means more ads, more data mining, and more creative thinking about new ways to commercialize the personal, cultural, political, and even revolutionary activity of users.

There is something vaguely dystopian about oppressed peoples in Syria or Iran seeking dignity and liberation inside a corporate sovereign that is, for its part, creating great wealth for its founders and asserting control over its users.

Coll has some interesting reasons for laving Facebook. In my case I had been on Facebook quite early on, driven there by my MIT grad students. It was interesting. But about two years ago I saw a disturbing trend. Namely that many of my "friends" were acquaintances of my children and then grandchildren. They were making statements which perhaps humorous amongst their closed groups could negatively reflect upon me. I did not agree with their comments and in fact found them a bit sophomoric. I also found that I was getting to see parts of their lives which frankly I had no interest in. Thus with discretion being the greater part of valor, to quote from Henry IV Part 1, I withdrew.

But more importantly I asked what value this had. Google has substantial value. I find things, I get information, I keep current, and frankly I am infinitely more productive because of it. It creates true value. I saw none of that in Facebook. In fact Facebook was making decisions about me which I felt not only wrong but potentially injurious. It was at first interesting to see the comments, at the beginning, but I was soon overwhelmed about details that frankly went well beyond sound judgement.

For a business to have viability one must seek the value proposition, what is it doing for me, and at what cost? Facebook was of no value, in fact it was potentially a cost. Linkedin has "value" by tracking professionals, albeit of limited value. My life would not change if it went away. But Facebook could in my opinion have potantial harm, thus my leaving.

Coll's article is worth the read.He has great insight to this and it is worth the read. It does pose the same question albeit in different terms. Somehow this issue has never been raised in terms of Facebook's long term value. Time will tell.
Labels: Commentary

CBO TESTIMONY

The CBO Testimony before Congress today atsted:

First, it is not possible both to keep taxes at their historical average share of gross domestic product (GDP) and to keep the laws unchanged for Social Security, Medicare, and Medicaid.

Second, keeping federal deficits and debt no larger than what we project under current law would involve difficult policy trade-offs.

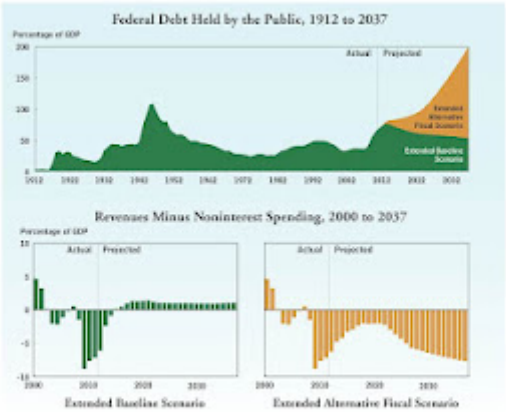
To be sure, the Congress might not enact those changes in law, or it might choose to allow more debt than would occur under current law or to reduce debt more quickly relative to GDP than would occur under current law. There are many possible combinations of policies that Congress might pursue depending on its policy goals, and CBO will make neither recommendations nor predictions about them. The point is simply that the path of debt under current law would still leave debt at a historically high level relative to GDP, and even achieving that path would require very large changes in current policies.

Clearly the issue of Medicare costs must be addressed.

Labels: Economy

TUESDAY, JUNE 5, 2012

CBO AND THE DEBT, STOP IT NOW



The CBO has just issued its report on the debt. It is chilling. They project a doubling of the debt, as a percent of GDP, exceeding 200%. Is anyone listening?

They state that the impact of this doubling of the debt will be:

Rising levels of debt would have other negative consequences beyond those estimated effects on output:

- *Greater debt would result in higher interest payments on that debt, which would eventually require higher taxes, a reduction in government benefits and services, or some combination of the two.*

- *Rising debt would increasingly restrict policymakers' ability to use tax and spending policies to respond to unexpected challenges, such as economic downturns or financial crises. As a result, the effects of such developments on the economy and people's well-being could be worse.*
- *Growing debt also would increase the probability of a sudden fiscal crisis, during which investors would lose confidence in the government's ability to manage its budget and the government would thereby lose its ability to borrow at affordable rates. Such a crisis would confront policymakers with extremely difficult choices. To restore investors' confidence, policymakers would probably need to enact spending cuts or tax increases more drastic and painful than those that would have been necessary had the adjustments come sooner.*

They argue that the guaranteed benefits such as health care will be a major driver. They state:

According to CBO's projections, if current laws remained in place, spending on the major federal health care programs alone would grow from more than 5 percent of GDP today to almost 10 percent in 2037 and would continue to increase thereafter.

Spending on Social Security is projected to rise much less sharply, from 5 percent of GDP today to more than 6 percent in 2030 and subsequent decades. Altogether, the aging of the population and the rising cost of health care would cause spending on the major health care programs and Social Security to grow from more than 10 percent of GDP today to almost 16 percent of GDP 25 years from now. That combined increase of more than 5 percentage points for such spending as a share of the economy is equivalent to about $850 billion today.

By comparison, spending on all of the federal government's programs and activities, excluding net outlays for interest, has averaged about 18.5 percent of GDP over the past 40 years.

If law-makers continued certain policies that have been in place for a number of years or modified some provisions of current law that might be difficult to sustain for a long period, the increase in spending on health care programs and Social Security would be even larger. Absent substantial increases in federal revenues, such growth in outlays would result in greater debt burdens than the United States has ever experienced.

Clearly many things must be done. Healthcare is an over riding burden. Two things must be done promptly. First increase the Medicare fees, by at least a full percent per payer, and increase Medicare age from 65 to 70 over the next decade. Second, focus on preventable disease such as Type 2 Diabetes by making the fatty pay! Since obesity is the cause of over 95% of Type 2 Diabetes and its sequellae then we must charge for those costs up front.

Otherwise the "giving away" "free"health care will result in a total economic collapse.
Labels: Economy

THE WEST AND CIVILIZATION

I recently saw some of Niall Ferguson's television series on his book. Now think I can see what this somewhat self promotion was meant to do, not for the BBC but PBS audience, namely in my opinion sell his book and make money, but frankly it was in my opinion filled with some many distortions in my opinion that one must wonder what the students walk away with.

Let me comment on but a few.

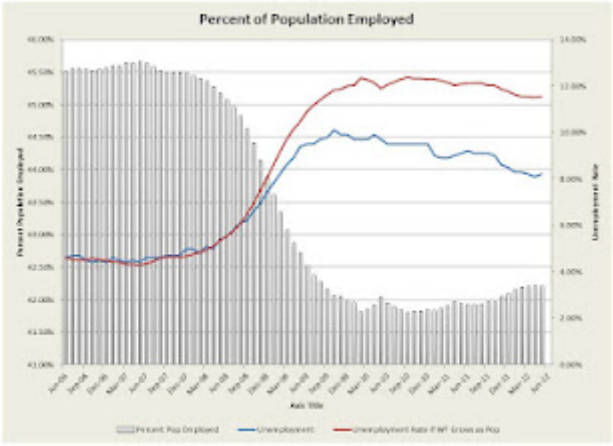
First the Protestant Work Ethic. Excuse me but did he ever hear of the Jews? What were they, chopped liver? They managed to add bundles to our civilization despite being whacked and hacked by everyone. Then the Catholics, that collection of loafers as far a Ferguson says. Dis he ever hear of the Penal Laws. The denied Catholics property, jobs, education, land, the right to vote or hold office, being in a profession, and work in any area competitive to a Protestant. One must likely be out of their "bloomin head" to ascribe anything but abject English Protestant hatred and inhuman cruelty to such actions.

Second, a forgotten or misplaced element of the West which was present from about 600 forward to today is the University. Yes, that very institution in which the good Professor seems to occupy space. The West had developed a center of learning open to anyone. It arguably can be dated back to about 600 with Columbanus, the Irish monk and his wandering scholars who established open institutes of education, for religions and lay folks, starting at Luxeuil and on to Bobbio. Here was taught languages, philosophy, and even crafts such as irrigation, water management, and agriculture. Then just after 1000 we have the formation of the great Universities at Paris, Oxford, Cambridge and the dozens of others, on grounds similar to Columbanus. Today we have in the West some of the best in the world and the envy of many outside the West. Somehow the good Professor seems to have missed this one.

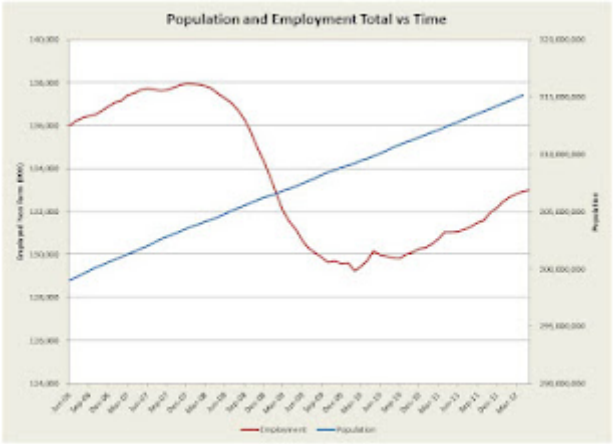
I am always suspect of ad hoc propiter hoc arguments from television based preachers of the Academy. Perhaps we should all be.
Labels: Academy, Commentary

FRIDAY, JUNE 1, 2012

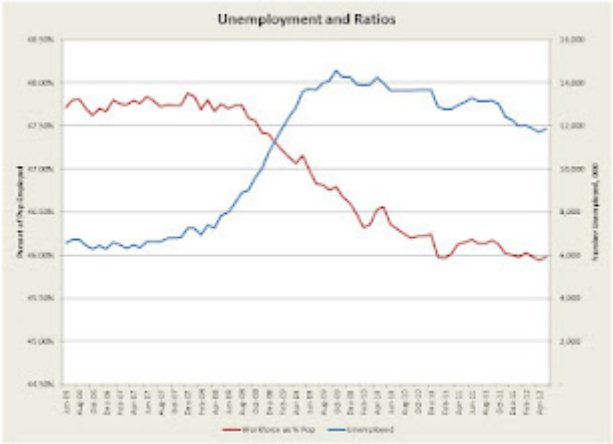
MORE DETAILS ON EMPLOYMENT



First, above, we see the total base of employment has shrunken, so that 8.2% is optimistic.



This point is made again in the above. The gap of the expanding employable base and those employed is increasing substantially.

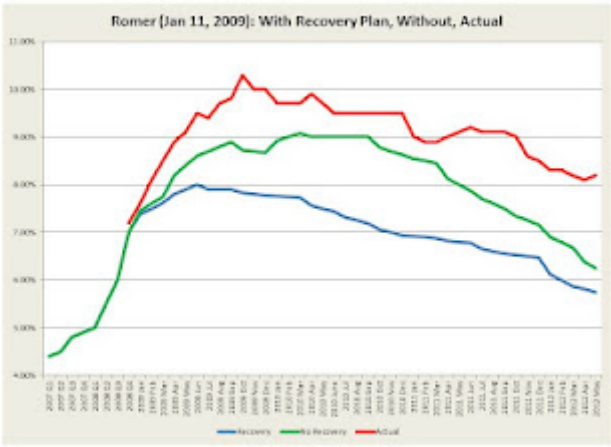


The above details this in another manner.

The above clearly shows the drop this past month and it demonstrates the approach of another Recession. What is critical to observe in the above is the employment gap, the net of jobs added less new potential employees added to the work force by growth. It was negative for May, that means job losses, net job losses. In fact over the tenure of the current Administration the net job increases is truly less than the net job losses. Some how the facts must get out there, we are collapsing our work force.
Labels: Economy

FRIDAY, JUNE 1, 2012

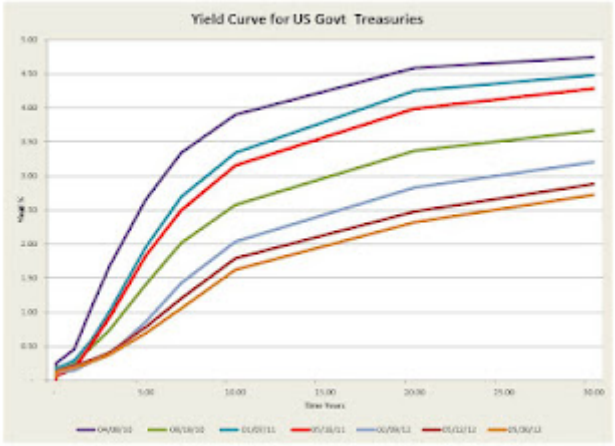
NO GOOD SIGNS ON HORIZON



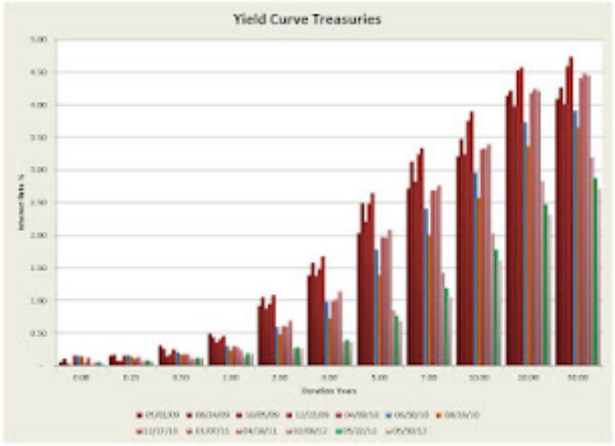
We are seeing increasing unemployment. I have not yet looked at all the data but this is no surprise. I suspect it will be revised upward as well. The divergence from Romer is amazing. I suspect based upon signs we are facing another Recession by year end.
Labels: Economy

WEDNESDAY, MAY 30, 2012

TREASURY SPREAD: GOING TO ZERO!



Today's spread is above, the lowest is over half a century. I wrote on this a week ago and now it has just gotten lower. Here is another view:



This is a problem because it implies a very low to negative growth rate world wide. Despite the fact that we are still facing significant inflation in food, clothing, autos, fuel. This will have a massive impact on such things as pension funds who have anticipated unrealistic returns, well in excess of 7%. The State and Local Pensions are now drastically underfunded with no potential for escape. That perhaps is the next economic bubble.
Labels: Economy

MONDAY, MAY 28, 2012

THE WRONG QUESTION

It appears that Becker is not in any way concerned about the excessive increase in College Tuition. Posner makes a similar argument and I defer comment on that until later.

He begins his argument with:

Student loans have increased the supply of young persons who go to college. In a competitive higher education market-which describes the American situation where thousands of colleges compete for students- a greater number of college students induces increases in tuition. However, the increased supply of places for college students moderates the increases in tuition.

Now this is a total nonsequitur. The increase in supply is really the result of "advertising" by Government and others to create a large pool of somewhat educated youth who can hopefully perform some useful function. For example, what good is a political science maj0or, none. Absolutely positively none. It can be said the same for an economics major, for as a "profession" they seem to all disagree with one another. Their field is more split than Greek theologians in the 4th century! Then how about a fine arts major, just where do we put them? You see it would be better to have trade schools, with electricians, plumbers, carpenters, and the like. You cannot outsource that, and there is a demand.

Now he continues:

Although students and their parents complain a lot about the rise in college tuition, since the early 1980s monetary and other benefits from college have risen even faster than tuition and other college costs. As a result, the rate of return on college education in the United States – benefits net of all costs- grew greatly during the past 30 years. The increased net return to college, despite the increase in tuition, explains why a larger, not smaller, fraction of young persons are going to college than did prior to the sustained rise in tuition.

Benefits? What benefits. In the 60s engineers were in high demand. Now they are sourced with foreign nationals, even in defense programs. The benefits are de minimis if at all. Educational

costs to starting salaries have exploded. In 1965 an engineer got $8.000-$10,000 per year salary, but tuition at MIT was $1,900. That was a 4:1 to 5:1 ratio. Now the starting may be $100,000 at the very best but tuition is $60,000. Not even 2:1! And that is for a real college educated person who can be put to work creating value. Not some English major who does not know where the bathroom is to be found. What is Becker basing his conclusions on. At least I have some facts.

Now the increase in costs are due to two factors; exploding Administrative costs and exploding maintenance costs.

Becker concludes with:

Young families with mortgages that exceed $100,000 under normal circumstances are not considered to be in dire economic straits, even though their homes can be taken if they fail to meet their mortgage payments, and they are only investing in more comfortable living arrangements. Young couples that contracted a similar level of debt when they were students have invested in raising their earning power, usually by a lot. So I find it difficult to comprehend why sizable mortgages are accepted while there are political and media outcries over comparable student loans that are based on usually highly productive investments in human capital.

First, one can monetize a property with a mortgage, if one was prudent. Namely the $100,000 debt on a $150,000 property can be sold and paid off. One cannot so readily monetize an education. Especially if it is in Liberal Arts. Who wants a History major, a Philosopher, and especially an Arts major. Students, and I suppose their families, have a duty to look into the cash flow potential of a job based upon an education. Following your dream is utter nonsense unless you accept the costs, and with Federal loan guarantees the costs are on the rest of us. So go follow your dream some where else.

So what can one say of the Becker piece.

First it has no basis in reasonable economic thought. People make decisions, or should, based upon level of investment, risk and return. Take for example chemists. The field is collapsing. We really do not need more, due to technology. But does a student understand that? In my recent experience the answer is no.

Second, if there is a benefit to society for educated and productive people, note I combined the two attributes as one, then society may thus seek to invest in that. That is yet to be proven.

Third, what of the ever expanding bubble in higher education? Is there a too big to fail mentality there as well. Does the taxpayer have a duty to keep say the University of California system afloat, why not let if collapse. If the price equals the cost then the demand will drop.

Fourth, should there be truth in advertising. We force food companies to include calories. Should we force Universities to include average lifetime earnings for each degree?

Somehow Becker seems to be justifying the unjustifiable.

The question is not what value is there in an education, but why does it cost so much! Universities have been allowed free reign, assuming someone else would take up the tab. The problem is like so many other profligate usurpers of the public trust, we the taxpayers will bear the cost. It ironically is that Quiet Generation, born before 1945, who paid their own way, then their children's and now their grandchildrens' way. The ones who are accused of getting too much Social Security and Medicare but who still work and pay into the system while taking what few pennies left to create a new generation of educated individuals. Those educated individuals may be able to then support the Baby Boomers who seem to be coming along now.
Labels: Academy, Economics

GENOMIC COMPLEXITY

There has been a great deal of work on genomic complexity of cancers and especially that of multiple somatic mutations in cancers.

As Berger et al state for prostate cancer:

We identified a median of 3,866 putative somatic base mutations (range: 3,192–5,865) per tumor; the estimated mean mutation frequency was 0.9 per megabase. This mutation rate is similar to that observed in acute myeloid leukemia and breast cancer but 7–15 fold lower than rates reported for small cell lung cancer and melanoma17–19. The mutation rate at CpG dinucleotides was more than 10-fold higher than at all other genomic positions. A median of 20 non-synonymous base mutations per sample were called within protein-coding genes. We also identified six high-confidence coding indels (4 deletions, 2 insertions) ranging from 1 to 9 base pairs (bp) in length, including a 2bp frameshift in the tumor suppressor gene, PTEN.

Similarly for melanoma the Nature discussion by Hayden states:

The team also confirmed some findings from earlier studies including the effect that sun exposure can have on the mutation rate of tumour DNA. Tumours from areas of the body that are not frequently exposed to sunlight had around 3 to 14 mutations every million base pairs, whereas one patient who was known to have had high levels of sun exposure had 111 mutations every million base pairs.

The relationship between sun exposure and mutation rates adds to the evidence for the role of sun exposure in melanoma development, says Laura Brockway-Lunardi, director of scientific programmes for the non-profit Melanoma Research Alliance in Washington DC, which helped to fund the work.

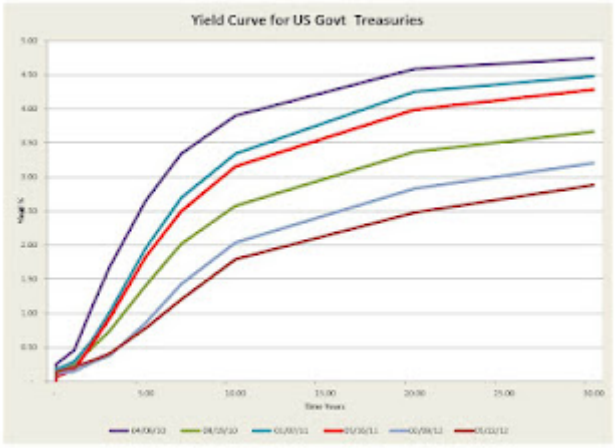
We also note that these mutations may or may not be related in some sequence or pathway. We would also not that for the melanoma mutations the 3-14 for non sunlight exposed and the 111 for sunlight exposed is significant and causal. However we have also argued that such might also be the case for backscatter X ray scanning as now used by the US Government to an excessive degree.
Labels: Cancer

MEMORIAL DAY 2012

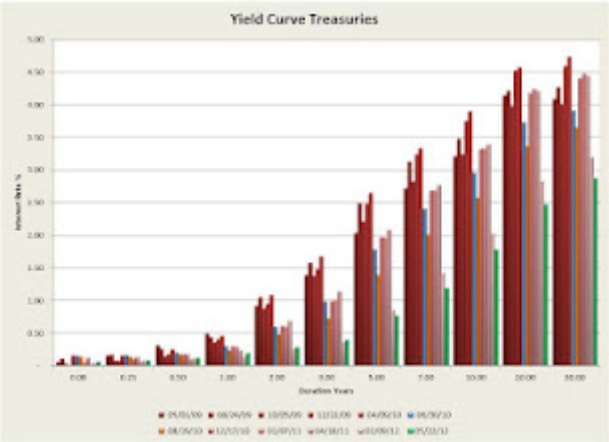
Normandy, grave by grave. In memory.
Labels: Commentary

WEDNESDAY, MAY 23, 2012

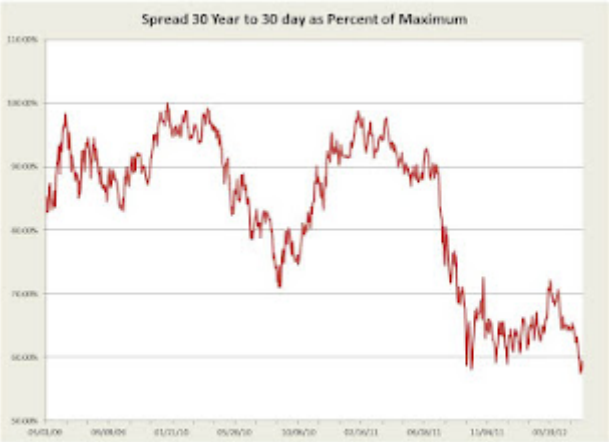
YIELD CURVE, MAY 2012



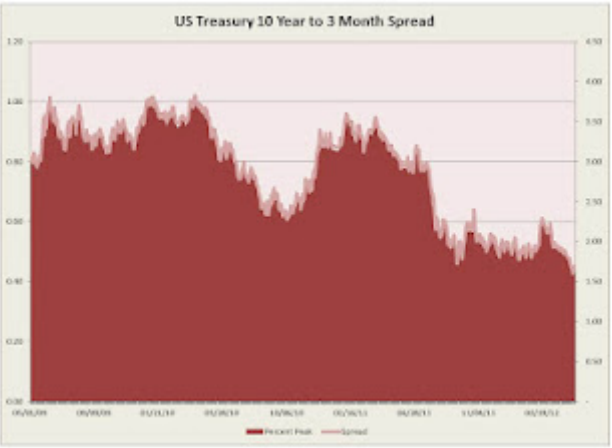
The above is the yield curve at selected dates over the past 2 years. The curve yesterday is one of the lowest ever. The drop in the 30 year is almost a factor of 2. The advantages are clearly to lower borrowing, if one can accomplish the task, but the second is the pressure downward on fixed investments and the taxing of those on fixed incomes.



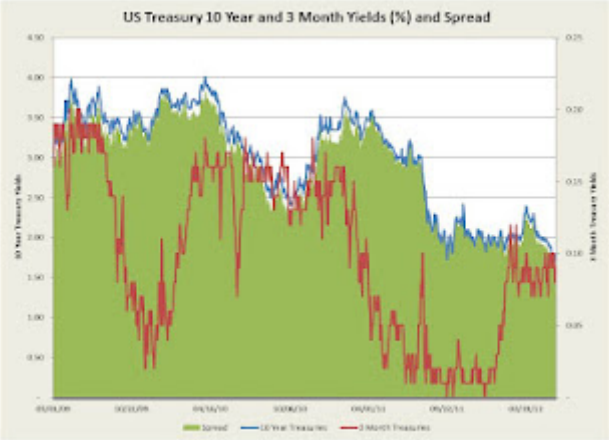
The above is another way to view it. Note how low we see the long term rates. Most likely driven by European fears. I suspect we may see another Recession before the Fall.



This is the 30 year to 30 day spread, the widest one would expect. It has reached an all time low!



This is the 10 year to 90 day spread, a typical metric, also at an all time low. The faith in any recovery has disappeared.



This is the same as above but we have combined them. Note the up tick on the 90 day but the down tick on the 10 year thus shortening the spread. This does not bode well for any recovery.

Labels: Economy, Yield Curve

WEDNESDAY, MAY 23, 2012

EBB AND TIDE OF EUROPE

Saw this on Zero Hedge, it tells a powerful tale. Beautifully done.
Labels: Commentary

ONGOING PSA DEBATE

The current debate over PSA levels, testing and care continues. The NY Times has two articles yesterday on the Task Force Report.

Let me comment.

First the title was *New Data on Harms of Prostate Cancer Screening.* The article was written by a woman, and yes that does mean something, but the title is basically false. The screening itself does de minimis harm unless there is something done improperly. Even saturation biopsy, 20 or more cores, can be performed in a properly prepped person with de minimis morbidity. Yes there are a few infections, and yes there is hematuria, and yes there is some minor nerve damage and discomfort, but the alternative is rather terrifying. Colonoscopies have similar issues plus perforation of the colon. Is morbidity present, yes, to an overwhelming degree, in my opinion and experience, not really.

But one should read carefully the next to last paragraph:

xxxxx said that some men might look at the data on risks and benefits and decide that they still want to be tested, and nothing in the recommendations would prevent that. He also noted that federal legislation passed in the 1990s requires Medicare to cover the cost of P.S.A. testing, ***and that law will remain in effect unless Congress overturns it****. Many insurance companies follow the lead of Medicare when it comes to reimbursement for health coverage.*

And the law will remain in effect unless Congress overturns it. Well, is that not what the Task Force is recommending. Let me remind the reader:

1. The Task Force is mainly concerned about the morbidity resulting from biopsies. That should be a decision made between the patient and their, in this case his, physician. Informed consent. It is not in the authority realm of the Task Force to tell me what discomfort level I should tolerate. If so then most likely no one would ever go to a Dentist as a child. However some discomfort to detect and remedy a PCa is much better than death from it.

2. It is true as we have argued that PCa comes in all shapes and sizes. And further as we have repeatedly reported and written on, PCa types are not yet identifiable. Does one have an indolent or aggressive form? In addition is there a cancer stem cell here we should try and find, perhaps. But we cannot and should not assume that since some are indolent we treat all people the same. Why not treat all women with breast lesions as DIC only, I rather not think so.

In the same edition of the Times there is a long discussion regarding preventive care. They state:

Could health care costs be reined in by improving access to preventive care? It's an idea that appeals to policy makers and many public health experts, but the evidence for it is surprisingly hard to pin down.

Is this not the same issue?
Labels: Health Care

CBO AND THE ECONOMY

The CBO has just issued a report looking at the impact of continued freeze in Congress, and the impact of such a Fiscal policy.

It states:

*CBO estimates that the combination of policies under current law will reduce the federal budget deficit by $607 billion, or 4.0 percent of gross domestic product (GDP), between fiscal years 2012 and 2013. The resulting weakening of the economy will lower taxable incomes and raise unemployment, generating a reduction in tax revenues and an increase in spending on such items as unemployment insurance. With that economic feedback incorporated, the deficit will drop by $560 billion between fiscal years 2012 and 2013, CBO project*s.

They conclude:

2.1.1.1 *What Might Policymakers Do Under These Circumstances?*
They could address the short-term economic challenge by eliminating or reducing the fiscal restraint scheduled to occur next year without imposing comparable restraint in future years—but that would have substantial economic costs over the longer run. Alternatively, they could move rapidly to address the longer-run budgetary problem by allowing the full measure of fiscal restraint now embodied in current law to take effect next year—but that would have substantial economic costs in the short run. Or, if policymakers wanted to minimize the short-run costs of narrowing the deficit very quickly while also minimizing the longer-run costs of allowing large deficits to persist, they could enact a combination of policies: changes in taxes and spending that would widen the deficit in 2013 relative to what would occur under current law but that would reduce deficits later in the decade relative to what would occur if current policies were extended for a prolonged period.

Well someone must do something, but I suspect we will have to wait until after the election.
Labels: Economy

TUESDAY, MAY 22, 2012

PROSTATE CANCER SCREENING, THE TASK FORCE

The USPSTF has issued its dictum on PCa screening with PSA. It states:

The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation).

This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.

It continues:

Men with screen-detected cancer can potentially fall into 1 of 3 categories: those whose cancer will result in death despite early diagnosis and treatment, those who will have good outcomes in the absence of screening, and those for whom early diagnosis and treatment improves survival. Only randomized trials of screening allow an accurate estimate of the number of men who fall into the latter category. There is convincing evidence that the number of men who avoid dying of prostate cancer because of screening after 10 to 14 years is, at best, very small. Two major trials of PSA screening were considered by the USPSTF: the U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial and the ERSPC (European Randomized Study of Screening for Prostate Cancer).

The U.S. trial did not demonstrate any prostate cancer mortality reduction. The European trial found a reduction in prostate cancer deaths of approximately 1 death per 1000 men screened in

a subgroup of men aged 55 to 69 years. This result was heavily influenced by the results of 2 countries; 5 of the 7 countries reporting results did not find a statistically significant reduction. All-cause mortality in the European trial was nearly identical in the screened and nonscreened groups.

The dissenting view stated:

Prostate cancer death was reduced by 21% in the screened compared with the control group and 29% after adjustment for noncompliance (5). The Task Force concluded that this decrease in prostate cancer–specific mortality amounted to few lives saved and did not outweigh …

The recommendations of the USPSTF carry considerable weight with Medicare and other third-party insurers and could affect the health and lives of men at high risk for life-threatening disease. We believe that elimination of reimbursement for PSA testing would take us back to an era when prostate cancer was often discovered at advanced and incurable stages. At this point, we suggest that physicians review the evidence, follow the continuing dialogue closely, and individualize prostate cancer screening decisions on the basis of informed patient preferences.

Now for our comments (see our draft book on PCa) :

1. We have discussed fatal flaws in our opinion in both studies relied upon. Simply they both used the old PSA threshold of 4 and did not include age dependency, percent free PSA and PSA velocity. In addition the European study had too great a time interval between tests.

2. No single PCa is alike. As we have been demonstrating for the past four years, the genetic makeup of PCa is complex and there are clearly certain specific markers for highly malignant PCa. By abandoning the test is throwing the baby out with the bathwater.

3. In my opinion this is a clearly age biased result, with the intent of removing care from the second highest cause of death amongst men. One wonders why!

4. Genetic makeup and family history are major drivers. PSA irregularities are one, along with PC3A testing, to ascertain PCa potential. Why eliminate it. The reason seems to be the cost of subsequent procedures, yet the Task Force argues it is the morbidity to the patient. Frankly morbidity in a competently performed procedure is less than a tooth extraction. Perhaps excess morbidity is more in the mind of the Task Force than reality.

What then is lost? We believe a great deal.

1. We are just beginning to understand the genetic makeup, just look at some of our recent postings, so that having the pool of data is indispensable. Having a genetic profile of multiple PCa would be the key to understanding the dynamics of PCa and its control.

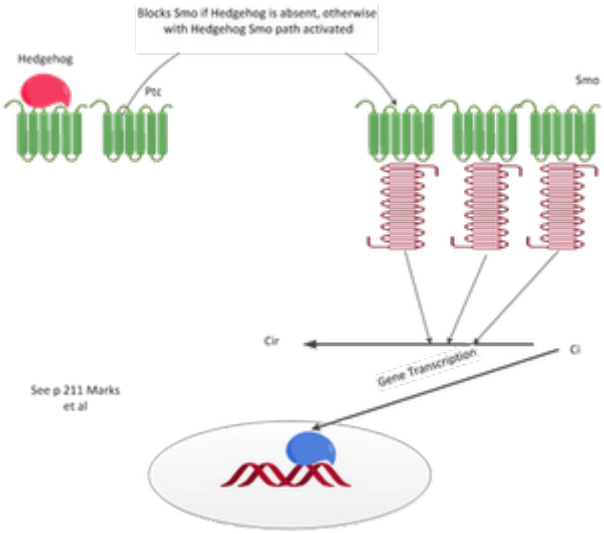
2. What is the value of one life. If one has seen the agony of bone mets in a PCa patient, the results of DIC, and the loss of any dignity in the final days with catheter changes by a less than friendly "health care worker", the morbidity issue pales in comparison.

Hopefully we can find ways to work around this less than useful Government cost cutting "death panel" regulation. Welcome to our new world of health care!
Labels: Cancer, Health Care

MONDAY, MAY 21, 2012

SPOP AND PROSTATE CANCER

SPOP is part of the Hedgehog signalling pathway[1]. The Hedgehog signalling pathway controls amongst other factors the formation of body segments in insects and in vertebrates the development of the neural tube, limbs and left-right asymmetry. In adult tissues Hedgehog is responsible for homeostasis, equilibrium between cells loss and gain while maintaining total mass and function. With an overactive Hedgehog pathway one sees excess cell proliferation and tumor growth[2]. We demonstrate that below:

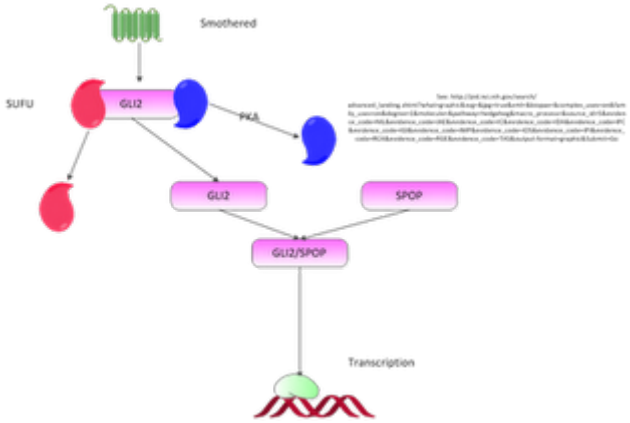


[1] http://pid.nci.nih.gov/search/MoleculePage?molid=203488 and http://pid.nci.nih.gov/search/search_landing.shtml?atom_id=208460,208462&what=graphic&jpg=on and pathway at http://pid.nci.nih.gov/search/advanced_landing.shtml?what=graphic&svg=&jpg=true&xml=&biopax=&complex_uses=on&family_uses=on&degree=1&molecule=&pathway=hedgehog&macro_process=&source_id=5&evidence_code=NIL&evidence_code=IAE&evidence_code=IC&evidence_code=IDA&evidence_code=IFC&evidence_code=IGI&evidence_code=IMP&evidence_code=IOS&evidence_code=IPI&evidence_code=RCA&evidence_code=RGE&evidence_code=TAS&output-format=graphic&Submit=Go

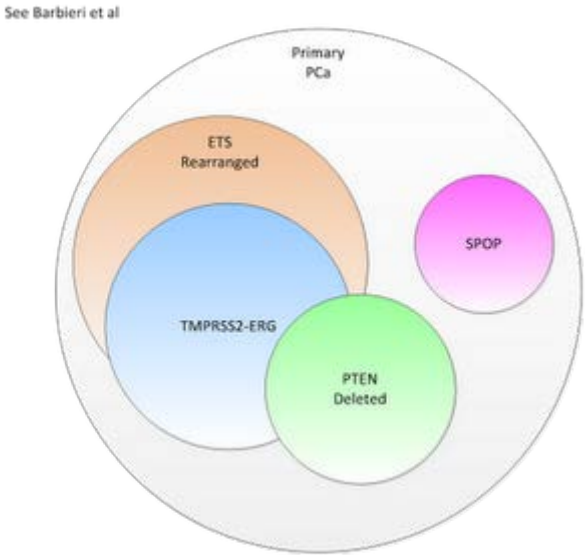
[2] See Marks et al p 210-212.

Thus SPOP has a controlling mechanism for cell replication. Here Hedgehog attaches to Patched and the Patched inhibition of Smothered is eliminated allowing Smothered to start a transcription process enabling replication.

Now upon the activation of Smothered a set of processes are activated and one product is a protein called the zinc finger transcription factor Gli, which when mutually supported by SPOP allows movement to the nucleus as a transcription factor activating the DNA to transcribe[3]. We depict that below:



From Barbieri et al we have the following putative relationships:



The authors argue that SPOP is a separate and significant marker for PCa. The pathway involved is somewhat understood and is a transcription driven pathway initiated by Hedgehog activation and Patched suppression with Smothered activation. From the NCI pathway databases

[3] See Pecorino, p. 168-170.

we have a putative requirement that SPOP is needed to activate GLI for subsequent transcription and cell reproduction.

Specifically Barbieri et al state:

As demonstrated by a subsequent analysis of significantly more genomes, there are only a few truly recurrent non-synonymous mutations in PCa. The most common recurrent non-synonymous mutation in PCa involves SPOP. The SPOP gene encodes for the substrate-recognition component of a Cullin3-based E3-ubiquitin ligase. Mutations in SPOP in PCa were reported originally in two systematic sequencing studies. We have now identified the presence of recurrent mutations in SPOP in 6–13% of human PCas in multiple independent patient cohorts.

Recurrent missense mutations are found exclusively in the structurally defined substrate-binding cleft of SPOP, and structural analysis suggests that these mutations will inactivate SPOP function by disrupting SPOP–substrate interaction.

Further, we found that loss of SPOP function in prostate cell lines resulted in increased invasion and altered gene expression; evidence of this expression signature was identified in primary tumours harbouring SPOP mutation.

Importantly, all SPOP mutations occurred in tumours that were negative for ERG rearrangement; these tumours displayed characteristic somatic copy number aberrations. Taken together, these findings support a distinct molecular class of PCa.

In a recent Nature Medicine article the same authors relate[4]:

Prostate cancer is the second most common cancer in men worldwide and causes over 250,000 deaths each year. Overtreatment of indolent disease also results in significant morbidity. Common genetic alterations in prostate cancer include losses of NKX3.1 (8p21) and PTEN (10q23), gains of AR (the androgen receptor gene) and fusion of ETS family transcription factor genes with androgen-responsive promoters.

Recurrent somatic base-pair substitutions are believed to be less contributory in prostate tumorigenesis but have not been systematically analyzed in large cohorts. Here, we sequenced the exomes of 112 prostate tumor and normal tissue pairs. New recurrent mutations were identified in multiple genes, including MED12 and FOXA1. SPOP was the most frequently mutated gene, with mutations involving the SPOP substrate-binding cleft in 6–15% of tumors across multiple independent cohorts.

Prostate cancers with mutant SPOP lacked ETS family gene rearrangements and showed a distinct pattern of genomic alterations. Thus, SPOP mutations may define a new molecular subtype of prostate cancer.

[4] http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.2279.html

This just adds another gene in the mix for PCa. Namely they authors argue that it is a different type. We would still ask the same questions:

1. What is the issue regarding the presence or absence of a CSC stem cell in PCa.

2. When does this mutation occur.

3. What causes the mutation.

4. SPOP is not a true kinase so what type of blocking would be possible to mitigate the presence of a mutant.

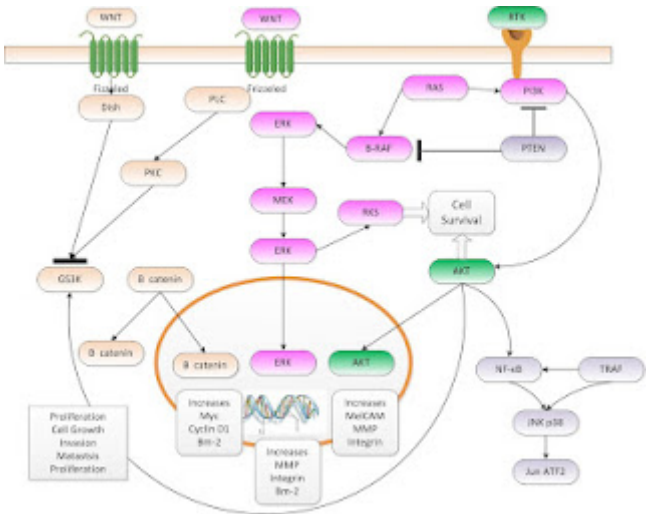
References

1. Barbieri, C. et al, Molecular genetics of prostate cancer: emerging appreciation of genetic complexity, Histopathology 2012, 60, 187–198.
2. Barbieri, C., et al, Exome Sequencing Identifies Recurrent SPOP, FOXA1 and MED12 Mutations in Prostate Cancer, Nature Genetics (2012).
3. Marks, F., et al, Cellular Signal Processing, Garland (New York) 2009.
4. Pecorino, L, Molecular Biology of Cancer, Oxford (New York) 2008.

Labels: Cancer

FRIDAY, MAY 18, 2012

MELANOMA AND PATHWAY BLOCKING



In a recent ASCO news release there is a report of blocking of BRAF and MEK in melanoma thus having the BRAF block the melanoma pathway and the MEK blocking the secondary squamous cell cancer pathway.

The release states:

Results from an expanded Phase IB trial show that combination therapy with two investigational targeted drugs – the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib – stalls cancer progression and with a lower level of skin side effects than published studies of the current standard single-agent BRAFtargeted therapy, vemurafenib (Zelboraf), have shown. The analysis included patients with advanced melanoma who had a V600 BRAF mutation and who had no previous BRAF-targeted treatment. Approximately half of all melanomas harbor a V600E mutation in the BRAF gene; in those patients, the nearby MEK pathway is also highly active. While the approval of vemurafenib last year represented a major research achievement, most patients eventually develop resistance to the drug. It is hoped that simultaneously targeting the two active pathways – BRAF and MEK – will provoke a stronger anti-cancer response and prevent, or further delay, treatment resistance.

The result is not unexpected but it does presage a broader application of multiple pathway inhibiting profiles.
Labels: Cancer

FRIDAY, MAY 18, 2012

SOCIAL JUSTICE AND CATHOLICS

Social Justice is a movement which argues that it is the Government's responsibility to provide others with what is perceived missing to establish what is perceived by them as an equity or to use the euphemism, a level playing field, and in reality an equality of outcome. (To better understand this position it is worth reading my book on Individualism and Neo-Progressivism)

In the NY Times today some author states:

A broad, upbeat theme of social justice will be enough for Obama to reach persuadable Catholics, who can interpret the message in concert with their beliefs. The president might quote Pope John Paul II, who once said, "Radical changes in world politics leave America with a heightened responsibility to be, for the world, an example of a genuinely free, democratic, just and humane society." They must hear the message often and at least 15 percent of the time in Spanish.

Now the interpretation of personal duty, rather than group duty, is a matter of concern regarding the treatment of others. One could argue that the Sermon on the Mount was a call to personal duty, not a call to the Government of Rome to establish programs for the poor. The duty is individual, and individuals may group together to provide necessary services to those in need but the taxing and forced participation is questionable at best. Those who support Social Justice support a program of forced participation in satisfying needs perceived by a few but supported by the many.

In contrast the same people will force the Church to supply services that it objects to. Yet the Church would object to that force but ironically some of the same voices will press for the forced contributions under the rubric of social justice.

One wonders how one achieves what is sought for the doing of good deeds when one is forced to do so under the rubric of Social Justice. Is it the duty of Government or of the Church or of the individual.

The author continues:

What would a Catholic voter outreach program look like? The Roman Catholic Church doesn't exactly let political operatives walk in the front door and set up shop, but there are several progressive Catholic organizations — Catholics United, Catholics in Alliance, Catholic Democrats — that the campaign could engage first to build a volunteer corps. Within each district office, the campaign could identify Catholic precinct captains to recruit Catholic door-knockers to reach out to their friends from church. Then there's advertising. It would be more difficult to construct this architecture from scratch, but however it's done, it's a must: a positive social justice message could be what tips the balance toward re-election for the president.

No, political operatives do not walk in the front doors, in fact one would suspect if they were allowed the tax benefit would be promptly revoked, albeit it appears not to be the case in other churches.

Catholics are individuals for the most part. With the general exception of the Sophists one finds in Jesuits, the arguments, if any, are limited. Catholics in this election will not be any block. If they ever were. Rome seems to have taken the position of admonishing Governments while leaving the individual free from any duty. I frankly find this difficult to rationalize with the teachings of th first seven centuries. Yet in many ways it was a response to Socialism and Communism, the concept of Social Justice.

Labels: Commentary

FACEBOOK AND THE VALUE PROPOSITION

When looking at any business opportunity one looks at how value is created and how the company can monetize this value. Value is relative to the user. For example, Microsoft had substantial value creating capacity, and yes it cost to attain it. It was the word processor, spread sheet, and to some degree the operating system. Google had substantial value. It allowed access to information and it created and environment to share it and to monetize it via advertising.

I was a very early Facebook user at MIT, students drove the use. I have not used it for two years. It has no value and in fact it has a negative value. Why? Because it allows somewhat crazy comments from those to whom I was linked to create my profile. It had negative value. It also lacked privacy from my perspective. Thus I left.

So when looking at Facebook I see another AOL. And why AOL, because when in the mid 1990s while teaching at Columbia Business School I did a case on AOL and stated that in my analysis at the time it was at best declining in value. That was before the Time Warner acquisition. I see possibly the same here with Facebook. Yes it is a "social media" and yes it facilitates such communications. But is it of singular value to a person, a company? Time will tell.
Labels: Commentary

CANCER MODELS:PREDICTION AND CONTROL

We will now consider what are the essential elements for modeling cancers. The first step is to re-establish the goals of a model and then its structure. Finally we will lead into the interrelationship between a model and the data which is used to justify it.This work is detailed in a recent White Paper.

Many authors have developed models concerning pathways and also cancer. The books by Klipp et al and that of Szlassi et al are excellent overviews of the area with significant detail. The Klipp et al book is a truly superb discussion regarding pathways and modeling alternatives. The books by Bellomo et al and Wang are directed specifically at cancer modeling but unfortunately they lack adequate pathway dynamics to be of substantial use. Yet they are the only books available within the focused area.

At the core, we want a model which reflects the following qualities:

1. Based Upon Reality: The model must at its core be based upon the known reality. It must conform with what we currently know and understand. Namely it must reflect in its core the elements which we consider critical and the temporal and spatial dynamics of those elements. The model must be based upon a tempero-spatial system of measurable quantities ;linked in some kinetic manner using reasonably well understood processes.

2. Predictability: Any modeling must, if it is to have any credibility, have the ability to predict, to say what will happen, and then to have that prediction validated. Although the ability may be statistical in nature the statistical confidence must be justifiable. We know all too well that many things are correlated, yet not causal, and not predictable.

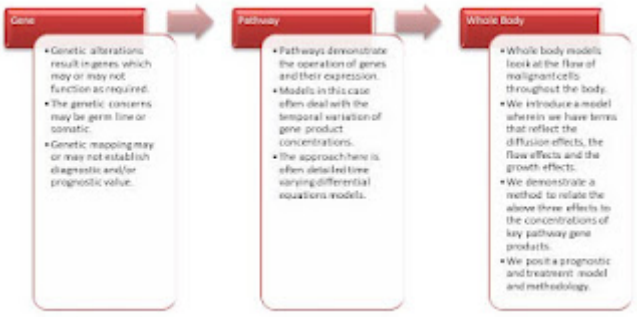
3. Measurable: One must be able to measure and then predict the quantities which make up the model. Many of the modeling systems include proteins but they react in some zero-one format. We know in reality that we have concentrations, or better yet specific numbers of proteins, produced in a cell. Yet we cannot yet measure the number of each of these proteins. We all too often can at best measure their presence or absence. However, is it not the case that it is the excess or the low density of some set of proteins which shift reactions, and that reactions are often concentration dependent.

4. Modellable: We want a system which can be modeled. It must reflect the measurable quantities in space and time and the tempero-spatial dynamics of them, using techniques that we can then use for prediction and validation.

In this paper we examine and analyze several models of cancer. Specifically we look at intracellular, extracellular and full body models. We attempt to establish a linkage between all of them. Many researchers have looked at the gene level, the pathway level and the gross flow of cancer cell level, namely whole body. Connecting them has been complex to say the least.

But herein we look at the pathway level and a whole body level and demonstrate the nexus, physically, and from this we argue that one can construct both prognostic tools as well as methodologies to deal with metastasis.

The following graphic lays out the flow of development and its implications as we detail them herein.



The key question we ask is just what is it we are modeling in cancer cell dynamics. Let us consider some options:

Intracellular Gene Dynamics:

This type of model focuses on the genes, and their behavior. It is basically one where we examine the gene type and its product.

Intracellular Protein Dynamics:

This type of model falls in several subclasses. All begin with protein pathways and the "dynamics" of such pathways. But we have two major subclasses; protein measures and temporal measures. By the former we mean that we can look at the proteins as being on or off, there or not there, or at the other extreme looking at the total number of proteins of a specific type generated and present at a specific time. By the latter, namely the temporal state, we can look at the proteins in some static sense, namely there or not there at some average snapshot instance, or we can look at the details over time, the detailed dynamics. In all cases we look at the intracellular dynamics only.

Let us consider the two approaches.

i. On-Off: In this approach the intracellular relationships are depicted as activators or inhibitors, namely if present they allow or block an element in a pathway. PTEN is a typical example, if present it blocks Akt, if absent it allows Akt to proceed and enter mitosis. p53 is another example for if present we have apoptosis and if absent we fail to have apoptosis. These are simplistic views. This is a highly simplistic view but it does align with the understanding available say with limited microarray techniques. This is an example of the data collection defining what the model is or should be.

ii. Density: This is a more complex model and it does reflect what we would see as reality. The underlying assumptions here are:

a. Genes are continually producing proteins via transcription and translation.

b. Transcription and translation are affected at most by proteins from other genes acting as repressors or activators. There are no other elements affecting the process of transcription and translation. Not that this precludes any miRNA, methylation, or other secondary factors. We shall consider them later. In fact they may often be the controlling factors.

c. The kinetics of protein production can be determined. Namely we know the rate at which transcription and translation occur in a normal cell or even in a variant. That is we know that the production rate of proteins can be given by a typical creation differential equation.

Here we have production rates dependent on the concentration of other proteins. The processes related to consumption are not totally understood (see Martinez-Vincente et al). We understand cell growth, as distinct from mitotic duplication, but the growth of a cell is merely the expansion of what was already in the cell when at the end of its mitotic creation. In contrast, we understand apoptosis, the total destruction of the cell, we also understand that certain proteins flow outside the cell or may be used as cell surface receptors, but the consumption of these is not fully understood. Yet we can postulate a similar destruction differential equation.

This is based upon the work of Martinez-Vincente et al which states[1]:

1. Martinez-Vincente, M., et al, Protein degradation and aging, Experimental Gerontology 40 (2005) 622–633.

All intracellular proteins undergo continuous synthesis and degradation. This constant protein turnover, among other functions, helps reduce, to a minimum, the time a particular protein is exposed to the hazardous cellular environment, and consequently, the probability of being damaged or altered. At a first sight, this constant renewal of cellular components before they lose functionality may appear a tremendous waste of cellular resources.

However, it is well justified considering the detrimental consequences that the accumulation of damaged intracellular components has on cell function and survival. Furthermore, protein degradation rather than mere destruction is indeed a recycling process, as the constituent amino acids of the degraded protein are reutilized for the synthesis of new proteins.

The rates at which different proteins are synthesized and degraded inside cells are different and can change in response to different stimuli or under different conditions. This balance between protein synthesis and degradation also allows cells to rapidly modify intracellular levels of proteins to adapt to changes in the extracellular environment. Proper protein degradation is also essential for cell survival under conditions resulting in extensive cellular damage. In fact, activation of the intracellular proteolytic systems occurs frequently as part of the cellular response to stress. In this role as 'quality control' systems, the proteolytic systems are assisted by molecular chaperones, which ultimately determine the fate of the damaged/unfolded protein.

Damaged proteins are first recognized by molecular chaperones, which facilitate protein refolding/repairing. If the damage is too extensive, or under conditions unfavorable for protein repair, damaged proteins are targeted for degradation. Protein degradation is also essential during major cellular remodeling (i.e. embryogenesis, morphogenesis, cell differentiation), and as a defensive mechanism against harmful agents.

We have also discussed this process with regards to the function of ubiquitin, which marks proteins for elimination. As Goldberg states[2]:

Proteins within cells are continually being degraded to amino acids and replaced by newly synthesized proteins. This process is highly selective and precisely regulated1, and individual proteins are destroyed at widely different rates, with half-lives ranging from several minutes to many days. In eukaryotic cells, most proteins destined for degradation are labelled first by ubiquitin in an energy requiring process and then digested to small peptides by the large proteolytic complex, the 26S proteasome.

Indicative of the complexity and importance of this system is the large number of gene products (perhaps a thousand) that function in the degradation of different proteins in mammalian cells. In the past decade, there has been an explosion of interest in the ubiquitin–proteasome pathway, due largely to the general recognition of its importance in the regulation of cell division, gene expression and other key processes1. However, the cell's degradative machinery must have evolved initially to serve a more fundamental homeostatic function — to serve as a quality-

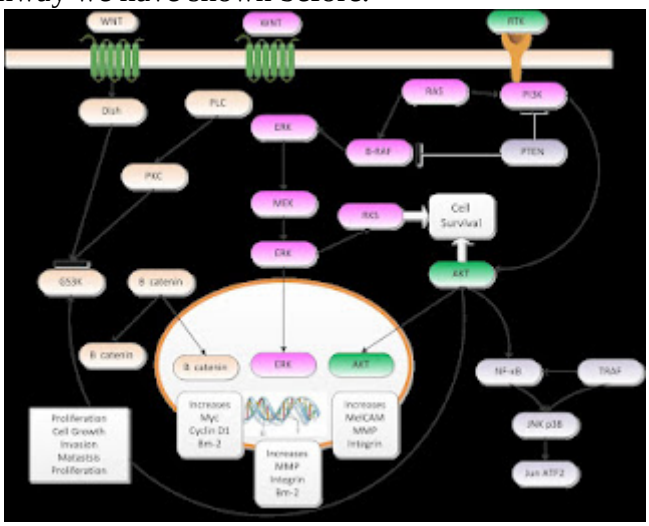
2. Goldberg, A., Protein degradation and protection against misfolded or damaged proteins, NATURE, Vol 426, 18/25 December 2003.

control system that rapidly eliminates misfolded or damaged proteins whose accumulation would interfere with normal cell function and viability.

Also we refer to the recent review work of Ciechanover which details the evolution of this understanding[3].

In contrast the proteins are consumed and thus the negative sign. In toto we have a combined equation as a total balance of proteins. This assumes we have a production mechanism for each of the proteins, namely their genes and the activators and repressors as required.

d. Pathway Dynamics must be meaningful. Let us consider the pathway as shown below. This is a typical melanoma pathway we have shown before.



Now let us consider PTEN blocking BRAF and Akt. Now physically it is one molecule of PTEN needed for each molecule of BRAF and PI3K. But what if we have the following: n(PTEN)n(PI3K).

Here we have PTEN blocking some but not all the BRAF and PTEN blocking all the PI3K. At least at time t. Do we have an internal mechanism which then produces even more PTEN? One must see here that we are looking at the actual numbers of PTEN, real numbers reflecting the production and destruction rates. We know for example that if we have a mutated BRAF then no matter how much PTEN we have an unregulated pathway.

Now it is also important to note that this “model” and approach is distinct in ways from classic kinetics, since the classic model assume a large volume and concentrations in determining kinetic reaction rates of catalytic processes. Here we assume a protein binds one on one with another protein to facilitate a pathway.

Thus knowing the dynamics of individual proteins, and knowing the pathways of the proteins, namely the temporary adhesion of a protein, we can determine several factors:

1. The number of free proteins by type
2. The pathways activated or blocked
3. The resultant cellular dynamics based on activated pathways.

It should be noted that we see pathways being turned on and off as we produce and destroy proteins. There is a dynamic process ongoing and it all depends on what would be a stasis level of proteins by type. The question is; are cells in stasis or are they in a continual mode of regaining a temporary stasis?

This also begs the question, that if as we have argued, that cancer is a loss of stasis due to pathway malfunction, then can this be a process of instability in the course of a normal cell? Namely is there in the dynamics of cell protein counts, unstable oscillator type modes resulting in uncontrolled mitotic behavior. Namely can a cell get locked into an unstable state and start reproducing itself in that state, namely an otherwise normal cell.

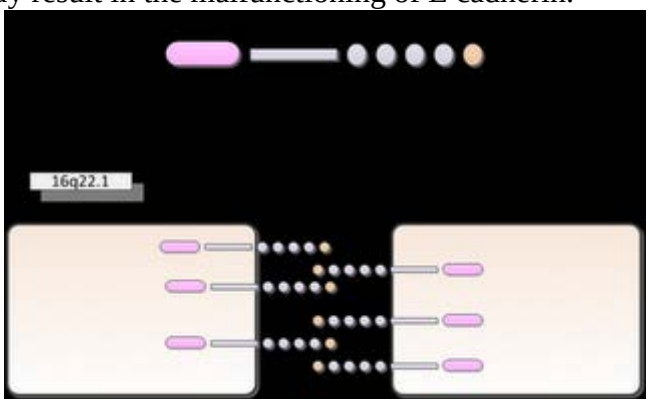
e. Total intracellular dynamics can be modeled yet the underlying processes are still not understood and the required measurements are yet to be determined.

Intercellular Dynamics:

Here we look at the intercellular dynamics as well, not just as a stand-alone model. By this methodology we look at intercellular communications by ligand binding and the resulting activation of the intracellular pathways. We must consider both the intercellular signalling between like cells but also between unlike, such a white cells perhaps as growth factor inhibitors and the like. We also then must consider the spatiodynamics, namely the “movement” of the cells, or in effect the lack of fixedness or specificity of function. This becomes a quite complex problem.

There are two functions we examine here:

a. Intercellular binding or adhesion: E cadherin is one example that we see in melanocytes. Pathway breakdown may result in the malfunctioning of E cadherin.



The above demonstrated E cadherin in melanocyte-keratinocyte localization. The bonds are strong and this stabilizes the melanocyte in the basal layer. If however the E cadherin is compromised then the bond is broken, or materially weakened, and the melanocyte starts to

wander. Movement for example above the bottom of the basal layer and upwards is pathognomonic of melanoma in situ. Wandering downward to the dermis becomes a melanoma. Thus the pathways activating E cadherin production is one pathway essential in the inter-cellular dynamics.

b. Ligand production and receptor production: Here we have cells producing ligands, proteins which venture out of the cell and become signalling elements in the intercellular world. We have the receptor production as well, where we have on the surface of cells, various receptors, also composed of cell generated proteins, which allow for binding sites of the ligands and result in pathway activation of some type. For example various Growth Factors, GF proteins, find their way to receptors, which in turn activate the pathways. Wnt is an example of one of these ligands which we have shown above.

It can also be argued that as ligands are produced and as the "flow" throughout the intercellular matrix, we can obtain effects similar to those in the Turing tessellation models. Namely a single ligand may be present everywhere but density of ligands may vary in a somewhat complex but determinable manner, namely is a wavelike fashion.

This is akin to the Turing model used in patterning of plants and animals[4]. Namely the concentration of a ligand, and in turn its effect, may be controlled by

Total Cellular Dynamics

In this case we would want a model which reflects the total body spatiotemporal dynamics This type of models is an ideal which may or may not be achievable. In a simple sense it is akin to diffusion dynamics, viewing the cancer cells as one type of particle and the remaining body cells as another type. The cancer cells have intercellular characteristics specific to cancer and the body cells have functionally specific characteristics. Thus we could ask questions regarding the "diffusion" of cancer cells from a local point to distant points based upon the media in between. The "rate" of such diffusion could be dependent upon the local cells and their ability for example to nourish the cancer cells as well. In this model we could define an average concentration of cancer cells at some position x and time t and we would have some dynamic process as well.

This is a diffusion like equation and is a whole body equation. Perhaps knowing what the rate of diffusion is on a cell by cell basis may allow one to determine the most likely diffusion path for the malignancy, and in turn direct treatment as well.

This is of course pure speculation since there has been to my knowledge any study in this area. Except one could imagine a system akin to PET scans and the like which would use as input the surface markers from a malignancy and then the body diffusion rates to plot out in space and time the most likely flow of malignant cells and thus plan out treatment strategies. Although this model is speculative we shall return again to it in a final review of such models since it does present a powerful alternative.

This concept of total cellular dynamics is in contradistinction to the intercellular transport. In the total cellular dynamics model we regard the model as one considering the flow of altered cells across an existing body of stable differentiated cells.

We may then ask, what factors drive cancer cells to what locations? One may putatively state that cancer cells will follow the path of least resistance and/or will proceed along “flow lines” consistent with what propagation dynamics they may be influenced by.

Total Cellular Dynamics: An Example

The concept of a model of Total Cellular Dynamics is somewhat innovative. It focuses on the movement of the cancer cells throughout the body. We will consider three possible possibilities:

1. No Stem Cells

2. Stem Cells but Fixed at Initial Location

3. Stem Cells which are mobile.

In Case 1 all malignant cells are clones of each other at least at the start. As the malignant cells continue through mitosis additional mutations are likely so that after a broad set of mitotic divisions we have a somewhat heterogeneous set of malignant cells, some more aggressive than others. As with most such cancer cells they also produce ligand growth factors which stimulate each other and result in the cascade of unlimited growth and duplication.

In Case 2 we assume that there was a single cell which mutated and that this becomes the CSC. The CSC replicates producing one CSC for self-replication and TICs which migrate. We assume that the CSC may from time to time actually double, but not at the mitosis rate of the base. Furthermore we assume the CSC sends out growth factors, GF, to the TICs. The GF flow outward in a wave like manner from the somewhat position stabilized CSCs to the TICs which are mobile and both diffuse and flow throughout the body. The GF must find the TICs which become a distant metastasis.

In Case 3 in contrast to Case 2, we assume mobile CSC and thus the CSCs also flow according to some set of rules.

Total Cellular Dynamics Models

Now depending on the case we assume we can model the flow of cancer cells according to some simple dynamic distributed models[5]. Thus we could have[6] a partial differential equation of the type found in McGarty (see White Paper).

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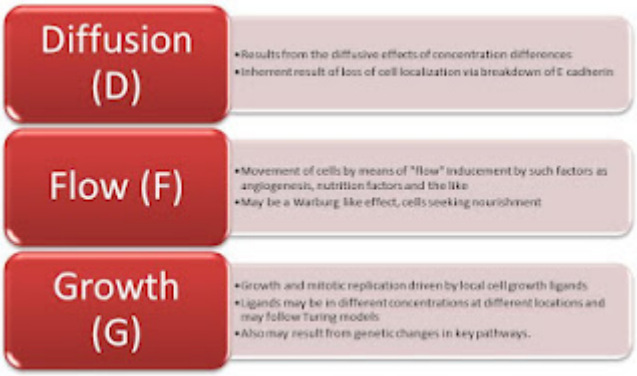
[6] McGarty, T., Stochastic Systems and State Estimation, Wiley (New York) 1974.

1. Szallasi, Z. System Modeling in Cellular Biology: From Concepts to Nuts and Bolts. MIT Press (Cambridge) 2006.

This provides diffusion, flow, and rate elements. The rate term, the F term, is a rate of change in time at a certain location and time specific. It is the duplication rate at that specific location due to the normal mitotic change. The last term may be both pathway and environment driven.

Now this description has certain physical realities.

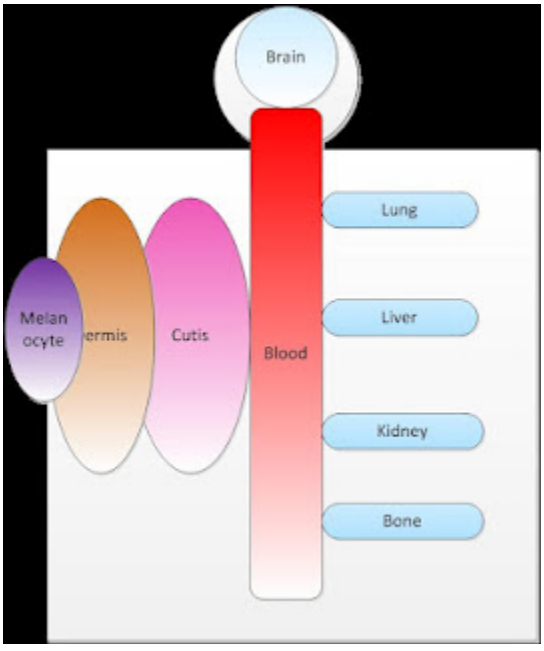


Here above we describe the three factors in terms of their effects and their causes. The three elements of the equation; diffusion, flow, and growth, are the three ways in which cancer cells move. We can summarize these as below:

1. Klipp, E., et al, Systems Biology, Wiley (Weinheim, Germany) 2009.

Factor	*Diffusion*	*Flow*	*Growth*
Physical Effect	Cancer cells begin to diffuse due to concentration effects.	Cancer cells are "forced" to move by a flow mechanism driven them in a direction along flow lines.	Cancer cells begin to go through mitosis and cell growth.
Genetic Driver	Movement is due to the loss of location restrictors such as E cadherin found in melanocytes and restricting their movement.	Flow lines may be developed by means of metabolic needs of the cell in search of the nutrients required for growth. This may be a combination of angiogenesis as well as a Warburg like effect.	Growth factor ligands attach to the surface of the cell. Flow of such ligands and their production may be influenced by a Turing flow effect thus accounting for complexity of location of growth.
Impact	Slow migration in local areas.	Cells have lost functionality and move to maximize their nutrition input to facilitate growth.	Cancer cells may find optimal areas for proliferation based upon factor related to ligand density.

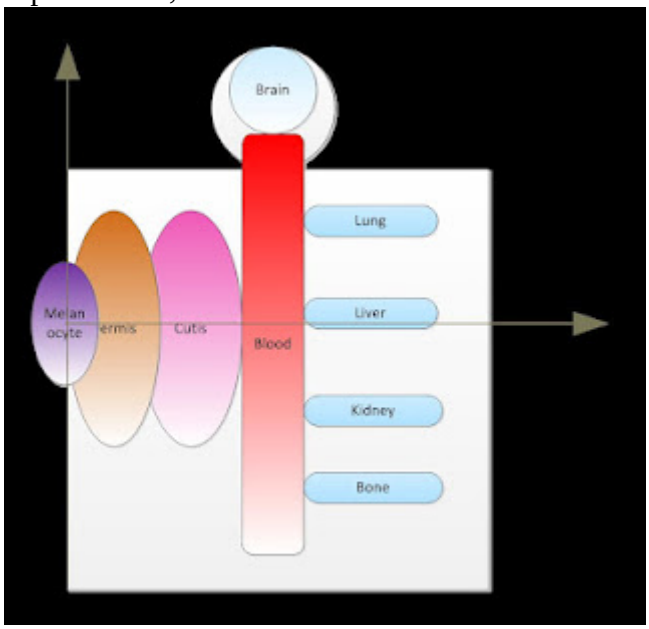
Now consider the following graphic as a human body,



We have a D, E, F, for each gross portion of the body. We also have a model as specifically below in the Table:

Organ	*D Diffusion*	*E Flow*	*F Production*
Epidermis	0.5	0.01	0.7
Dermis	0.4	0.02	0.5
Cutis	0.3	0.05	0.2
Blood	5.0	0.5	0.01
Brain	0.1	0.01	0.2
Liver	2.0	0.2	0.3
Lung	3.0	0.3	0.4
Kidney	1.5	0.4	0.5
Bone	2.5	0.5	1.0

The above numbers are purely speculative. But if we can ascertain them then we get a solution of p(x,t) in time. Note that here we have a two dimensional space. Thus we have the above constants applying only to this artifactually spatial model. Distance is measured in terms of movement across the interfaces. For simplicity we assume that all other space is impenetrable by any means. This we have production, flow and diffusion in each area.



Note that in the above we have laid out the x and y coordinates such that we have blood flow in the center, namely the metastasis flows via blood, and then enters organs as shown. The "location" of the organs are distances. Note also the origin of the malignancy is at (0,0).

Now we can relate the constants to the pathway distortions which are part of the malignancy as well.

The question is how do we determine these constants so that we may verify the model. Let us assume we can do so via examination of prior malignancy, not an obvious task but one we shall demonstrate. One must be cautious also to include in the determination pathway factors for each malignancy and its state and stage. Thus the three constants will be highly dependent upon the specific genetic makeup of the initial malignancy.

Turing Tessellation

In 1952 Alan Turing, in the last year and a half of his life, was focusing on biological models and moving away from his seminal efforts in encryption and computers. It was Turing who in the Second World War managed to break many of the German codes on Ultra and who also created the paradigm for computers which we use today. In his last efforts before his untimely suicide Turing looked at the problem of patterning in plants and animals. This was done at the same time Watson and Crick were working on the gene and DNA. Turing had no detailed model to work with, he had no gene, and he had just a gestalt, if you will, to model this issue. Today we have the details of the model to fill in the gaps in the Turing model.

The Turing model was quite simple. It stated that there was some chemical, and a concentration of that chemical, call it C, which was the determinant of a color. Consider the case of a zebra and its hair. If C were above a certain level the hair was black and if below that level the hair was white. As Turing states in the abstract of the paper:

"It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system.

The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on Hydra and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading."

Now, Turing reasoned that this chemical, what he called the morphogen, could be generated and could flow out to other cells and in from other cells. Thus focusing on one cell he could create a model across space and time to lay out the concentration of this chemical. He simply postulated that the rate of change of this chemical in time was equal to two factors; first the use of the chemical in the cell, such as a catalyst in a reaction or even part of the reaction, and second, the flow in or out of the cell. The following equation is a statement of Turing's observation.

It allows one to solve for a concentration, C, as a function of time and space. It requires two things. First is the diffusion coefficient to and from cells and second the functional relationship which shows how the chemical is used within a cell.

Determining the Coefficients

The question now is how does one link the coefficients in the models. For example if we believe that diffusion D depends on E cadherin concentration, namely as E cadherin decreases then D increases we may postulate a simple linear relationship between diffusion constants and protein concentrations, where the constants are to be determined. We know that the more E cadherin the stickier is the cell and the less diffusion that occurs. Thus the above is at the least a first order approximation. In a similar manner we can relate F to PTEN and p53.

This is merely suppositional. But we do know the following:

1. The genes which are expressed for adhesion and replication are known.

2. We know the pathways for these genes

3. We know the intracellular models controlling these genes.

4. We know that functionally an excess or paucity of a gene has a certain effect.

5. We know that in general in small amounts the world is linear.

6. We know that we can use regression techniques based upon collected data to determine coefficients in a general sense.

Thus we have a fundamental basis to express the relationships for all gross constants in terms of linearized versions of the protein concentrations.

Now we have related intracellular concentrations, which themselves may be temporally and spatially dependent, to the total parameter values for the flow of cells throughout the body. We may also want to relate these to organ specific parameters as well.

Thus what we have achieved is as follows:

1. Model relating intracellular and whole body.

2. Methodology to determine the constants.

3. Methodology to go from patient data to prognostic data.

4. Methodologies to establish possible treatment methodologies. Namely what gene controls will result in what whole body reactions.

We can now summarize this models we have considered. First we should emphasize that for the most part those working in the field have developed pathway models which exhibit a non-temporal mode, it is some steady state model, and the model assumes a protein to protein connection, as if there were a single protein molecule produced and that the interacting proteins were there or not. Part of the simplicity of the models is determined by the limits of what can be measured. We have herein attempted not to limit the results by what can be accomplished currently but has extended the model to levels which assist in a fuller representation of reality. However even here we may very be falling short.

For we have deliberately neglected such things as miRNA, methylation, and the stem cell paradigm just to name a few.

We combine all four methods in a graphic below. We summarize the key differences and differentiators. Currently most of the analytical models focus on pathways. This can generally be supported by means of microarray technology and even rough estimates of relative concentrations may be inferred by such an approach.

The risks we see even in the above models is the absence of exogenous epigenetic factors and the inclusion of a stem cell model. The latter issue is one of major concern. For example if we have true cancer stem cells, CSC, then we have a proliferation of differing cell types. The use of microarrays is for the most part and averaging methodology, not a cell by cell methodology. If we collect cells from say a melanoma tumor. how much of that is a CSC and how much a TIC. And frankly should we identify CSCs only and perform our analysis on those cells alone.

[3] Ciechanover , A, Intracellular Protein Degradation: From a Vague Idea through the Lysosome and the Ubiquitin-Proteasome System and onto Human Diseases and Drug Targeting, Rambam Maimonides Medical Journal, January 2012, Volume 3, Issue 1

[4] Turing, A., *The Chemical Basis of Morphogenesis*, Phil Trans Royal Soc London B337 pp 37-72, 19459.

[5] See Andersen p 277 of Bellomo et al for an variant on what we are proposing here. The Andersen model is somewhat similar but lacks the detail we present herein. Also there is in the same volume a paper by Pepper and Lolas focusing on the dynamics of the lymphatic cancer system, p 255. Bellomo, N., et al, Selected Topics in Cancer Modeling, Birkhauser (Boston) 2008.

Labels: Cancer

WEDNESDAY, MAY 16, 2012

AMBIGUITY OF EXPECTATIONS

Training versus education. Friedman makes some comments in the NY Times today regarding the explosion of on line courses, MIT, Harvard, Stanford. I suspect that he did not take the course and further I suspect he has no point of reference on what is accomplished.

As he states:

These top-quality learning platforms could enable budget-strained community colleges in America to "flip" their classrooms. That is, download the world's best lecturers on any subject and let their own professors concentrate on working face-to-face with students. Says Koller: "It will allow people who lack access to world-class learning — because of financial, geographic or time constraints — to have an opportunity to make a better life for themselves and their families."

When you consider how many problems around the world are attributable to the lack of education, that is very good news. Let the revolution begin.

Well I also spent last year taking Organic at the local community college. I also tried my hand at MIT 6.002x, which as I had noted I taught back in the 1960s as a junior faculty at MIT. Frankly the materials was a bit easier but the software access near impossible, and yes I am somewhat computer literate.

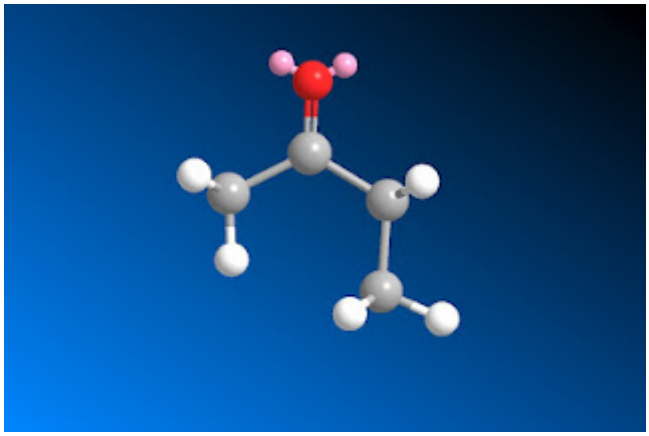
Taking this on line does not make you an MIT student. But. And this is the real but, my community college course was almost identical to the current MIT course, and the instructor was reasonably good. But that was just a little of what MIT offers on campus. There, in Cambridge, you got to understand how a good researcher thinks, not what you get at a community college, a bit too high school like. It is the how to think which results in the true learning process, the Hidden Curriculum. It is not that you can answer the questions but how you answer them, and at MIT it is with insight into fundamentals, you learn to intuit the answers, not work through all the details. That is not what is done at a community college.

The other issue is the ability to ask questions, to eliminate any ambiguity in a real time manner. Missing with 1 million students.

There are dramatic differences. Friedman seems to not have the depth of understanding to see them. Hype is all too often a deadly ally in promoting things. Frankly I would not change a thing at the community college, it works, the people are good, it is cheap, and for many it is the best step. Having another video lecture is just that, more stuff.
Labels: Academy

SUNDAY, MAY 13, 2012

COLLEGE AND COLLEGE DEBT



College is not for everyone, at least not for those who cannot figure out a return on the investment. At eighteen, as a senior, even at seventeen, one should know what it costs and what one may obtain in income to pay it off.

The NY Times has a piece today bemoaning the costs of college debt. As they recount:

xxxxx, 23, wouldn't seem a perfect financial fit for a college that costs nearly $50,000 a year. Her father, a paramedic, and mother, a preschool teacher, have modest incomes, and she has four sisters. But when she visited xxxxx, she was won over by faculty and admissions staff members who urge students to pursue their dreams rather than obsess on the sticker price.

"As an 18-year-old, it sounded like a good fit to me, and the school really sold it," said xxxxx, a marketing major. "I knew a private school would cost a lot of money. But when I graduate, I'm going to owe like $900 a month. No one told me that."

The first test of adulthood is that prior planning prevents poor performance. In 1959 I knew I could not afford college if I had to pay. Thus as part of my equation was not getting a loan but a scholarship, it was free. Thus between jobs and scholarships, that was in the days when being just smart was all that counted, the days when discriminating was not part of the selection process, and scholarships were awarded solely on the basis of performance. Things were simple, do better than a lot of others and you got a free ticket.

It is not so simple today. Just look at college applications. did you cure cancer in your junior year, did you save some starving third world village over mid year break, about that symphony you wrote? And yes, did you score a perfect score on the SATs and find those seven mistakes that the CEEB had made? And if you did, you got the opportunity to pay $60,000 per year tuition with a 12% inflation rate!

The answer, there must be alternatives. For many courses you do not need the massive and costly buildings, just a cinder block building with windows and some heat.

Could not the person mentioned by the Times have done the calculation with her parents? How about, we cannot afford this, can you? That is what parents must do from time to time. Yes, it makes them feel they are not up to what others do, but perhaps they are not.

Then again, would one hire someone who made such a decision as this student? Is this reflective of a much wider cultural problem. For most of us education is a means to getting a job, yes work. It is the apprentice world of the Middle Ages. Yet somehow it has become a follow your dream world, a nonsensical world which may very well never have existed. For the very wealthy also sent offspring off to be educated to enter the family business, and only rarely to follow their dream.

The worst thing ever to happen is the "follow your dream" advice, it works for a few, a very few.
Labels: Academy, Economy

HAPPY MOTHER'S DAY

Somewhere in the early 1940s is my best guess. But any how Happy Mother's Day to all.

But I really did like the hair styles. And yes, I was blonde.
Labels: Commentary

FRIDAY, MAY 11, 2012

MI6, LEAKS, AND PLAYING WITH INTELLIGENCE

When I was working in a different world I had a fellow named Eric Ackerman as a Deputy. Group Commander, RAF, and having worked for RV Jones during the War, he was also MI6 if memory serves me correct. Now Eric knew that world well and we often spoke. It was Eric who

parachuted into Norway to retrieve the guidance system of a V2, it was Eric who bugged the Soviet phone lines in Berlin, and on and on. Thus Eric was real, he really did this stuff, and fortunately lived to speak of it decades later. Eric was one of those silent heroes on WW II. And having been both successful and survived, I often looked to Eric for advice.

One of the key rules of intelligence is always keep sources and methods quiet, always, really always, otherwise you just muck it all up, yes that is a paraphrase of the MI6 handbook. Now the CIA had learned a bit from MI6, not everything, but a bit. Yet this current set of leaks is a disaster.

So says the Guardian. Specifically:

Detailed leaks of operational information about the foiled underwear bomb plot are causing growing anger in the US intelligence community, with former agents blaming the Obama administration for undermining national security and compromising the British services, MI6 and MI5.

The Guardian has learned from Saudi sources that the agent was not a Saudi national as was widely reported, but a Yemeni. He was born in Saudi Arabia, in the port city of Jeddah, and then studied and worked in the UK, where he acquired a British passport.

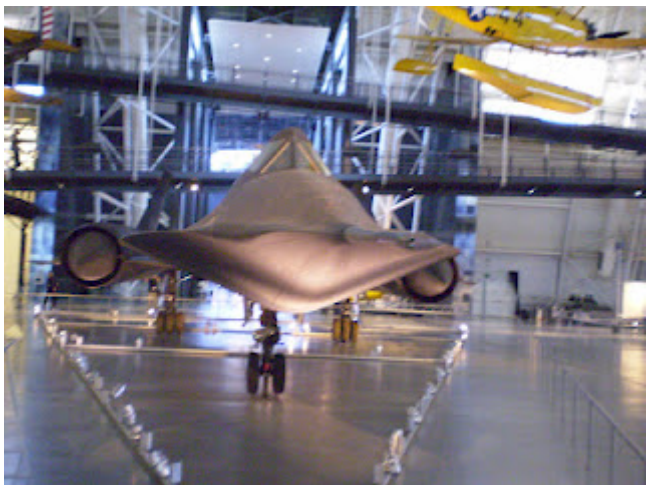
It is amateur night, and it is a shame that all has been placed at risk. The prime directive in this world of clandestine work is that it is clandestine, secret, kept under cover. The same should be the case as regards to black ops, they are black, in the dark, covered.

The risk now is that no one trusts you ever again, and in this world trust is the first thing you lose, but this time it is lost forever. Yes indeed, amateur night. I wonder what Eric would have told me?
Labels: Commentary

WEDNESDAY, MAY 9, 2012

INTELLIGENT INTELLIGENCE

In the old days, when it was the US vs the USSR, we had CIA vs KGB. We coveted sources and methods, and there was a multilayer cover of who and what was gathering intelligence.



The current scheme of things seems to make public our sources and methods, never done before, in any intelligence gathering community. The old way, just keep it quiet, it just disappeared. It allowed one options, secured your sources, and gave some sense of security for those to follow. However being part of an ongoing election campaign ad makes one a bit nervous. Ya think.
Labels: Commentary

THE FALL OF ROME

I have read through the book, The Fall of Rome by Ward-Perkins. The motivator was from a posting by DeLong who quoted from the work as:

"In less than a century after the barbarian nations settled in their new conquests, almost all the effects of the knowledge and civility, which the Romans had spread through Europe, disappeared. Not only the arts of elegance, which minister to luxury, and are supported by it, but many of the useful arts, without which life can scarcely be contemplated as comfortable, were neglected or lost."

Now knowing something of the events in the seventh century, I thought I would look through what the author stated. In my opinion, it is a bit Gibbonesque in approach, namely a Brit looking upon Rome and seeing what they want to see, not necessarily reality.

I believe that the change occurred from the time of Constantine to that of Charlemagne. Constantine dies in 337 AD; Charlemagne started his rule as Roman Emperor in 800 AD. It was this period where we see the change, albeit one could argue the slow decline of Rome even up to Constantine and the rocky road even after Charlemagne. Yet the period of 337 to 800 AD is in many ways what some historians call the Dark Ages, and what DeLong refers to.

But the key period in my view was from 600 AD to about 650 AD. Why? Well this was a major transition, from Rome as we know it being destroyed to the beginning of the Muslim invasion of what was old Roman territory. For Gibbon, and one can only guess for DeLong, the Catholic Church was at fault. In reality it really was a complex set of issues, some Church related, and others the natural flow of humanity. But by focusing on those middle fifty years one can see that

all was not lost, just transforming. Historians for the most part just jump over this, and unfortunately they miss the key changes in the jump.

Let me remark as to what happened:

1. Columbanus, the Irish monk, set forth and established what we could call the first set of public universities. They were at monastery like settlements but open to all. They focused on studying Latin, Greek, Hebrew, and the classics as well as the religious works. For the most part Columbanus and his followers were somewhat disconnected from the heresy scandal of the Greeks. They were not part of any Pelagian debates or Arian controversies. However they did battle with Gregory, Bishop of Rome, the title Pope was yet to be used since there were many equal bishops, Rome being the most equal of equals. Columbanus rattled Gregory over the date of Easter, and although he never won the debate, his correspondence is intellectually challenging. It also upset Gregory who refused to allow the Irish to convert the Angles and Saxons. Instead Gregory sent Augustine, an Italian bishop, to Canterbury in 599 AD. This was the first split between Ireland and England. However Ward-Perkins makes no reference to this effort. Columbanus managed to educate the Merovingians, the Lombards, and a collection of Germanic tribes, all the while Gregory never learned Greek to speak to his Eastern brethren. I believe that this was a seminal event in the break, one driven in many ways by the Emperor in Constantinople.

2. Justinian in the sixth century created a new legal code, an extension of the Roman law. At the same time the Merovingians worked on development of Salic law, a slightly and in some cases materially different set of laws. This construct set into motion another conflict. The conflict of a dying and decaying Roman system and evolving western view of the individual. Again there is not note of this.

3. The Byzantine emperors were a major factor in the decline. Constantine moved from Rome to Constantinople. That left Rome undefended and created a dramatic loss of population. It went from well over 1 million in 150 AD, the time of Hadrian and Marcus Aurelius, to less than 50,000 by the time of Gregory. In fact by 600 AD the Coliseum was stripped of all is white marble and was an open pit for wandering hordes. By Justinian's time the control of Rome was from Ravenna and Gregory managed a city initially as its mayor and then as its Bishop. He had a city which was vacated and impoverished. Why? Because people went to where the power was, in Italy it was Ravenna, and in the Empire it was Constantinople. Then in 602 the Emperor Maurice, who had been holding the Persian at bay, was slaughtered by Phocas, one of the officers in his army, and Phocas was then slaughtered by Heraclius in 610 AD. It was then Heraclius who managed the war with Chosroes, the Persian King. The Empire looked East, not West; Persia was on the attack, as it had been for millennia before. Heraclius then had to deal with this issue. Again Ward-Perkins leaves out these issues totally. His view was West looking, failing to see and appreciate the Eastern threat. Sound familiar.

4. Now we come to the Arabs, a major player. Yemen had always been the portal of the trading routes, south to Medina, then Mecca, then Sanaa, then Aden. Goods were brought from the East, India and China and up the trade routes. The control of Aden went from locals, to Jewish tribes, to Ethiopian and then to the Persians. This cut trade off. This was a critical event in East West

trade; it stopped the effort entirely, especially from 610 through 650 AD. From this comes the Prophet, from Medina, to Mecca to Medina to Mecca. Then the development of the Muslim agglomeration of tribes, the ability of the Arabs, under a single belief, to coordinate their efforts. The details of this as part of the tale and its critical importance is in my opinion missing from Ward-Perkins. I would also argue that the complexity of the Trinity may very well have played a role in the structure of the Muslim faith, Arian belief was a harbinger of the issues which would arise. Christianity was made much more complex by the introduction of the complexities of Greek philosophical elements, leading to several centuries of vitriolic debates.

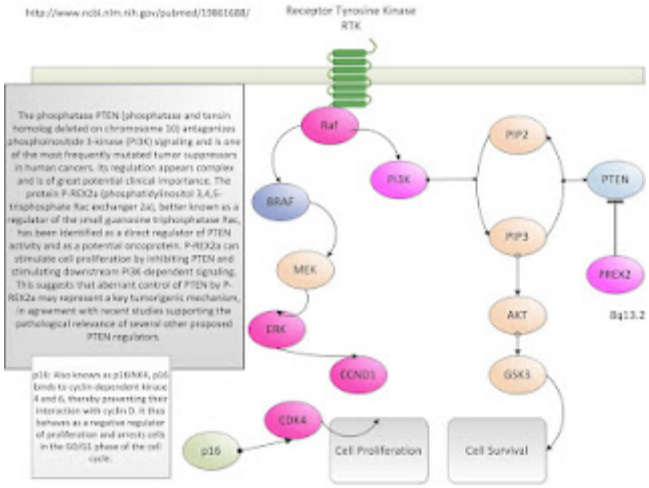
5. Why the collapse of North Africa? Simply Alexandria and the other areas were at war with Byzantium, religious war, due to the issue of various heretical battles. Thus when the Arabs arrived in Alexandria, it was akin to the English in New Amsterdam, it was better than what was there before, what was to come had yet to be seen. Alexandria was happy to be rescued from Constantinople. Rome was no part of this. Again not context of this is exposed by Ward-Perkins.

6. By 615 Isidore of Seville had been working on his encyclopedia, collecting and gathering his information, and Span was culturally stable and progression, it would be a good fertile soil for the Muslim moves. Again, Ward-Perkins fails to recognize the ongoing intellectual developments.

7. Technology, this was taken from Rome and moved eastward. Rome was stripped of its expertise. Thus there just was not chance to continue. Yet the Merovingians, the Franks, were able to develop and sustain technology for building and roads, but without the massive slave workforce of Rome. Without slaves, in massive numbers, life styles could not be maintained. The Merovingians were ruthless, read Gregory of Tours, but they were not massive slave holders as was Rome. Rome lived on slaves. Again, in my opinion, an issue of this magnitude is missing from Ward-Perkins.

If any period is worth study, especially to understand the change from Rome to our current era it is 600-650 AD. It is a pity Ward-Perkins gives it short shrift in my opinion.
Labels: Books, Commentary

PREX2 AND MELANOMA



There is an article in Nature today discussing the role of PREX2 in melanoma. PREX2 controls PTEN and it was observed that mutations there inhibited PTEN.

As the review of the article states:

Berger and his colleagues also found potentially damaging PREX2 mutations in 14% of 107 tumours that were not part of the initial study. And when they transplanted human skin cells containing PREX2 mutations into mice that had been engineered to develop skin cancer, four of the six different PREX2 mutations accelerated development of the tumours in mice. This led the researchers to suggest that PREX2 might have a similar role in human skin cancers.

There is always the risk in murine models that the pathways may be different, controlled by factors such as other ligands and having other variable intercellular dynamics. This has been, I would argue, some of the difficulty in the Goldstein model for PCa.

PREX2 itself is probably not a good drug target, because the mutations found in the gene do not cluster in any single location that might be easily pinpointed by a drug, says cancer researcher Levi Garraway, also at the Broad Institute, who led the study. However, Garraway says, the discovery should help researchers to improve their knowledge of the biological pathways that are disrupted in melanomas. In turn, that could lead scientists to genes and proteins in other parts of those pathways that might be better drug targets.

The pathway issue keeps coming back as a dominant factor. We show BRAF and PTEN above and BRAF is now a partially controllable mutation. Broadly speaking kinase inhibitors are now somewhat well understood. PREX2 however does not fall in that category.

PREX2 also seems to work differently from BRAF and NRAS, which are considered to be 'classic' oncogenes — overactive genes that have the potential to cause cancer and which are often mutated in the same ways. By contrast, the various PREX2 mutations identified by Berger and his colleagues occurred in different places in the protein. All seemed to lead the cell to make more of the protein than usual, rather than making the protein itself overactive.

One of the issues which seems to be coming to the fore in pathways is the details of the pathway dynamics or kinetics. This is an example of a yet to be determined kinetic model.

The summary of the article states:

Melanoma is notable for its metastatic propensity, lethality in the advanced setting and association with ultraviolet exposure early in life. To obtain a comprehensive genomic view of melanoma in humans, we sequenced the genomes of 25 metastatic melanomas and matched germline DNA. A wide range of point mutation rates was observed: lowest in melanomas whose primaries arose on nonultraviolet-exposed hairless skin of the extremities (3 and 14 per megabase (Mb) of genome), intermediate in those originating from hair-bearing skin of the trunk (5–55 per Mb), and highest in a patient with a documented history of chronic sun exposure (111 per Mb).

Analysis of whole-genome sequence data identified PREX2 (phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2)—a PTEN-interacting protein and negative regulator of PTEN in breast cancer2—as a significantly mutated gene with a mutation frequency of approximately 14%in an independent extension cohort of 107 human melanomas. PREX2 mutations are biologically relevant, as ectopic expression of mutant PREX2 accelerated tumour formation of immortalized human melanocytes in vivo. Thus, whole-genome sequencing of human melanoma tumours revealed genomic evidence of ultraviolet pathogenesis and discovered a new recurrently mutated gene in melanoma.

Now the PTEN control element is key in many cancers, such as prostate and many others.

As Fine et al state in their discussion of PREX2 and its effect on PTEN:

The P-REX2a gene is located on chromosome 8q13, a region of frequent amplification in breast, prostate, and colorectal cancers which has also been linked to aggressive cancer phenotypes and metastatic progression. We investigated P-REX2a expression by qRTPCR in a breast tumor data set thoroughly annotated for PI3K pathway alterations. P-REX2a showed a significant two-tailed association with PTEN status (p=0.027) and the median PREX2a expression was 3 fold greater in tumors that retained PTEN than in those that did not.

Additionally, gene expression data sets from other cancer databases demonstrate increased expression of P-REX2a in various tumors including breast and prostate compared to that in normal tissues. Mutations in P-REX2a were not found in a breast tumor mutation survey, however, our analysis of publicly available databases yielded numerous somatic mutations in P-REX2a in other tumors including those of the colon, pancreas and lung, making it one of the most commonly mutated GEF's in cancer (Fig. S6). We thus suspected that P-REX2a might be a PTEN-regulating factor that is co-opted in tumors to stimulate PI3K signaling.

Thus the PREX2 nexus has been established and was known as early as 2009. The nexus with PTEN control is a major issue. The question may be if PREX2 mutations are stronger influences than say PTEN mutations.

There is also the issue regarding the melanoma cancer stem cell issue as well as we have been

discussing elsewhere. Unlike a blood line stem cells or even prostate stem cells, the melanoma stem cell must most likely be a melanocyte, and one of the issues is how many melanocytes are stem in character, or is the stem cell not yet a melanocyte and if so what is it.A recent prior posting on prostate stem cells raises that issue as well.

I found one of the remarks especially compelling when the state:

In particular, we discovered that PREX2 mutations are both recurrent and functionally consequential
in melanoma biology. Although its precise mechanism(s) of action remains to be elucidated in melanoma, PREX2 appears to acquire oncogenic activity through mutations that perturb or inactivate one or more of its cellular functions. ***This pattern of mutations may exemplify a category of cancer genes that is distinct from 'classic' oncogenes (often characterized by highly recurrent gain-of-function mutations) and tumour suppressors (inactivated by simple loss-of-function alterations). Instead, (over)expression of certain cancer genes with distributed mutation patterns may promote tumorigenicity either through dominant negative effects or more subtle dysregulation of normal protein functions***

It will be interest to follow the implications of the last statements as indicated.

One other factor of interest was the calculation of mutation rates. They state:

This corresponded to an average mutation rate of 30 per Mb. However, the mutation rate varied by nearly two orders of magnitude across the 25 tumours . The acral melanomas
showed mutation rates comparable to other solid tumour types (3 and 14 mutations per Mb), whereas melanomas from the trunk harboured substantially more mutations, in agreement with previous studies. In particular, sample ME009 exhibited a striking rate of 111 somatic mutations per Mb, consistent with a history of chronic sun exposure.

This is an interesting observation since it appears to confirm, albeit on this small sample, the impact of UV radiation, and I could argue radiation in general. Whether this gives additional merit to my prior work on X Ray scanners is still an open issue.

This is an interesting result and most likely will be followed by more detailed studies. There always are the issues regarding the clear causative nature and the details of the pathways.

References

1. Fine, B., et al, Activation of PI3K Pathway in Cancer through Inhibition of PTEN by Exchange Factor P-REX2a, Science, 2009, pp 1261-1265.
2. Berger, M., et al, Melanoma Genome Sequencing Reveals Frequent PREX2 Mutations, Nature, May 2012.

Labels: Cancer

TUESDAY, MAY 8, 2012

NO REGRETS

Science has an interesting article on aging. The key point seems to be:

Responsiveness to regret was specifically reduced in successful aging paralleled by autonomic and frontostriatal characteristics indicating adaptive shifts in emotion regulation. Our results suggest that disengagement from regret reflects a critical resilience factor for emotional health in older age.

They continue:

The experience of regret is elicited by counterfactual thoughts, that is, comparing "what is" with "what could have been." Thus, regret is typically induced by presenting people not only with the actual outcomes of their choices but also with missed opportunities (i.e., alternative outcomes that could have been obtained had the choice been different). The influence of missed opportunities on future choices can be regarded as an indicator of regret responsiveness.

Thus it appears that "no regrets" is a good life style. It is always interesting to examine these types of studies. For there may be very good people who regret not doing more and outright evil folks who have no conscience. It appears that that element is not considered.
Labels: Science

THE DEFICIT

The CBO reports a $721 deficit for the first seven months. That is a $1.236T deficit for the fiscal year.

The CBO states:

The federal government incurred a budget deficit of $721 billion in the first seven months of fiscal year 2012, CBO estimates in its latest Monthly Budget Review—$149 billion less than the shortfall reported during the same period last year. Without shifts in the timing of certain payments, however, the deficit so far this year would have been only $92 billion smaller.

Because of the large inflows of tax revenues, the federal government usually runs a budget surplus in April—though that did not occur in 2009, 2010, and 2011. This April, the Treasury realized a surplus of $58 billion, CBO estimates, in contrast with the $40 billion deficit reported for the same month last year. The results in both years were influenced by timing shifts of certain payments; adjusted for those shifts, the surplus in April 2012 would have been $27 billion, compared with a deficit of $13 billion in April 2011.
2.1.1.2 *April Collections Were Up By 10 Percent*
Receipts this April were $319 billion—$30 billion, or 10 percent, higher than collections last April, CBO estimates. The largest boost to net receipts came from a $14 billion decline in the amount of refunds issued. Refunds were lower, in large part, because some that ordinarily would have been recorded in April were made in prior months.

Withheld income and payroll taxes rose by $10 billion (or 7 percent), while nonwithheld receipts from those sources, largely from tax filings, rose by just $2 billion (or 1 percent). In addition, net corporate income tax receipts were $3 billion higher, and all other receipts $1 billion higher, on net, in April 2012 than in April 2011.
2.1.1.3 *Total Receipts Through Seven Months Increased by 6 Percent*
Including collections associated with the mid-April filing deadline, receipts through the first seven months were about $1.38 trillion—$74 billion higher than receipts recorded in the same period last year, CBO estimates.

The April collections are often dominated by Tax filings. Yet the 6% increase in total receipts is positive.
Labels: Economy

TUESDAY, MAY 8, 2012

A TOWN MEETING

I recently went to my Town Meeting to observe what was happening on a local town funded development. Now the things that happened and I have no idea if they were planned or just happened that way, were classic old school politics, somewhat heavy handed and almost threatening. Now these are my observations and opinions and those of one who infrequently attends the meetings. But having been in politics in some way or another in my almost 20 countries of even temporary residence I found this somewhat sharp to say the least.

So let us say you are the Mayor and you and the Board have some proposal which benefits someone other than say all of the people. I am not in any way assuming less than honorable intentions and motives.

1. Minimize the Number Attending. Take Measures to Block the Parking Lot before the Meeting to Dis-incent those who were interested in attending from attending. Thus I arrive for the 7:00 PM meeting at 6:30, I am always early, but I found the parking lot over flowing. Apparently they Mayor had scheduled the handing out of certificates to High School grads starting at 6:00 PM and thus every family got there by 5:30 and there was no room for the Meeting. Nice trick, since by 7:00 they High School folks were being released and mobbed the entry way and lingered so it was near impossible to enter.

2. Reduce the Number of Attendees Allowed in the Meeting Room: I was amazed that there were 6 to 8 rows of RESERVED seats, occupied by people who appeared to me to be just sitting there. I had seen COMCAST do that trick with its union people at Harvard a few years ago at an FCC meeting. This was a typical union trick, stuff seats so even if some managed to get to the meeting they could not get in.

3. Make it Uncomfortable to Stay: The heat seemed to be jacked up to 80F and the windows were closed, “so as to better see the screen”. When people complained it seemed to me that the complaints were used just as a distraction.

4. Make It Clear You Have the Power: The police were in full force, with bullet proof vests, hands to the ready on their 9 mm weapons, all in crew cut and pigeon chested and scanning the room staring at any dissident. In my opinion it appeared as a small armed force, anticipating whatever.

5. Make Questions Difficult to Ask: I observed that even if you made it there, even if you survived the head, even if you found a place to stand, you next faced the challenge of getting your question in. There was a timer, 3 minutes, and the sound system was less than sterling, and there always was an interrupt to clarify. By that time the time was up.

6. Never Answer the Question: The answers were often a quest for additional clarity and often less than expository as far as I could see.

Thus, was this deliberate, and agenda, typical, just normal? Frankly I have no way to ascertain. But if one observed that nothing truly was answered, one could at least say it was exemplary of how to avoid answering. So I guess all politics is local.
Labels: Politics

PROSTATE CANCER STEM CELLS

There has been a great deal of work on stem cells (see our White Paper). We may think of such cells as being part of the embryo, and in the placenta at birth. They are thought of as the universal cell generator. Theoretically the stem cell should become whatever cell type we may

want it to be. In a more narrow sense there may be a variety of localized stem cells, namely cells which replenish local cells which are worn away such as on the skin or in the colon. It is not the mature cells which do the reproducing but it is the few stem cells which reside in say the basal layer of the skin which reproduce and create off spring which are just plain old keratinocytes.

In this note we examine in some detail the prostate stem cell, and in turn we generate the ability to consider the cancer stem cell issue in broader detail. We have discussed this issue in our draft volume on Prostate Cancer Genomics, and this is an additive section as that volume progresses.

The focus is on stem cells. It does not address the pathways which are different or activated. That in itself is a critical question. Namely what differentiates a stem cell from a mature non stem like cell when we examine the pathways? Thus when looking at PCa we see that pathway changes are then most likely pathway changes in the stem cell alone, yet if the agglomeration of stem cells is such that the non-stem constituents reflect the genetic makeup of the stem cell, then we would expect some parity in pathway dynamics. This will be an issue we examine in a later report.

The cancer stem cell theory has been developed over the past decade or so. For many years the theory was that cancer was clonal, namely one single cell was at fault and its progeny were the direct result of that genetically modified parent, a single parent, and that as the cancer evolved there may be increased genetic defects but again all were from a single parent.

Cancer stems cells are a construct which predicates the development of mature cells in a cell line as coming from a set of stem cells, akin to the blood cells arising from the bone. In contrast to the linear model of Vogelstein, say in the colon, the epithelial cell of the colon wall has some genetic disruption, and after multiple disruptions this epithelial cell becomes cancerous, dividing without bounds and failing to remain where is was supposed to. Typically an adenoma develops which after the final genetic hit becomes an adenocarcinoma.

For example, we have examined the prostate cancer cell, and in so doing have used a non CSC model, namely it is a basal or luminal cell which becomes genetically changed. If however we are wrong and there is an equivalent prostate cancer stem cell, as some have conjectured, then management of cancer of the prostate is quite a different thing. As we have expressed before, if one has diffuse HGPIN in the prostate and then after several high density prostate biopsies it disappears, is that inferentially valid for a prostate CSC?

The cancer stem cell construct is fundamentally different. It is not a mature cell which takes the genetic hits but the stem cell. The malignant stem cell acts almost as a force at a distance, and can impact other cells as the stem cell itself can reproduce, albeit at a somewhat slower rate than what it may influence.

Arguably if one can remove the stem cell then one removes any future malignancy, even to the extent of having other cells enter apoptosis for failure of having an active stem cell.

As Weinberg notes, there is the theory of clonal development of cancer which states that the cancer cells are pluripotent and have developed from a single source and that they have the

capability of reproducing and do so in an autonomous manner[1]. Then there is the theory of the cancer stem cell, the theory which states that there is the equivalent of a stem cell as we know in blood cells, which have the capability but that the majority of malignant cells do not necessarily have that capacity.

The NCI presents an excellent summary of Cancer stem cell, CSC, research[2]:

The theory of the cancer stem cell (CSC) has generated as much excitement and optimism as perhaps any area of cancer research over the last decade. Biologically, the theory goes, these cells are distinct from the other cells that form the bulk of a tumor in that they can self-perpetuate and produce progenitor cells, the way that traditional stem cells do. The progenitors' job is then to repopulate tumor cells eradicated by treatments such as chemotherapy or radiation.

But for all the attention and fanfare CSC research has received, the findings reported to date are far from clear-cut, investigators acknowledge. For example, most of the studies that have identified human CSCs have used mouse xenograft assays and cells from only a small number of human tumor samples, making it difficult to draw firm conclusions. In addition, other researchers haven't always been able to replicate initially reported findings. And while these tumor-initiating cells, as they are also called, have been described as being a rare class, several studies have found that the number of cells that can form tumors in these mouse experiments is actually quite large, suggesting that perhaps CSCs aren't such a privileged breed.

As we shall discuss herein, the CSC does not yet have a steady state definition or description. Furthermore it is also difficult to tag and identify. In the above definition, there is the issue of what makes the stem cell different and how many are there and how do we identify it. The CSC is in one sense the single cell which can regenerate a full cancer growth. But does that mean in vivo or in vitro or both? Murine models have been used extensively but there are serious questions regarding their extensibility.

We shall discuss some of these issues in this report. Now the NCI goes on to say:

In other words, the idea of just what cancer stem cells are, and their role in different cancers, appears to be changing.

"The [stem cell] model has not been adequately tested in most cancers," said Dr. Sean Morrison, who directs the Center for Stem Cell Biology at the University of Michigan. "I think that there are some cancers that do clearly follow a cancer stem cell model…But it will be more complicated than what's been presented so far."

They continue by noting a significant conclusion of the CSC theory, the fact that the CSC is the controlling cell, not just any cell. Specifically they state:

[1] Weinberg, Cancer, pp 416-417.

[2] http://www.cancer.gov/ncicancerbulletin/072710/page4

Unlike the random or "stochastic" model dominant in cancer research, which holds that nearly any cancer cell has the potential to form a tumor, the cancer stem cell model is one of a hierarchical organization, with the pluripotent cancer stem cell sitting ready and able to amass all of the components of the original tumor.

It's also thought, with some experimental evidence to support it, that CSC pluripotency allows these cells to adapt and to resist chemotherapy, radiation therapy, and even current molecularly targeted therapies. If true, then these treatments may not harm the most lethal tumor cells, those that can lead to a recurrence with the production of a new set of progenitors.

Despite numerous studies published in the last 16 years that identified CSCs for different cancers—including colon, brain, pancreatic, and breast cancer—the consensus among researchers seems to be that the evidence is strongest for the first cancer in which a population of tumor-initiating cells was discovered, acute myeloid leukemia (AML), as well as for other blood cancers.

The above has substantial positive and negative impact. A single stem cell may control everything, for a while. If however it undergoes mitosis then we may have many stem cells. Or we may keep a single one. For example if a stem cell in mitosis reproduces a single stem cell plus a non-stem cancer cell, then we maintain single CSCs, while we multiply the malignant non CSC cells. However, if the CSC in mitosis just multiples itself for a while, then we end up with a collection of very powerful and spreadable bombs of CSCs.

The NCI also continues:

"The reason why it's so much stronger for hematologic malignancies are because hematopoiesis research goes back 40 or 50 years and it's very stem cell-based," said Dr. Jean Wang, a stem cell researcher at the University of Toronto. "Whereas in solid tumors, there's less of a foundation for identifying the normal cellular hierarchies and for [cell-surface] markers that identify different populations of cells like stem cells and progenitors."

The above comment has some merit but one must also recognize that the hematopoietic cells are fundamentally generated in a specific location, the bone, and there may very well be no such locations specificity for the many other cells we are considering. Nevertheless, we continue:

Even so, Dr. Wang believes the existence of CSCs is pretty well demonstrated for breast and brain cancers. But, she cautioned, "I don't know if it applies to all cancers. In a lot [of cancers] it does seem to apply. But most of the markers we have right now are still very rough." Despite the evidence for CSC-like cells in a growing number of cancers, the theory clearly has its skeptics, who point to problems such as shortcomings in the mouse xenograft assay and the variable specificity of the cell-surface markers used to demarcate a CSC from a non-CSC.

"I still feel that it's a concept yet to be proven," said Dr. Barbara Vonderhaar, who, along with colleagues in NCI's Center for Cancer Research, recently published a study identifying a population of CSC-like cells in estrogen receptor-negative breast cancer. "It's certainly a good

idea, but it's only a hypothesis at this point. We still don't have definitive proof that cancer stem cells exist."

The CSC concept is "a work in transition," said Dr. William Matsui, from the Johns Hopkins School of Medicine, whose lab studies the role of stem cells in hematologic cancers. "To me, as a clinical person, the ideal model is one where you can find something that is going to work in humans. We're far from that."

The existence of CSCs in PCa has been examined and as with many cancers is still open for discussion. However as we shall discuss later the CSC model does have certain interesting uses in the progression and metastasis of cancer.

For example:

Cell Proliferation: If we assume that the CSC is the dominant cell that proliferates and all others do not, albeit being cancer cells themselves, then the growth of PCa in terms of cells is complex but one can then more easily explain indolent PCa.

Metastasis: We know that metastasis occurred by lymphatic and hematological means. However PCa cells, non-CSC PCa cells may break loose and yet not result in classic metastasis. The issue then is one where it may be necessary for the CSC to move by these means.

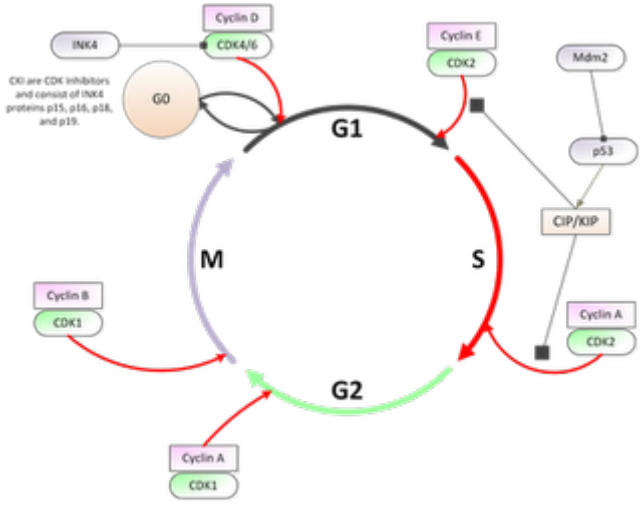
Many other such issues will arise and we discuss the CSC idea here and we return to it later in the work.

Now we can view the stem cells as shown below. There is a stem cell which can give rise to a new stem cell of ultimately a Post Mitotic Differentiated Cancer Cell. The PMDC cannot replicate, whereas the stem cell can. For metastasis it is thus necessary to send out a few stem cells, not PMDC cells.

The Stem Cell Paradigm

The first issue is a definition of a stem cell. We may understand stem cell from the hematopoietic stem cells found in the bone which give rise to a variety of blood cells and other types of cells. In fact almost all cells in the body which require some form of replenishment have such stem cells. Consider the skin. The basal layer has stem cells to generate the keratinocytes. In fact it may be argued that melanocytes have their own stem cells as well.

Cells are reproducing via the cell cycle as we show below and discuss in Appendix B. With a stem cell, it is only that cell which does the mitotic division; all other cells are just mature functioning cells subject to normal cell death or apoptosis.



The question is however, which cells. Which cells are the stem cells? Are all cells reproducing or just some select class of cells. The concept of stem cells makes the issue one of a small select group of cells. These are the stem cells.

As Alberts et al state (pp 1417-1421):

Humans renew the outer layers of their epidermis a thousand times over in the course of a lifetime. In the basal layer, there have to be cells that can remain undifferentiated and carry on dividing for this whole period, continually throwing off descendants that commit to differentiation, leave the basal layer, and are eventually discarded.

The process can be maintained only if the basal cell population is self-renewing. It must therefore contain some cells that generate a mixture of progeny, including daughters that remain undifferentiated like their parent, as well as daughters that differentiate. Cells with this property are called ***stem cells****.*

They have so important a role in such a variety of tissues that it is useful to have a formal definition. The defining properties of a stem cell are as follows:

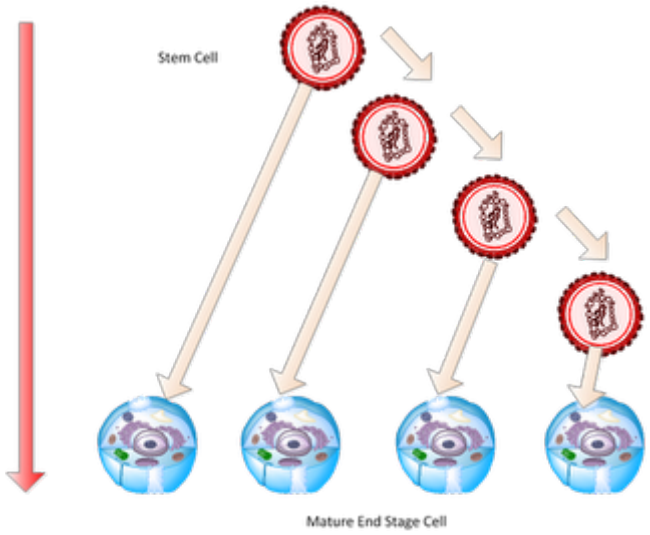
1. It is not itself terminally differentiated (that is, it is not at the end of a pathway of differentiation).

2. It can divide without limit (or at least for the lifetime of the animal).

3. When it divides, each daughter has a choice: it can either remain a stem cell, or it can embark on a course that commits it to terminal differentiation.

Stem cells are required wherever there is a recurring need to replace differentiated cells that cannot themselves divide. The stem cell itself has to be able to divide—that is part of the definition—but it should be noted that it does not necessarily have to divide rapidly; in fact, stem cells usually divide at a relatively slow rate.

We present below a simplified example of a specialized stem cell. The stem cell is the only one of its kind to divide. The mature cells do not generally divide; they are just functional and proceed to mature. The stem cell always produces at least one of its own kinds, another stem cell, and then one of the mature like cells. Note the initial stem cell. In this example we allow it to divide and produce one stem cell and one maturing cell. Thus at some point this process just keeps the number of stem cells constant but can produce an ever growing number of maturing cells.



Now when we examine the above we can see that if the stem cell divides once every hour, and the life of a mature cell is say 24 hours, then we have a growth effect. We must have a cell stability of one replenishment per one destroyed. During a growth state however, the stem cells are reproducing quickly and cells are added. The stem cell responds to surface stimulants to enter into cell cycle production.

As Tang et al state:

Normal adult stem cells (SC) have several fundamental properties: they are generally very rare, can self-renew, have tremendous proliferative potential but normally (i.e., in their niches) are quiescent, and can differentiate along one or several different cell lineages.

The most defining property of a SC is its ability to self-renew while being able to differentiate into all different lineages of progeny and even to reconstitute an organ, as exemplified by a single hematopoietic SC (HSC) to reconstitute the whole blood and rescue an irradiated mouse. SC development is a continuous and dynamic process, in which cells with distinct self-renewal, proliferative, and differentiation abilities may co-exist.

For example, mouse HSC are heterogeneous populations of cells containing long-term HSC (LT-HSC), which can sustain life-long self-renewal and reconstitution, and short-term HSC (ST-HSC), which can sustain self-renewal and reconstitution for only 8 wk. The ST-HSC generate

multi-potent progenitor (MPP) cells exhibiting only limited self-renewal capacity, which then further develop into lineage-restricted progenitor (or precursor) cells that have lost self-renewal ability.

Although this paradigm of LT-HSCST-HSC early progenitors (MPP) late progenitors differentiated cells in mouse bone marrow can, in principle, be applied to other SC developmental processes, in reality, little is known about most tissue SC lineages and we often name the subsets of cells in a specific tissue/organ with certain self-renewal and differentiation abilities simply stem/progenitor cells. Such is the case with the putative prostate epithelial stem and progenitor cells.

Consequently, throughout this review, we shall frequently use the term '(prostate) stem/ progenitor cells.'

The above feature of maturing into various lineages is clearly seen in blood cells but one may question just where it functions say in prostate cells. Is there a single stem cell which generates either a basal or luminal cell or if so where does it reside, and how does this differentiation occur? This is the point made by Tang et al towards the end of the above quote.

Cancer stem cells are a variant of the benign stem cell. Namely a cancer stem cell is a cell which behaves like a stem cell in terms of cell proliferation but now has genetic changes which reflect malignant behavior. In an NIH report the authors define cancer stem cells as follows:

A consensus panel convened by the American Association of Cancer Research has defined a CSC as "a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor." It should be noted that this definition does not indicate the source of these cells—these tumor-forming cells could hypothetically originate from stem, progenitor, or differentiated cells.

As such, the terms "tumor-initiating cell" or "cancer-initiating cell" are sometimes used instead of "cancer stem cell" to avoid confusion. Tumors originate from the transformation of normal cells through the accumulation of genetic modifications, but it has not been established unequivocally that stem cells are the origin of all CSCs.

The CSC hypothesis therefore does not imply that cancer is always caused by stem cells or that the potential application of stem cells to treat conditions such as heart disease or diabetes, as discussed in other chapters of this report, will result in tumor formation. Rather, tumor-initiating cells possess stem-like characteristics to a degree sufficient to warrant the comparison with stem cells; the observed experimental and clinical behaviors of metastatic cancer cells are highly reminiscent of the classical properties of stem cells.

The stem cell theory, and there seems now to be significant evidence of its validity in prostate cancer, is principally that the clonal theory has merit to a point but that the development is more complex and the cancer stem cell plays a critical role in fostering growth of the cancer cells, most of which has less aggressive a growth characteristic if any at all.

Lawson and Witte present a recent overview of this concept as applied to the prostate and PCa. Recent studies apparently indicate that the cancer stem cells, CSC, are necessary to sustain later stages of the development of the malignancy. Only a small subpopulation of the cancer cells, the CSC population, has a demonstrated ability to maintain the malignancy as well. Lawson and Witte present two theories of this CSC process. One is called the stochastic theory which is that all cells are equally malignant. The other theory, the one for CSC, called the hierarchical theory is that only the CSC has the ability to multiply.

The CSC or in this case the PSC, prostate stem cell, yields a TAC, or transition amplifying cells, then yield progenitor cells, LP or BP, and then finally a luminal or basal cell. This is slight contrast to the Goldstein model. This model applies for both benign as well as cancer cells, at least as viewed by Lawson and Witte.

Now if one looks at the CSC theory, then we see a CSC has progeny, and yet those progeny may not have the ability to multiply. Thus the explosive exponential growth of cancer is not as clear in a CSC model, because almost all of the progeny of the CSC are no reproducing progeny. Thus the growth models for a CSC based malignancy are more complex and are dependent on limited CSC reproduction and non-CSC reproduction. However the CSC model also argues for there being some CSC support for the progeny which are not CSC. The dynamics of cell growth then becomes quite complex here, for the stem cells replicate themselves at a slow rate but are replicating other cells at a higher rate. However the other cells do not replicate themselves they just go through a standard cell process. If the cells are benign then they go through apoptosis as seen in red blood cells and the skin keratinocytes.

We quote Lawson and Witte as follows:

Models of prostate epithelial differentiation. The traditional model for prostate epithelial differentiation proposes that PSCs residing in the basal cell layer give rise to intermediate, transit-amplifying cells that produce large numbers of terminally differentiated secretory luminal cells …. This model implies a linear differentiation scheme in which basal and luminal cells comprise one lineage and basal cells are essentially luminal cell progenitors …

This hypothesis is supported by the existence of cells of intermediate phenotype that express both basal- and luminal cell–specific cytokeratins in both fetal and adult stages of prostate development … Intermediate cells can also be identified in in vitro cultures of primary prostate epithelium … Several studies have also suggested basal cells can differentiate into luminal cells in vitro … Alternative theories for prostate epithelial differentiation propose basal and luminal cells may represent separate epithelial lineages … This is similar to prevailing models for epithelial differentiation in the mammary gland, a tissue that is anatomically and functionally analogous to the prostate …

Now there have been several others who have examined the stem cell model for PCa. Another of recent merit is that of Hurt et al. They summarize their work as follows:

Recent evidence supports the hypothesis that cancer stem cells are responsible for tumor initiation and formation. Using flow cytometry, we isolated a population of CD44+CD24-

prostate cells that display stem cell characteristics as well as gene expression patterns that predict overall survival in prostate cancer patients. CD44+CD24- cells form colonies in soft agar and form tumours in NOD/SCID mice when as few as 100 cells are injected.

Furthermore, CD44+CD24- cells express genes known to be important in stem cell maintenance, such as BMI-1 and Oct-3/4. Moreover, we can maintain CD44+CD24- prostate stem-like cells as non-adherent spheres in serum-replacement media without substantially shifting gene expression. Addition of serum results in adherence to plastic and shifts gene expression patterns to resemble the differentiated parental cells.

Thus, we propose that CD44+CD24- prostate cells are stem-like cells responsible for tumor initiation and we provide a genomic definition of these cells and the differentiated cells they give rise to. Furthermore, gene expression patterns of CD44+CD24- cells have a genomic signature that is predictive of poor patient prognosis. Therefore, CD44+CD24- LNCaP prostate cells offer an attractive model system to both explore the biology important to the maintenance and differentiation of prostate cancer stem cells as well as to develop the therapeutics, as the gene expression pattern in these cells is consistent with poor survival in prostate cancer patients.

Jordan et al characterize cancer stem cells as having three characteristics:

1. Self-Renewal: at the end of mitosis of the stem cell, either one or both retain all the characteristics of the parent. The stem cell goes through a mitotic doubling and when it does it always retains one or two stem cell daughters.

2. Capability to generate multiple lineages. This means that a stem cell can generate offspring which can become anyone of many cell types.

3. Potential to proliferate extensively. The cell can keep replicating, it has no limitation within reason and thus contains the elements ultimately for metastasis.

A normal stem cell may mutate to a cancer stem cell or a normal progenitor cell may morph back to a cancer stem cell.

As Delarbra et al state:

Although monoclonal in origin, most tumors appear to contain a heterogeneous population of cancer cells. *This observation is traditionally explained by postulating variations in tumor microenvironment and coexistence of multiple genetic subclones, created by progressive and divergent accumulation of independent somatic mutations.*

An additional explanation, however, envisages human tumors not as mere monoclonal expansions of transformed cells, but rather as complex tridimensional tissues where cancer cells become functionally heterogeneous as a result of differentiation.

According to this second scenario, tumors act as caricatures of their corresponding normal tissues and are sustained in their growth by a pathological counterpart of normal adult stem cells, cancer stem cells.

The statement starts with the accepted monoclonal hypothesis and then departs to a polyclonal alternative view. It retains the CSC, cancer stem cell, paradigm for solid tumors as well. In the context of HGPIN we see a change in the cells and we have heard the argument that they have made one or several of the unchangeable steps towards PCa. Thus using the CSC theory one would expect that it would be from one or several of these cells that PCa would arise. In addition, we could assume that there is no unique pathway mutations or changes which result in PCa but a plethora of them. Simply stated, cancer is complex, it finds ways to migrate forward no matter what the path.

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A recent study by Deleyrolle et al has focused on the stem cell and its dynamics[3]. The reviewers state:

The method, published in the online journal PLoS ONE in January, may rev up efforts to develop stem cell therapies for Alzheimer's, Parkinson's and other diseases. It may also help get to the root of the cancer-stem cell theory, which puts forth the idea that a tiny percentage of loner cancer cells gives rise to tumors.

"Math is going to be the new microscope of the 21st century because it is going to allow us to see things in biology that we cannot see any other way," said Brent Reynolds, Ph.D., an associate professor of neurosurgery at UF's McKnight Brain Institute and a member of the UF Shands Cancer Center. "Stem cells and the cells that drive cancer may be as infrequent as one in 10,000 or one in 100,000 cells. The problem is how do you understand the biology of something whose frequency is so low?"

Inspired by a 2004 essay by Joel E. Cohen, Ph.D., of The Rockefeller University and Columbia University that described the explosive synergy between mathematics and biology, Reynolds and postdoctoral associate Loic P. Deleyrolle set out to build an algorithm that could determine the rate stem cells and cancer stem cells divide.

[3] http://www.eurekalert.org/pub_releases/2011-01/uof-gfm012011.php

High hopes to treat or prevent diseases have been pinned on these indistinguishable cells, which are often adrift in populations of millions of other cells. Scientists know stem cells exist mainly because their handiwork is everywhere — tissues heal and regenerate because of stem cells, and somehow cancer may reappear years after it was thought to be completely eliminated.

Nature has an interesting poster on the cancer stem cell, CSC[4]. The poster states:

The concept of the cancer stem cell (CSC) has taken off rapidly over the past 10 years. CSCs are cells with properties that are similar to those described for tissue stem cells: self-renewal and asymmetric division resulting in the generation of daughter cells destined to differentiate, enabling the regeneration of a tissue. Initial research into the properties of CSCs was based on identifying and verifying markers of this subset of cancer cells.

However, most studies have now moved on to understanding the biology of CSCs and the cancers in which they maintain tumour growth, as well as how and why they are able to serially generate a tumour. It is thought that a key element regulating the biology of stem cells is their niche — cells and extracellular matrix that support self-renewal and survival. As we begin to understand the pathways that are crucial for the properties of CSCs, including signals provided by the niche, we will hopefully be able to effectively target this cell population.

Linked to the identification of CSCs is the cell of origin. These are cells that when mutated are able to give rise to a tumour. Although these cells may share properties with CSCs, in most cases it is not yet clear whether these cells are one and the same. This poster highlights some of the recent findings regarding the biology of CSCs and the identification of cell types from which cancers can arise.

As regards to prostate cancer they state:

In the normal prostate, epithelial cells with tissue-regenerating capacity that are Sca1+, CD49fhi, TROP2hi, CD44+, CD133+ and CD117+ (mouse) or CD133+, CD44+, CD49fhi and TROP2+ (human) seem to reside in the basal layer of the prostate. However, studies in mice indicate the existence of luminal cells with progenitor characteristics that can regenerate the prostate after androgen withdrawal. As castration resistance is also a property of basal stem cells in the prostate, it suggests a complex cellular hierarchy.

Studies in mice indicate that prostate tumours can arise after transformation of basal stem cells and luminal progenitor cells. A subset of cells that are CD133+, a2b1 + and CD44+ and have basal cell characteristics have been shown to be tumorigenic, but whether these cells can serially propagate tumours in mice has yet to be verified.

Again and interesting experiment can be performed:

1. Take biopsies from N men with HGPIN diagnosed on initial biopsies. Perform sampling from say 20 cores.

[4] http://www.nature.com/nrc/posters/cancerstemcells/csc_poster.pdf

2. Wait 9 months, and rebiopsy, again with near saturation cores, 20+ .. There are three possible outcomes:

a. HGPIN remains
b. PCa has been determined
c. HGPIN regresses and only benign cells are left

3. The question is why did (c) above happen? What percent of the HGPIN have regressed? If the percent of HGPIN that have regressed equals the probability of having actually excised the cancer stem cell or cells, we can calculate this, then by chance we have removed the CSC from the HGPIN and this would affirm its existence by inference.

Now a similar article appears in Science which speaks to colon cancer and the cancer stem cell theory[5]:

In normal colon tissue, intestinal stem cells (ISCs) that reside at the base of mucosal wells, named crypts, expand through mitosis and move upward toward the crypt tip. The cells then undergo cell cycle arrest and terminal differentiation, finally becoming the mucosal epithelium of the colon. In the recent study, the investigators identified in mouse ISCs a gene signature that was specifically marked by high expression of the ephrin type-B receptor 2 gene(Ephb2), which encodes a receptor tyrosine kinase, the leucine-rich repeat–containing G protein–coupled receptor 5 gene (Lgr5), which encodes a G-coupled protein receptor of unknown function, and ~50 other genes.

This gene signature also defined a specific population of stem-like cells at the base of colorectal tumor structures in mice that were morphologically similar to normal mouse intestinal crypts. The authors then similarly inspected tumor samples from 340 colorectal patients and discovered a 10-fold increase in the relative risk of recurrence in patients whose tumors displayed high expression of the human counterparts of the mouse ISC genes, relative to patients whose tumors showed low expression of these genes.

To test whether the mouse colorectal tumor cells with the ISC gene signature were cancer stem cells; the investigators isolated the cells and introduced them into an immunodeficient mouse model. The stem-like cancer cells demonstrated both a tumor-initiating capacity and self-renewal capability in vivo.

These findings pinpoint potential markers that may allow a clinician to predict a patient's future with respect to recurrence. These differentially expressed genes also may give rise to therapeutic targets that quell cancer stem cells.

What is clear is that the CSC is becoming a viable model for understanding cancer at another level.

[5] http://stm.sciencemag.org/content/3/81/81ec64.short?rss=1

We first relook at the progression and regression dynamics. The key driver for the analysis herein has been the regression often seen in HGPIN. Knowing that most likely the methylation of GSTP1 has given rise to development of PIN we then ask what gives rise to its regression and why have the HGPIN cells themselves not only stopped growing but have disappeared. Again we have seen this in melanomas, and this is also the Rosenberg effect in certain sporadic cancer regressions.

To look more closely we first return to the stem cell model for cancer which we developed earlier. The stem cell theory states that there are a certain number of cancer stem cells which in turn may replicate themselves but also create what are termed post mitotic differentiated cells. Not really stem cells but cells which exhibit the phenotypic characteristics of a cancer cell. One of the questions one may pose is do these PMDC exhibit a different genotypic character as well or are they controlled by some epigenetic factors.

Now we can also see as Weinberg has noted (Weinberg p 419) that a progression may occur in a somewhat more complex mechanism as we depict below. Now from the stem cell arises Transit Amplifying Cells and then the PMDC.

Now in reality there may be multiple genetic hits which give rise to the stem cell, the pluripotent self-replicating core of a cancer. The Figure below provides a generic profile, namely we may see many genetic changes, some leading to cancer as in mutation 3 below and others just wandering off into self-replicating cells but not with a malignant tendency.

Finally when we return to the HGPIN model we see the benign cell migrating to a dysplasia, say HGPIN, and then to a malignant cell, but then there is the regression back to a benign cell. The question is then; what pathway elements takes us one way and what elements take us back. And what happened to the dysplastic cells? Did they just die, apoptosis, or were they scavenged?

Wang and Shen have written a quite useful review of the cancer stem cell thesis for prostate cancer. There is no definitive conclusion but the review covers a wide path through what has been accomplished to date.

Recall as we have written before the cancer stem cell (CSC) model, and it is a model, hypothesizes that there are certain core cells which control the malignant growth of other cells and that the other cancerous type cells do not in and of themselves have the ability to continue to grow. In fact it could be concluded, although not part of the current theory, that removal of a CSC from a tumor, say the only CSC, would result in the apoptosis of the remaining cells. Namely, a remission.

In contrast to the CSC model we have the clonal model which says that the cells have progressed through a set of pathway modifications that have resulted in a single cell which takes off and multiples and that the progeny have identical genetic makeup or further genetically modified makeup but all and equally malignant.

These are two fundamentally different views of cancer. One could also state that recent work with melanoma as we have discussed also posit that the CSC "communicates" to progeny to have them multiply and that arguably the loss of the CSC

There is a great deal of difficulty in identifying the CSC, usually attempting to do so via surface markers such as CD44 and the like.

Wang and Shen then discuss the controversy regarding the CSC concept. They state:

Much of the confusion in the literature arises through inconsistencies in nomenclature within the field. In particular, due to the wide use of xenotransplantation as a functional assay for CSCs, transformed cells that can initiate tumor formation in this assay are often referred to as CSCs in the literature. However, a tumor initiating cell (TIC) represents a different concept from that of a CSC, as TICs unquestionably exist within tumors and their identification does not by itself imply a hierarchical organization of a tumor.

Indeed, the majority of cells within a tumor could potentially possess TIC properties and nonetheless follow a clonal evolution model. Consequently, it is important to distinguish CSCs that have been strictly defined by their position and function within a lineage hierarchy in vivo from CSCs that have been identified as rare TICs in transplantation studies.

A similar confusion arises with respect to the cell of origin for cancer, which corresponds to a normal tissue cell that is the target for the initiating events of tumorigenesis. In principle, a normal adult stem cell could be a logical cell of origin for cancer, as it would retain the ability to self-renew and generate a hierarchy of differentiated lineages within a tumor. However, it is also possible that a cell of origin could correspond to a downstream progenitor cell or conceivably even a terminally differentiated cell that acquires stem cell properties during oncogenic transformation.

Our argument has been that the CSC may most likely exist and that it has undergone certain pathway changes and that as a result it may influence the growth of not identically genetically changed cells to multiply but not in and of themselves have the potential to multiply.

Wang and Shen continue:

The identification of normal cells that can serve as a cell of origin for prostate cancer is highly relevant for understanding the applicability of a CSC model, and is currently under intense investigation. The cell of origin may also have clinical significance, as in the case of breast cancer, distinct tumor subtypes have been proposed to originate through transformation of different progenitors within the mammary epithelial lineage. Thus, it is conceivable that there may be distinct cells of origin for other epithelial cancers, and different cells of origin may give rise to clinically relevant subtypes that differ in their prognosis and treatment outcome.

Thus there are either basal cells or luminal cells as the cell of origin. Goldstein et al in Witte's lab had developed a murine model demonstrating the basal cell as the cell of origin. However there may be strong issue regarding this model as applied to human prostate cancer. It represents

a viable pathway but not necessarily the only. The issue is one of pathways as well as one of intercellular communications with debilitated pathways.

Now to follow the Wang and Shen model we have the following. Fist we show a normal prostate gland with basal and luminal cells.

Then we show their view of a Tumor Initiating Cell in either the basal or luminal layer. The Goldstein et al murine model argue for the basal layer and there are others arguing for the luminal.

The Wang and Shen model is as follows.

1. A normal prostate cell has both luminal and basal cells.

2. TICs may be formed in either basal or luminal cells.

3. Neoplasia starts with intro acinar proliferation.

4. Carcinoma starts when it expands beyond the gland and starts up its own quasi-glandular structures.

Now what causes this? Genetic changes result in pathway changes. We show two pathways below. We lose PTEN and we may activate myc and other parts of the pathway control mechanism.

We now make a different argument. If there exists a true PCa CSC then perhaps one may putatively validate it as follows. The logic then is:

1. Assume a PCa CSC exists.

2. Assume that the PCa CSC replicates its CSC self at a low rate and is initially confined to the prostate gland.

3. Assume that the PCa CSC can influence the growth of TIC which themselves cannot sustain a malignancy. Specifically we assume that the TICs require the CSC for continued growth and further the CSC does so via cell growth as well as intercellular communications.

4. Now let us assume we have performed an 18 core biopsy on a 60 cc prostate gland and find histologically extensive high grade focal prostatic intraepithelial neoplasia. According to Wang and Shen they are most likely TICs and furthermore there may be a CSC somewhere so that eventually we see a PCa. There may be one or a few CSC in one or all of the glands yet we have no definitive marker to indicate as such.

5. Now assume we perform a second multi core biopsy on the gland and say do 22 cores in a 60 cc gland. This is the same gland but say 9 months later. We would arguably expect one of two possible outcomes. First that the HGPIN remains in place and possibly has expanded. Second

that there was a CSC and the HGPIN had become classic PCa with say Gleason 2 or 3 at a minimum about the HGPIN clusters.

6. If however, we examine the cores and find no evidence of any neoplasia or PCa, namely the gland has totally reverted to benign histology, we may have a reasonable argument that perhaps the CSC was present initially, and it was somehow removed along with the HGPIN in the initial biopsy leaving the TIC alone behind. Thus the TICs requiring a CSC to survive go into an apoptotic state and are removed from the prostate. Perhaps.

We have seen that specific situation occur and one could then argue that the Wang and Shen model for CSCs may be a viable model and further if such can be shown more extensively than we may have a basis for PCa progression.

There is an interesting article by Clevers in Nature Medicine which is an up to date review of the cancer stem cell issue. In light of the flurry of reports stating the wonders of having identified genes which appear in many tumors, prostate being the case, and my previous remarks that perhaps is the CSC is in fact existent, that then one should be identifying it and its genetic makeup as well as the dynamics of its pathways.

Now Clevers suggests a four step process, albeit with limited experimental evidence, but a superb start. It is as follows:

The above are the first two steps. Perhaps a dysplasia or neoplasia but with the kernel of a stem cell. This is the first "hit" theory. The epithelium starts to grow in a strange manner. Say a polyp in the colon or HGPIN in the prostate. Then we see a second hit and the formation of extraepithelial growth.

Then the third hit for the author and we see transmission via the blood stream. Then the fourth hit and the explosion from a few to almost all cancer stem cells.

Whether this is a good or bad model is yet to be seen. As Clevers states:

Central to the cancer stem cell (CSC) concept is the observation that not all cells in tumors are equal. The CSC concept postulates that, similar to the growth of normal proliferative tissues such as bone marrow, skin or intestinal epithelium, the growth of tumors is fueled by limited numbers of dedicated stem cells that are capable of self-renewal. The bulk of a tumor consists of rapidly proliferating cells as well as postmitotic, differentiated cells. As neither of these latter two classes of cells has the capacity to self-renew, the contribution of these non-CSC tumor cells to the long-term sustenance of the tumor is negligible.

The increased focus on the CSC is truly needed because if it is indeed a key paradigm in cancer then it and not large tumor masses should be examined. Clevers concludes with:

Epilogue: are CSCs and clonal evolution mutually exclusive?

To date, the CSC field has treated tumors as genetically homogeneous entities, by and large ignoring the fact that the observed tumor heterogeneity may result from underlying genetic differences. However, it is well known that most solid tumors show extensive genomic instability. Moreover, genetic defects in a large variety of molecules that are involved in the maintenance of the integrity of the genome are well-known drivers of oncogenesis. Even in a disease like CML, so clearly driven by stem cells, clonal evolution can be seen at work when imatinib is administered: the malignancy becomes tumor-resistant through the emergence of clones that carry mutations in the target of imatinib, the BCR-ABL1 fusion gene75. And the progression of CML into ALL blast crisis is caused by the emergence of subclones that harbor inactivating lesions in the cyclin-dependent kinase inhibitor 2A (CDKN2A, also known as ARF) gene in addition to the BCR-ABL1 translocation76. The evidence for clonal evolution in the pathogenesis of cancer is so overwhelming that it appears inescapable that all models should be integrated with it.

The recent rapid advances in DNA sequencing are now allowing the global analysis of genomic changes of cancer cells. These analyses have confirmed many previously known common genetic alterations in cancer, and they have also revealed some new common mutations as well as unexpectedly large numbers of rare mutations. As a next step, this technology can be applied to chart genetic heterogeneity within individual tumors as well as between primary tumors and their local recurrences and metastases.

It should thus be possible to map, in both space and time, the genetic evolution of a tumor.

The last sentence is the most compelling. Cancer may be more than just a cellular disease; it may require the spatial domain as well. This is an exceptionally good review and should be a focus for future research.

PCa Stem Cell Recognition

Recent work by Qin et al. examine the more detailed nature of the prostate cancer stem cell (PCa CSC). We here look at that as a starting point and then examine some of the surrounding literature to see if the results from that work can be extensible. The cancer stem cell model is one which akin to the stem cell model above states that there are a class of stem like cells which have been mutated and the development of cancer results from the turning on of these cells.

Before proceeding let us review a few issues. It should be noted that we are simplifying the analysis to intensify several points and let the reader focus on the literature to assist in resolving some of the lost complexities. Now:

1. Stem cells have certain characteristic and the only one we focus on here is that for the most part they are the only cells of a class which have the ability to reproduce. In a stable environment, the stem cells reproduce at a rate equal to the loss of mature functional cells. Thus in the skin, the basal stem cells reproduce at a rate equivalent to the death and loss of the keratinocytes, no more or less. Let there be an injury then they produce more by being activated by some ligand on some receptor on the stem cell. Cells reproduce until equilibrium is reached.

2. Mature cells, derivative from stem cells, do not reproduce. They just do what they were intended to do, no more or less.

As Wang and Shen state in a recent article (2011):

The cancer stem cell (CSC) model proposes that cells within a tumor are organized in a hierarchical lineage relationship and display different tumorigenic potential, suggesting that effective therapeutics should target rare CSCs that sustain tumor malignancy…CSCs are instead defined in practical terms through the use of several functional assays. The most frequently used methodology involves xenotransplantation of flow sorted populations of primary cancer cells into immunodeficient mice. In this assay, CSCs are defined as a subpopulation of cells within a primary tumor that can initiate tumor formation in mice following transplantation, unlike the remaining tumor cells

This is a definition limited to the assay produced. It is not a broad based definition.

Wang and Shen then discuss the types of prostate cells:

In human and mouse, the normal prostate gland epithelium contains three primary differentiated cell types.

1. *Luminal cells are columnar epithelial cells that express secretory proteins as well as markers such as cytokeratin 8 (CK8), CK18, Nkx3.1, prostate-specific antigen and high levels of androgen receptor (AR).*

2. *Basal cells are localized beneath the luminal layer and express markers including CK5, CK14 and p63, but express low levels of AR.*

3. *A rare third type of cells termed neuroendocrine cells express endocrine markers such as synaptophysin and chromogranin A, but do not express AR.*

Then they allege:

Prostatic intraepithelial neoplasia (PIN) is often considered a precursor of prostate cancer, and is characterized histologically by luminal epithelial hyperplasia and a progressive loss of basal cells …

Here we have previously expressed concern regarding counter-examples. Namely it is known that there are patients where a diffuse HGPIN may be present upon a high density sampling and then after a second high grade sampling the HGPIN is totally gone. The question is why? If as many agree HGPIN is the precursor of PCa and if moreover HGPIN is already a representation of a CSC mutation, then what has reversed the mutation. Perhaps it was the fortuitous removal on the CSC in the initial sampling? We have argued that such may be inductively deduced from examining the number of times this occurred related to the statistical chance of such happening.

In a recent paper, Qin et al state[6]:

Prostate cancer (PCa) is heterogeneous and contains both differentiated and undifferentiated tumor cells, but the relative functional contribution of these two cell populations remains unclear. Here we report distinct molecular, cellular, and tumor-propagating properties of PCa cells that express high (PSA^{+}) and low ($PSA^{-/lo}$) levels of the differentiation marker PSA. $PSA^{-/lo}$ PCa cells are quiescent and refractory to stresses including androgen deprivation, exhibit high clonogenic potential, and possess long-term tumor-propagating capacity.

They preferentially express stem cell genes and can undergo asymmetric cell division to generate PSA^{+} cells.

Importantly, $PSA^{-/lo}$ PCa cells can initiate robust tumor development and resist androgen ablation in castrated hosts, and they harbor highly tumorigenic castration-resistant PCa cells that can be prospectively enriched using $ALDH^{+}CD44^{+}\alpha2\beta1^{+}$ phenotype.

In contrast, PSA^{+} PCa cells possess more limited tumor-propagating capacity, undergo symmetric division, and are sensitive to castration. Altogether, our study suggests that $PSA^{-/lo}$ cells may represent a critical source of castration-resistant PCa cells.

Specifically:

1. *$PSA^{-/lo}$ PCa cells are quiescent and refractory to anti-androgen and chemotherapy*
2. *These cells express stem cell genes and can undergo asymmetric cell division*
3. *They also possess long-term tumor-propagating capacity in intact male mice*
4. *$PSA^{-/lo}$ PCa cells are highly tumorigenic and resist androgen ablation in vivo*

We depict the details from the paper and show it below:

[6] http://www.cell.com/cell-stem-cell/abstract/S1934-5909%2812%2900126-9

As Merville states in commenting on the work of Qin et al[7]:

In cell lines and mouse model experiments, the low-PSA cells resisted chemotherapy and thrived under hormone deprivation, the two main prostate cancer drug treatments, the researchers found.

Low-PSA cells were found to be both self-renewing and capable of differentiating into other prostate cancer cell types upon division, a hallmark of stem cells called asymmetric cell division. "Asymmetric cell division is the gold standard feature of normal stem cells," Tang said. "Using time-lapse fluorescent microscopy, we were able to show asymmetric cell division by filming a low-PSA cell dividing into one high-PSA cell and one low-PSA cell."

When the team implanted the two cell types in hormonally intact male mice, the rapidly reproducing PSA-positive cells caused faster growth and larger tumors in the first generation. However, after that the low-PSA cells generated larger, faster-growing tumors and tumor incidence in the high-PSA cells dropped.

In fact, the low-PSA prostate cancer cells possess indefinite tumor-propagating capacity. In contrast, when implanted in the castrated mice, the low-PSA prostate cancer cells developed much larger tumors than the corresponding high-PSA cells. In another experiment, mice with tumors generated by either cell type were then castrated and treated with hormonal therapy.

Low-PSA tumors grew better in these doubly androgen-deprived mice than the high-PSA tumors. "These findings closely resemble progression observed in patients after androgen-deprivation

[7] http://www.eurekalert.org/pub_releases/2012-05/uotm-sip050412.php

treatment and reflect reduced PSA-producing cells in patient tumors after androgen depletion," Tang said.

As Jeet et al state regarding their view of the prostate related stem cell:

Stem cells are unspecialized cells that can self-renew and differentiate to yield a diverse range of specialized cell types of a tissue or organ. The mouse prostate comprises dorsal, lateral, ventral, and anterior lobes, each containing three regions of proliferating cells—distal, intermediate, and proximal. It has been suggested that the prostatic stem cells reside in the proximal region of the mouse prostate.

These findings, together with tissue recombination approaches (that allow the study of mesenchymal-epithelial interactions in developing tissues), led to the elegant work that developed a new prostate regeneration system by combining CD117 (a prostate stem cell marker predominantly expressed in the proximal region) positive fractions from C57BL/6 mouse donors with rat embryonic urogenital sinus mesenchymal stromal cells. These cells were then placed under the renal capsule of athymic nu/nu mouse hosts to generate functional, secretion-producing prostates. This is the first model to demonstrate the ability of mesenchyme to trigger prostate genesis thus opening up possibilities for developing insights into the earliest changes that evolve into cancer.

Jeet et al argue that their worked demonstrates the ability of these identified stem cells to have a form of prostate related pluripotency. They like many others have been using cell markers as a means of tracking the stem cell. One may then ask what is the cell receptors and activating ligands which result in the stem cell ability to perform its regenerative functions.

As Zhang stated:

Importantly, Staege and Max also noted that tumor stem cells in EFT have been identified. These tumor stem cells expressed some markers of embryonic stem cells. There are cell populations with the phenotype of embryonic stem cells in the adult body. It remains unclear as to whether such cell populations are permissive for EWSR1-FLI1 induced transformation and whether EFT is derived from these cell populations.

Zhang has extended this identification somewhat but the issue of good markers remains.

Yet as Gupta et al state:

Some of the controversy surrounding the CSC model seems to arise from confusion regarding the definition of CSCs, leading to two key objections against the use of this term.

The first objection derives from the fact that, unlike the case for normal stem cells, which are usually oligo or multipotent, it is currently unclear whether CSCs can give rise to multiple differentiated cell types….

A second key objection to the CSC model is that it is currently unclear whether the normal cellular precursors of CSCs are, in fact, bona fide stem cells. It is clear, however, that the traits used to define CSCs do not rely on knowledge of their cellular origins within normal tissues. Accordingly, the CSC model must stand or fall on the basis of experimental characterizations of cancer cell populations

The Gupta et al observations are quite important. Namely, is a stem cell born or made. Namely is there an unbroken lineage from stem cell to stem cell? Also his first observation is the pluripotency issue, namely, are stem cells able to generate a broad number of cells or are stem cells cell-specific? The current nature of the Gupta et al observations do raise issues as to how well we understand the stem cell model.

As Tang et al conclude:

The hypothetical model of hierarchical organization of PCa cells has several important implications. Above all, it can help explain how the tremendous heterogeneity associated with the PCa can be generated. The rare PCa SC that persist in a tumor will continue to generate a repertoire of progenitor cells that in turn will develop into a spectrum of cells at different stages of differentiation , thus engendering the heterogeneous phenotype of the tumor. The model posits that the tumorigenic stem/progenitor cells are mostly undifferentiated cells as supported by the observations that most CD44 and CD133 cells are AR. The model also implies that most differentiated, luminal-like cells, which constitute the bulk of the tumor, might be much less or even non-tumorigenic (Figure 6A). In support, prospectively purified CD57 cells are non-clonogenic and non-invasive [44] and prospectively purified PSAþ cells are less tumorigenic than the isogenic PSA_ cells.

They also note the positive and negative PSA in the prior paper by Tang.

There is a great deal of concern as regards to where the stem cells come from. Namely the issue of the cells of origin. Previously we had reviewed the Goldstein model, where they had indicate a basal stem source as compared to a luminal cell source.

Wang and Shen state:

The identification of normal cells that can serve as a cell of origin for prostate cancer is highly relevant for understanding the applicability of a CSC model, and is currently under intense investigation. The cell of origin may also have clinical significance, as in the case of breast cancer, distinct tumor subtypes have been proposed to originate through transformation of different progenitors within the mammary epithelial lineage hierarchy. Thus, it is conceivable that there may be distinct cells of origin for other epithelial cancers, and different cells of origin may give rise to clinically relevant subtypes that differ in their prognosis and treatment outcome.

They consider several sources. For basal cells they state:

Although prostate tumors display a strongly luminal phenotype, this does not exclude the possibility that basal cells could be a cell of origin for prostate cancer. In particular, it is

possible that transformed basal cells could differentiate to generate large numbers of luminal cancer cells. For example, prostate-specific conditional deletion of Pten by a probasin-Cre driver allele has been shown to result in a basal cell expansion accompanied by increased number of intermediate cells, suggesting a basal cell of origin … An important recent study from the Witte laboratory has used similar approaches with primary human prostate tissues to show that basal cells are a cell of origin for human prostate cancer

The Witte lab results are those of Goldstein et al which we have discussed at length (See Appendix A).

In contrast we have luminal cell origin as stated as follows:

Other studies have provided evidence that luminal cells can serve as cells of origin for prostate cancer. For example, pathological analysis of high-grade PIN samples, which still retain basal cells, suggest that molecular events associated with human prostate cancer initiation such as upregulation of c-MYC and shortening of telomere length occur exclusively in luminal cells but not their basal neighbors …

In Moscatelli and Wilson, the authors state:

There is nothing inherently contradictory in the results described by Wang et al. and Goldstein et al., because it is possible that both basal and luminal stem/progenitor cells may independently serve as cells of origin for prostate cancer.

Indeed, it is also possible that oncogenic stimuli may differ in their effectiveness in transforming distinct cell populations. The tumors that arise from different target cells may also vary in their biological behavior and genetic profiles.

There are also indications that normal prostate stem cells may reside in both the basal and the luminal compartments. Thus, if stem cells are preferentially targeted during malignant transformation, both compartments may contain cells of origin for prostate cancer.

Most of the scientific evidence indicates that prostate stem cells reside in the basal layer and give rise to the secretory luminal cells via transit-amplifying cells, which are intermediate in phenotype between stem cells and terminally differentiated cells.

There is definitive evidence that

(i) secretory cells of the adult murine prostate derive from cells that express p63, a transcription factor that is expressed by all basal cells in the prostate , and

(ii) p63- expressing basal cells are required for prostate development. In addition, prostate basal cells (human and murine) have greater proliferative activity in vitro and in vivo than luminal cells.

The molecular signature of prostate stem cells also identifies a basal-like phenotype, as they express cytokeratins 5/14, p63, and integrin ⍺6 (11). There is also evidence, however, that the luminal compartment may contain stem/progenitor cells and that these give rise to basal cells.

Experiments involving labeling cells with the synthetic nucleoside bromo-deoxy-uridine to detect those that are proliferating indicate that slow-cycling stem cells are concentrated in the proximal region of prostatic ducts adjacent to the urethra and that both basal and luminal compartments contain slow-cycling cells. Cells from this region have substantial growth potential in vivo and in vitro and can be serially passaged in vivo at least four times. It is not known whether CARNs are concentrated in the proximal region, but if so, CARNs may comprise some of the slow-cycling proximal luminal cell population.

These results provide a possible means to address the CSC signature issue. However, it is not clear that the result is definitive nor of immediate clinical use.

Stem cells are known in hematopoietic cell generation. They are isolated, separate and their ability to develop the full plethora of blood cells is well known. The stem cell concept applied to say prostate cells or skin cells is of more recent structure and is in many ways still open for debate. Taking that construct one step further and considering a cancer stem cell is possible even more of a conjecture. We can accept the concept of a cancer stem cell in the many blood cancers. We know that CML may very well have a translocation, as is found in other leukemias. Yet the establishment of the same for say prostate and melanoma malignancies is I believe still a work in progress.

For example as Jeet et al state:

Different stages of prostate cancer progression: (a) prostatic intraepithelial neoplasia, a premalignant lesion considered to be a precursor to invasive carcinoma; (b) primary localized adenocarcinoma, dependent on androgen stimulus and can be treated by androgen ablation; (c) androgen-independent prostate cancer, tumor then becomes androgen independent and metastasizes to other organs (e.g., lung, bone, and lymph node)

The linear progression we have disputed in prior writings based upon clinical observations. The reason is that we have observed the remission of diffuse HGPIN in patients at first biopsy and then the absence in subsequent. Not just reduction of HGPIN, but total elimination. Our hypothesis is that there has been the presence of a stem cell and its removal during the first extensive core biopsy, usually 16 or more cores, not classic sextant biopsy.

Stem cells are a powerful paradigm which may very well align with the clonal model. For if it is the stem cell which has suffered the genetic change then if this cell has the controlling powers attributed to it, then the stem cell model will also tell us a great deal regarding treatment, and our inability to do so.

For example, a stem cell will itself generate other stem cells as well as non-stem cells.

There are many questions still posed regarding the cancer stem cell:

1. What are the pathway dynamics and are they the same in the non-stem like cells?

2. What is the driver for the kinetics of a CSC? Namely do we have a dramatically different set of kinetics?

3. What is the mechanism for the progression of subsequent mutations in a CSC?

4. How do we identify the CSC in a sample biopsy? Are there specific cell markers and are they consistent or do they change?

5. What are the driving ligands which activate a CSC?

6. Do stem cells have true pluripotency or are they cell specific?

7. What are the stem cell surface ligands and receptors which promote mitosis and how are they transmitted across a group of cells?

8. What causes a stem cell, specifically a CSC, to evolve and how does that occur?

We can continue with a great number of these types of questions. However if one hopes to be able to model cancer pathway dynamics one must first address the issue of the CSC, for if the CSC has the definitive characteristics that we have discussed then it and it alone is what should be focused upon. Furthermore the examination of cells for pathway markers may very well have to be done only on the CSC, which then argues that we need sophisticated techniques to identify them and extract them as well.

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MONDAY, MAY 7, 2012

MANAGING OBESITY

As the NY Times states today in an editorial:

Some experts suggest that young patients at risk of diabetes need to be detected earlier and treated more aggressively. But the long-term goal should be prevention of obesity and of diabetes.

Congressional Republicans, meanwhile, are bent on dismantling health care reforms that could greatly assist in curbing the obesity epidemic. The Republican-dominated House last month narrowly passed a bill that would eliminate the Prevention and Public Health Fund, established under the reform law, in part to pay for lowering the interest rate on subsidized student loans for a year.

This is one of the most blatant distortions of physical reality that in my opinion I have ever read. There is no reform needed. Kids eat too much and the parents are solely at fault. It is merely of input less output equals net accumulation.

1. Department of Agriculture guidelines and Federal demands make it easy for kids to bulk up.

2. Kids are kept from walking anywhere, buses and other forms of reduced exercise are crowding out any form of exercise.

3. There is no penalty for being fat. Drugs do NOT solve anything, is it akin to putting a patch on a melanoma, out of sight out of mind, yeah!, until it mets to the brain.

Treatment is simple and zero cost. Weigh the little fatsos and then send a bill home to mom and dad, if there is one around!

Why in God's name blame the Republicans for not funding another Government program. That is not the solution to the problem. We clearly know the problem, and the solution, and the price is better than free.

The issue is not that there is another victim to be saved. It is that Government has become a co-conspirator in the process. Cigarettes were managed by taxing them out of existence, and making a social stigma to those who smoked. Today a pack of Cigarettes is so expensive that it exceeds gasoline. And lung cancer deaths related to smoking have begun to drop accordingly. Imagine what would happen if we taxed carbs. This is a classic case of a positive Pigou tax, albeit one even the Romney camp's advisers eschew.

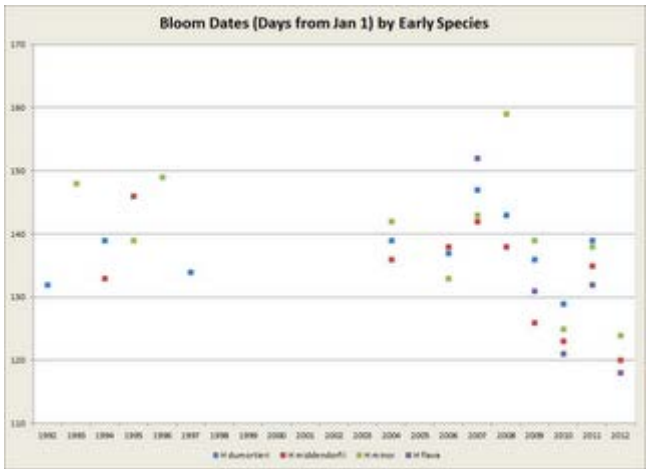
Carbohydrates create masses of free radicals in the body, eat a candy bar, especially one of the large ones sold and you have an explosion of the free radicals. Then what, they continue to explode in the body, damaging everything in their path, including DNA. Metformin and insulin do not solve this problem. Only positive economic punishment does.

Labels: Diabetes, Health Care

SUNDAY, MAY 6, 2012

GLOBAL WARMING

Now I am not a dyed in the wool believer in global warming but:



The above is some 20 years of my tracking the first bloom date of a set of species of Hemerocallis. The bloom date is measured in days from the first of the year. It does not take much to see what is happening, the slope is very much downward. In fact this year is the earliest ever, by a lot. Compared to the early 90s we are down tens of days, and that is substantial.

Just an observation. The details are in my garden web blog.
Labels: Global Warming

RESENTMENT AND POLITICS

Roger Scrunton wrote (Arguments for Conservatism, pp 157-158):

However the party that founds its rule on resentment will never feel at ease in the world that it creates. It will be like the puritan, as defined by H . L. Mencken, subject to 'the haunting fear that someone, somewhere, might be happy'. It will suspect that people are proceeding with the old way of life, expressing their energies, enjoying their successes, achieving the peace and happiness which the resentful are forever denied. The ruling party will tirelessly search for the weeds of human industry, the first frail tendrils of ownership, the timid attempts of people to grow together in their 'little platoons'. It will never be certain that the emigres, Jews, bourgeoisie, kulaks or whoever have been finally destroyed, and will be haunted by the sense that for every one killed another comes to replace him. The order of resentment will be forced to confiscate not only the free economy but also the clubs, societies, schools and churches which have hitherto been the natural instruments of social reproduction. In short, resentment, once in power, will move of its own accord towards the totalitarian state.

In many ways this is what we are seeing in the "hate the rich" approach of the current cycle.

Labels: Politics

DATA, AVAILABILITY AND THE INDIVIDUAL

One of the most interesting things I have noticed is that we now have thousands of people on blogs using real data. The St Louis FED must be inundated by users to get the data. Federal Govt sites are the worst, they make you wander about and often hide the data in pdf files. It is as if they try to keep it hidden.

But not withstanding we get it and people are finding out real things, like the numerator and denominator in unemployment. We have been arguing since 2008 that the DoL cooked the books, now people are seeing for themselves. Then they can dive down and better understand.

Yet you can tell those who get and those who don't. If they just cut and past a St Louis FED graph, well they are the amateurs. If they download the ST Louis FED data and create a new graph, they are involved with the facts, not just watchers, they have been thrown into the data, they see the process, they have that Heidegger dasein. Otherwise I would say they are passersby in lie.

As this data become more available and as people become more observant, they will soon work around the number crunchers in DC who hold forth less than truthful prognostications. This will be an interesting change.

One may they ask where are the macroeconomists in all this, just cutting and pasting!
Labels: Commentary, Economy

SATURDAY, MAY 5, 2012

TEACHER APPRECIATION

I noticed that next week is national teacher appreciation week. Now there are two of them whom I remember as formative. One was Brother Edward, above, who was my Junior Year Math (Fifth Form) teacher. In months he took me from doing poor geometry to excelling in calculus, analytic geometry and solid geometry.

The other is Tony Brown, who I still have lunch with from time to time. A veritable Damon Runyon character, who taught senior English. The joys of private school is we did Beowulf in Old English and Chaucer in Middle English. After 4 years of Latin and one of Greek, this was an eye opener. Tony is a New York version of Mr. Chips, if such could be conceived, yet does exist.

Then again I did go with Tony and the boys for a martini before my final French exam, did well but could have been better.

So to all you teachers out there, thanks, including my daughter Kris who plows the fields every day with her fourth graders. Frankly she must spend as much time per week as I did starting an international company, just no one notices.
Labels: Academy, Commentary

I DON'T REALLY THINK SO

Rajan writes in Foreign Affairs the following:

Rather than attempting to return to their artificially inflated gdp numbers from before the crisis, governments need to address the underlying flaws in their economies. In the United States, that means educating or retraining the workers who are falling behind, encouraging

entrepreneurship and innovation, and harnessing the power of the financial sector to do good while preventing it from going on track.

Now let us examine this set of words:

1 *educating or retraining the workers who are falling behind*

The problem is that the problem with the economy is that is has become more technical and the population is such that technical people are NOT trained, the must work hard and have a modicum of intellectual talent and personal dedication to perform. Yes, math is tough, and engineering is hard, which is why we have so few Americans in the field. As I have noted many times it was Norbert Wiener in the early 1950s who foresaw this change, and gave much warning as to what would happen.

Thus Rajan is missing the point. What will we do with more lawyers, macroeconomists, sociologists, and the like. They are for the most part non productive. We clearly do not need any more Romer types whose predictions are consistently worthless. They cannot agree and do not produce anything of value. But alas students go there and find jobs repeating the mistakes of the past. This all the while when the Chinese produce the scientists and engineers, as does India.

The problem in the US today and for the next generation is we facilitate the "education" of non-producers. The goal of having everyone college educated is truly foolish. First, they are just not equipped to do so. Second, we need plumbers and electricians, I can do the latter just in case. We do not need more political scientists and fine arts majors. We should not fund such efforts. Also we eliminated Teacher's Colleges. Namely educating just plain old teachers. It was cheap. Now we educate English majors at ten time the price. Why?

2 *encouraging entrepreneurship and innovation*

Entrepreneurs will exist even in Hell. Entrepreneurs manage to work around Governments and Governments, this current one especially, has set up so many challenges that the entrepreneur will go elsewhere. Governments do and can do nothing to facilitate the entrepreneur. They have a lifeblood different from most others. I set out to 20+ countries to start a business with nothing but my plane ticket, my credit card, and a clean suit! My Government really did nothing to assist. Nor did I ever expect it to do so. In fact every time I dealt with any government it was placing roadblocks. Except strangely in Russia!

Thus again Rajan misses the point. Governments are just a pain, they are useless, other than keeping one safe and protecting property rights. Which the current Administration has done a great deal to destroy. Just look at the bond and shareholders in auto companies.

3 *harnessing the power of the financial sector to do good while preventing it from going on track*

Financial markets do create liquidity. Liquidity is good. Financial markets may at times facilitate the raising of capital. Note that I say facilitate. It is incumbent upon the entrepreneur to pitch

their ideas and the financial market just has the black book of contacts. I have never met a banker who added any value beyond the contacts, and yes they have value.

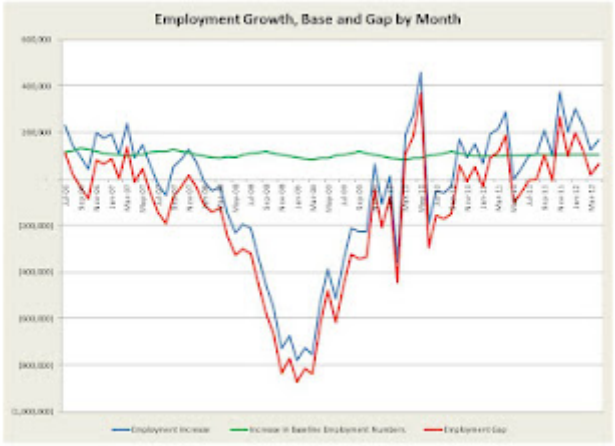
Now I miss Rajan's point of Government harnessing the power of financial players. Just what does that mean? Government should prevent them from taking risks with people's money. The solution there is say a "death penalty" approach, you lose money you pay, you lose lots of money you really pay! There must be a downside risk, a personal fear of abject terror, personal terror, which makes the financial markets stabilize.

You see the concept of Hell and eternal damnation did have a purpose. But if we cannot get a new Inquisition for the Financial Institutions and their ilk, then we need to have Government take action, that is a Lockean role of protecting property. It is a classic example of externality. If I hold assets and some greedy fool takes action that destroy the assets the bloody fool should pay, and in the most extreme form possible, and the bloody fool should know that ab initio.

That in my view is the only way to regulate what is otherwise the wild wild west.
Labels: Economics

FRIDAY, MAY 4, 2012

ADDITIONAL JOB NUMBERS



First if we look at the above, we have plotted:

1. Monthly increase in baseline numbers. This is the population adjusted increase in employment based on a fixed participation rate as of June 2008. That is the "stand still rate".

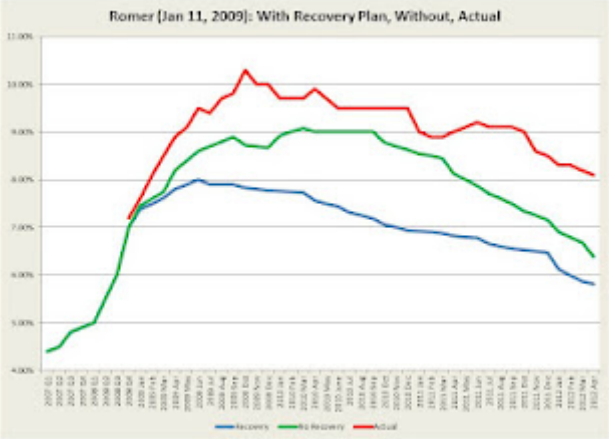
2. Increase in employment: This is the actual recorded monthly increase.

3. Gap: The difference between baseline and actual.

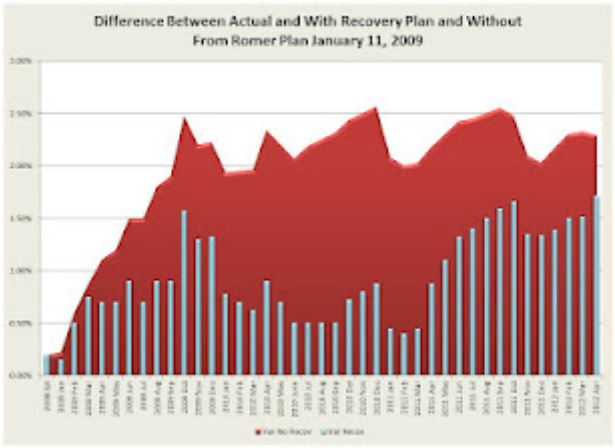
We see the low period in late 08 and early 09. We have been slightly positive in the past few months but not by much. The recovery is quite slow.

However the above shows the decreasing participation rate by men and women. Men are falling out of the workforce in droves. This is a very troubling sign and it clearly shows no signs of abatement.
Labels: Economy

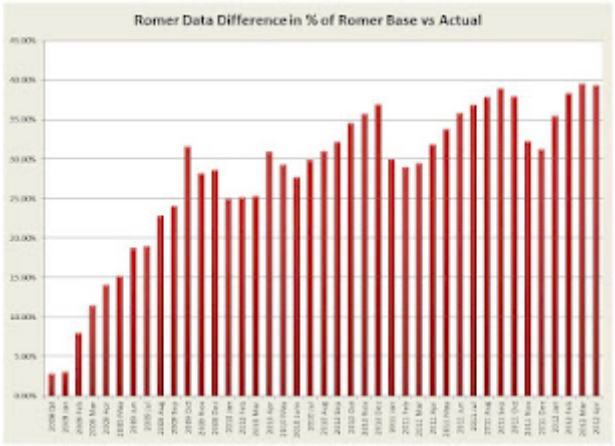
EMPLOYMENT APRIL 2012



As usual we start with the Romer curve. By this time we should have been well below 6% as per Romer. Not close.

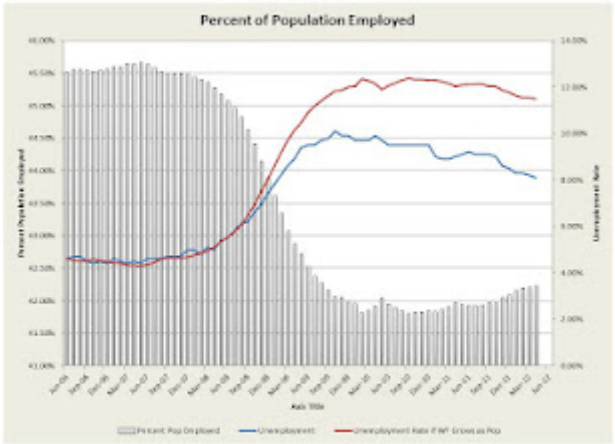


The above shows the difference from Romer, and as we see it is growing.



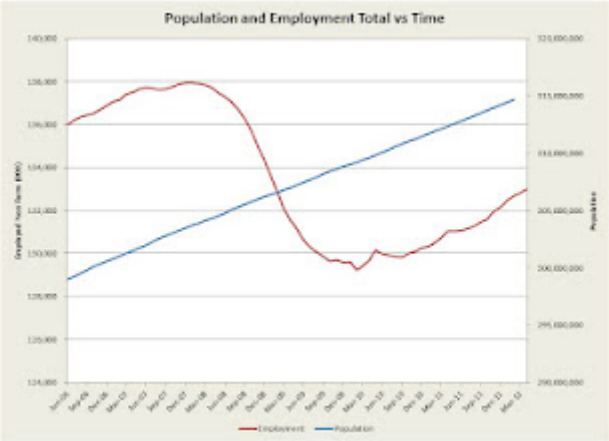
Finally the variation in percent, sustained at highest level.

Conclusion, the economists who "solved" this problem in 2009 were seemingly clueless based upon results.

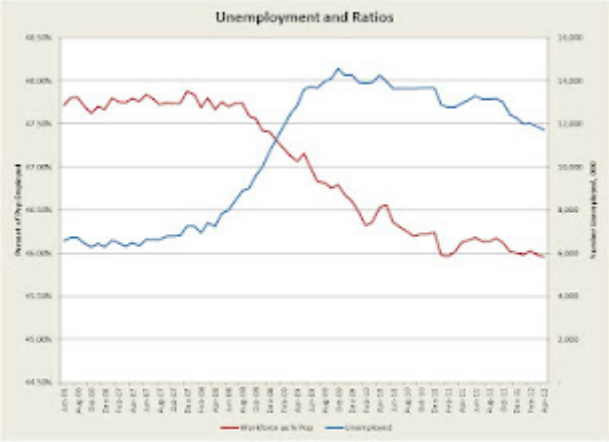


Now above we have the stated unemployment and the unemployment if we had the same percent of population in the work forces as of June 2006. We are at 8.1% but using 2006 data and

adjusting for population growth we are at 12.8%. There has been a very weak decrease in unemployment if at all from the adjusted levels. This to me is the major concern. We thus fail to get tax revenues from this base and we also pay them benefits. This is one of the major reasons for the deficit growth.



The above shows what now appears to be a structural employment deficit. Namely we have employment growth ticking upward somewhat with population but the drop shows no signs of ever closing. It appears as if we will have this long term "lost" group of employees.



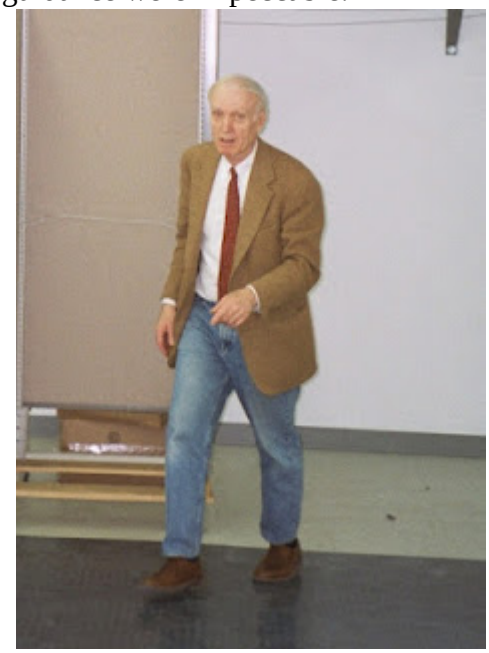
This is best evidenced by the above where we show workforce as percent of population. It has dropped and is still dropping. Frankly that is the way Government keeps unemployment low by driving people out of the workforce.

I believe we will be facing a growing structural change and this must be fixed if we are to ever correct ourselves.
Labels: Economy

THURSDAY, MAY 3, 2012

PASSING OF A GOOD FRIEND

The course of one's life is often moved as the result of one's friends and their good sense and integrity. I just learned that my long time friend and support, Ken Curtin, has passed away. Ken was a true mensch, a man who could be trusted, relied upon, would sustain you when things were bleak, and whose advice and guidance were impeccable.



Ken was an engineer by training from Cornell, and then became an investment banker. It was often through Ken's eyes that I understood Wall Street. Often a necessary evil, but workable. Ken was behind many entrepreneurs and was always insightful as to how best to present one's ideas.

Ken was a powerhouse, driving some 65 miles each way to his office, in his small Saturn, back and forth across the Cross Bronx, a road I would never venture upon, but one which he navigated well, a metaphor for his way of doing things.

Ken was quite close with my Partner Peter Mroczyk, another true friend, and the two of them made an inseparable pair. They both will be sorely missed. Rest well my friend.
Labels: Personal

WEDNESDAY, MAY 2, 2012

ON LINE EDUCATION

Just after my note on 6.002x the NY Times et al released the note that Harvard and MIT will be expanding their on line courses.

Now here is the challenge:

Many education experts are more hopeful about the new enterprises.

"Online education is here to stay, and it's only going to get better," said Lawrence S. Bacow, a past president of Tufts who is a member of the Harvard Corporation and a visiting professor at the Harvard Graduate School of Education. Dr. Bacow, co-author of a new report on online learning, said it remained unclear how traditional universities would integrate the new technologies.

"What faculty don't want to do is just take something off the shelf that's somebody else's and teach it, any more than they would take a textbook, start on Page 1, and end with the last chapter," he said. "What's still missing is an online platform that gives faculty the capacity to customize the content of their own highly interactive courses."

Now I am not so sanguine. Let me discuss a few issues:

1. Peer reviewing is one suggestion. For example if 6.002x had been other than engineering, the grading would be impossible for 120,000 students. So a suggestion, peer grading. The problem is that the faculty member is trying to bring the student up to their level, not having a iPhone group grope. This I fear would be a real dumbing down.

2. A lost step. In the late 1950s when I was in High School, I took a course on College Chemistry on TV at 6 AM. I believe it was from NYU but not certain. It was called Continental Classroom. I missed the lecture on the mole. Avogadro's Number. Well for several weeks I just could not figure it out. We had no libraries near by, yes it was NY City, but Staten Island, and no Internet, and I was a sophomore so I could not ask the Chem teacher who taught seniors. So there I wandered for three weeks mole less! Things like this will happen, how do you remedy that, again it seems what is set up is a Facebook like community. But beware the personality dynamics there. What if As are the top 10%. That was not 6.002x, yet! Namely one little bit of ambiguity can lead to total loss. It would be a five second clarification, due to the poorly phrased comment, but there is no way to do this in the current MIT system. I could see that in the student's comments. Thus I wonder how many of the 120,000 just got lost.

3. Authoring tools are not there yet. I had some discussions with friends at the Med School on this issue. Anatomy we can do, just look and memorize. But what of introductory radiology. Kerley B lines, what are they, where are they what causes them, how should you examine the plain film, what next? How does one create a conversational motif? BTW these are all the issues we discussed when I taught the first Multimedia Communications course at MIT in the Fall of 1989. Again a bit too early, but it was MIT. As I noticed in this course at MIT, the authoring tools are just what I would expect of MIT students, functional, no ability to rescue the student if there is an ambiguity, and a bit arrogant, like "you really don't get it do you, after all I wrote this for idiots like you, what a waste of my time...".

4. Heidegger used his construct of Dasein, and its adjunct "throwness", as a means to describe our ontological being. Throwness is in essence the ability to understand a hammer by the act of hammering. To have a successful On Line system I believe that one must have a Heideggerian throwness, or at-hand ontological experience, namely you must be part of the experiment, the experiment which demonstrates what the principle is. If on the other hand your throwness is understanding and experiencing the weakness of the software you missed the point.

5. Seeing How Others Think: One of the most valuable reasons for a class experience is seeing how others think. I believe that that is one of the most critical elements of an education. You may arrive with certain ways of doing things and then you observe what others may do, you adapt, you optimize. On a computer in my experience it is just the opposite. You further internalize and the current designs just further internalize and reinforce your existing practices. There once was a book by a Psychiatrist on the MIT staff called the Hidden Curriculum. Namely do not do what the Prof says to do but do what he wants you to do. Yet how do you find that hidden curriculum? That is the social environment. That often is the most critical part of education.

These will be major challenges. The issues I discussed with the MIT course, they are easy since it was engineering, but will be much more complicated when the answers are not 3.1416.
Labels: Academy

THE MIT 6.002X COURSE

On-Line courses are laudable and the MIT 6.002x course was also. But. Now my bona fides here may help, you see I taught 6.02 from 1969-1971 at MIT, hundreds of students and many lectures. So not only did I take the course, but I taught it, taking over from Paul Grey who became President of MIT.

Thus I signed up to see how its was. Well, in my opinion, not really ready for prime time, and it did get over 120,000 sign ups.

My issues were as follows:

1. The numerical answers required using Excel and cutting and pasting. The SW used was unforgiving otherwise. If you calculated and answer and it did not contain enough significant digits, you were wrong. Getting close enough was not doable. You had to be on target.

2. The Lab SW was near impossible to figure out at first, you had to try everything until you found the right tool, such as ammeter. It was a logo that finally worked. Hunt and peck was the working standard. That generally is not the way one works in a lab.

3. The entry of equations into the online system was in my opinion a disaster. No hint where to find their entry mechanism, no way to figure it out, so that was the end. Frankly at this point I gave up. I was spending more time trying to use their interface and not the course material. Looking back I spent 80% on SW interface and 20% on the material.

4. The text was somewhat useless, too much of too little. Again it may have been a matter of style but I found it lacking.

5. When I was teaching this there was always the issue of understanding what the MIT way was. Namely you had to intuit the answer, somewhat along the lines of "let the force be with you". This meant that on one hand you could crank thru the details on the other hand if you really understood the ideas you could intuit the answer. The second issue was the "Hidden Curriculum" , namely what was really being asked to know, and often the text was the main obstacle.

6. Thus is the a positive step. From my perspective it enticed over 100,000 people to try their hand. That was very positive. It made them find ways to work together, very positive.

7. But, the SW used by MIT was classic MIT, half baked. Now I do not want to annoy the CS folks, but this was not Google, where if you had a problem you clicked somewhere and got your answer. This in fact was worse than Microsoft, they at least gave you gibberish. This was that you had to reach out to the "community" and seek an answer. God and bad.

8. If you really did not want to spend your life figuring out the MIT interface and just test yourself on the material this was a big defeat. If however you were willing to put up with the clunky interface, after all it was free, then you had an opportunity to see something.

The problem is how does MIT get feedback, real positive and corrective feedback. That is truly the problem and the challenge.
Labels: Education

MONDAY, APRIL 30, 2012

LAMBERTVILLE, APRIL 2012

One of my periodic updates on Lambertville, on the banks of the Delaware. This is the old canal which rode along side the Delaware River, and in parts still remains. Down the road a piece is where Washington crossed over that famous Christmas night and kicked off a set of positive moves on his part. The Delaware is wide and was filled with ice that night. No small stream this river.

I am always amazed that most folks fail to realize how much of the Revolution was fought in our back yards. Unlike the Civil War, the remnants are few, but the consequences are important.
Labels: Commentary

MONDAY, APRIL 30, 2012

COLLEGE EDUCATION: GOALS, OBJECTIVES AND COSTS

Unlike many pure libertarians, I believe that the Government can provide for positive incentives that will benefit all. Take College education. The US needs more engineers and scientists, and not to mention physicians.

In contrast to the all negative bantering of Krugman, the Petulant Princeton Professor, I believe that the Government can be a positive contributor. In fact it has shown in the past how to do this. In the later 1950s after Sputnik the US had a great demand for scientists and engineers, and it created undergraduate and graduate scholarships for those who could achieve at the higher levels. Namely it rewarded success, and in a sense punished failure, if the Draft could be called such, by providing scholarships to US citizens who majored in the engineering and science areas. You also got a Draft deferment.

Now the inimitable Krugman states:

College graduates, then, are taking it on the chin thanks to the weak economy. And research tells us that the price isn't temporary: students who graduate into a bad economy never recover the lost ground. Instead, their earnings are depressed for life.

What the young need most of all, then, is a better job market. People like Mr. Romney claim that they have the recipe for job creation: slash taxes on corporations and the rich, slash spending on public services and the poor. But we now have plenty of evidence on how these policies actually work in a depressed economy — and they clearly destroy jobs rather than create them.

Perhaps what the young need more than anything else is a dose of reality. Getting a BA in Fine Arts is perfectly fine if you have a billion dollar trust fund and you want to prepare for your Grand Tour. Or a degree in Ancient History is great if you also have that Trust Fund. But if you want a job then perhaps you do what anyone else would or should do, look at who is hiring, look at the costs and see if you will ever get a return on your investment, Just going to college often does not help. I have hired many High School grads over the years because they can work. The MBA type may very well have excessive expectations and no competence.

At eighteen, and it really has changed little in sixty plus years, one must make a decision based upon facts and reality. If you really do not like math, and you really just want to coast through an easy college, think of all those Hispanic immigrants I see at 6 AM on a January morning on the corner in Morristown seeking some pay for the day ... for they are your competition, not some Chinese laborer in Harbin.

Thus perhaps it would be helpful for the Government to renew those Science and Engineering scholarships, national tests, best performers win, no other requirement, no sex, no race, just how well one does. Just smart motivated US citizens. And yes, there is no funding for the arts or any other area not strategic to our national success, including economics. The Chinese and Indians do this, we should do it as well. Bring back the fifties!
Labels: Education

SUNDAY, APRIL 29, 2012

TYPE 2 DIABETES, CHILDREN, AND THE CAUSE

The NY Times has a piece bemoaning the rise of Type 2 Diabetes in children. We have been concerned with that to the extreme. In our book, Obesity and Type 2 Diabetes, we argued that this epidemic would become a pandemic. There have been almost 100 downloads per week of the DRAFT. On the other hand people like Harvard economists have dismissed the issue, and they would rather focus on taxing gasoline. The pandemic will collapse our health care system, since Type 2 Diabetes patients just will not die quickly! They can be kept alive at enormous costs. However the early cure is simple, stop eating!

But the cause, the US Department of Agriculture and its exploding budget of fat foods! The solution, twofold, stop all in school meals, let parents send kinds with brow bags or have them shed some weight, and second disband the Department of Agriculture. We prime the pumps at school and then watch as the fat munchkins go to fast food outlets after they get dropped off from the school bus.

As the Times notes:

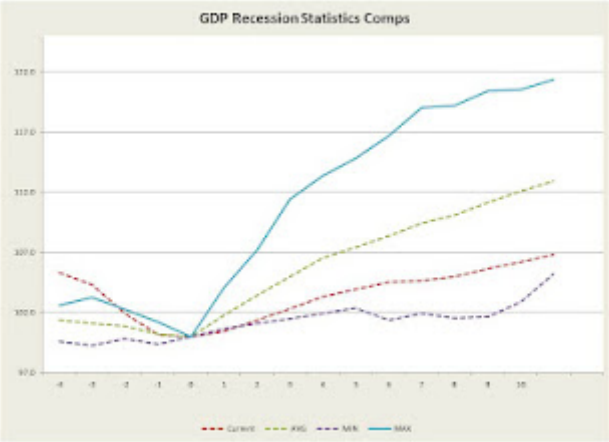
... a college senior from ... learned that she had type 2 diabetes when she was 16. Her grandfather had had both legs amputated as a result of the disease, and one of the first questions she asked was when she would lose her legs and her eyesight. A doctor scolded her for being fat and told her she had to lose weight and could never eat sugar again. She left the office in tears and did not go back; soon after, she joined the study at Columbia. Like many of the children in the program, she did not even know how to swallow a pill.

She believes that the disease "is not a death sentence," she said, if she is careful about controlling her blood sugar. But it has been a struggle. Her family tends to be overweight, she sometimes craves sweets and she has orthopedic problems that have required surgery and have made it hard for her to exercise. She is also being treated for high blood pressure.

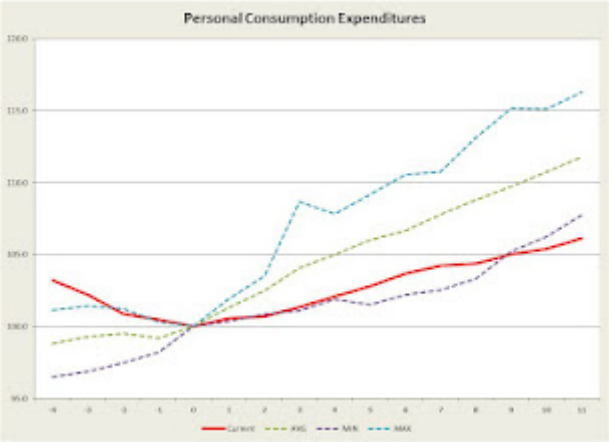
A few weeks ago, because her blood sugar shot up despite the diabetes pills she was taking, she began using insulin.

And in a few months she will be having kidney, nerve, and eye problems, then heart problems. And we will be paying. Thank God the physician at least said she was fat! Tears were not the answer, self-control was, and it requires a family effort. The problem is we consider her a victim when in reality she is a self inflicted burden on society. The child with leukemia is not at fault, while the obese teen is. And the solution is so simple, stop eating!
Labels: Diabetes

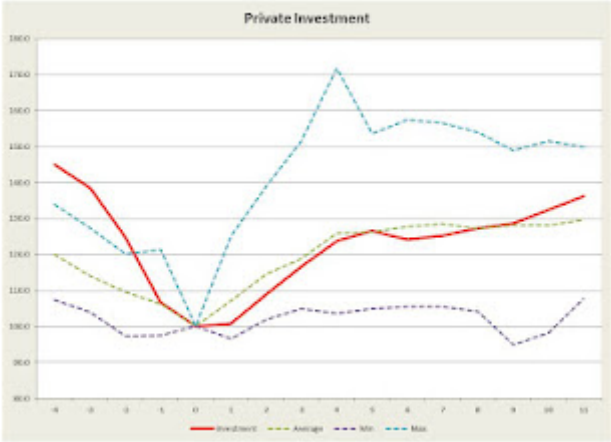
RECESSION STATISTICS: Q1 2012



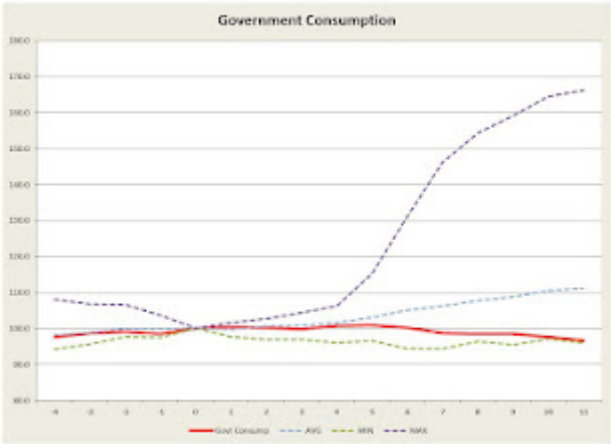
As before we use the St Louis FED data showing the min, max and average metrics for the GDP and its components. The GDP above, the total metric, lags the average recovery but does exceed the worst. Yet there is a major concern that even the worse is nearing where we are now. Growth is consistently slow. There now is a clear concern that the recovery may be so weak as to fall below the min curve.



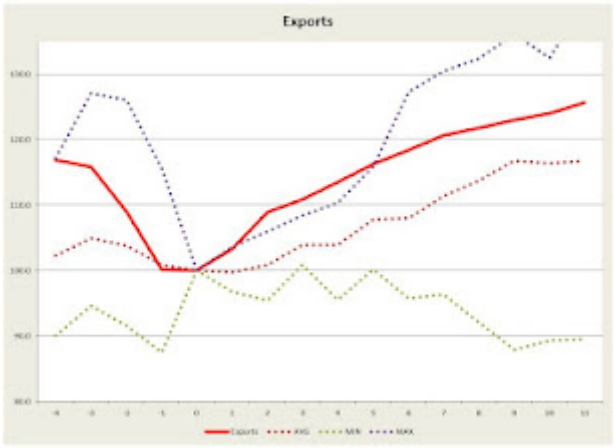
Consumer consumption is a problem since it now defines the bottom at this point as shown above. This has been the aggregate demand argument but it is a combination of fear and reduced credit as well as unemployment, real not the DoL type. The consumption number is a major concern since at one level fewer taxpayers means less revenue and more unemployed means higher benefits and thus expenditures.



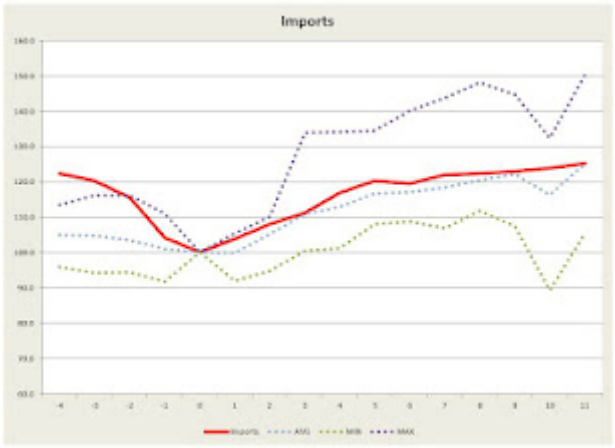
Government consumption is now lowest. I find this amazing given the deficit and its continued explosion. This is shown below. The real issue is what are we truly measuring here. It must also be made clear that min, max and avg are not necessarily the same recession recovery so the data may be highly mixed.



The following are the stats on Imports and Exports. First Exports have exceeded the average recovery which is good.



Imports have met average. This is most likely due to reduced consumer demands. However imports reduce GDP and since imports have been several multiples of exports even a flat number may still create a negative effect.



Bottom line, things seem to be getting worse not better.
Labels: Economy, Recession Statistics

HERBERT SPENCER: A REVIEW

I wrote this a couple of years ago in reviewing the book by Francis. It is worth restating.

The biography of Spencer entitled "Herbert Spencer and the Invention of Modern Life" by Mark Francis is a recent addition to the body of works of an interesting 19th century polymath. Spencer was both a philosopher and advocate of Darwin's evolutionary ideas as well as one who opined frequently on matters of political import. In many ways Spencer was a true polymath, one who wrote seminal works on psychology and sociology and wrote extensively on biology and integrated that with the new ideas promulgated by Darwin. Spencer was praised by many of his contemporaries and was also in many ways the typical Victorian, hardened in that period but also having his views shaped by it also.

Overall the book addresses Spencer, his life and his views. However, the author, in my opinion, is more interested in detailing how Spencer fits his personal view of Spencer than Spencer truly was as a person and as an influence on his world. Spencer, in his most lasting work, The Man Versus The State, clearly is an individualist and as such in many ways has become a major cornerstone for many libertarians. Yet Francis seems to reject this view and, for the most part, this book is a tirade against that position of individualism which Spencer clearly took.

Spencer was well known for his views on psychology, sociology, biology, and especially the views on Darwinism and individualism. For Spencer all of life, all of existence was a continually evolving process. The author continually returns to that fact in all of its aspects.

Spencer was well read from the time he started to write through the 1930s. Then he was attacked unjustly by the left wing in American academia, centered at the time at Columbia University, a hotbed of Communists and Marxists. For it was in the mid 1940s that Spencer was vilified by the one-time Communist history professor at Columbia University, one Richard Hofstadter.

Hofstadter in his book Social Darwinism uses Spencer's ideas on Darwin in a somewhat self serving and twisted manner to attack both Spencer and the free market capitalism as it evolved over the century from 1850 to 1950. Hofstadter was well known in leftist circles as one who could readily take a few apparently disconnected points and with what could be at best described as shabby research methods produce polemics against the conservatives and right wing advocates in the body politic.

Hofstadter was also well know to write "soft" history, what we would expect in a New Republic piece, rather than hard academic history. Hofstadter was polemical in his style and greatly deficient in primary sources. He was all too often just a recorder of old press clippings using these as the window to the world he wanted the reader to see rather than addressing the reality via primary sources.

In a recent work by Prof. T. Leonard at Princeton University (See Origins of the Myth of Social Darwinism: The Ambiguous Legacy of Richard Hofstadter's Social Darwinism in American Thought) Prof. Leonard states about Hofstadter and Spencer the following, while reviewing the issues in "Social Darwinism in American Thought", also called "SDAT":

"Richard Hofstadter, like many New York intellectuals in the 1930s, embraced radical reform. He joined Columbia University's Communist Party unit for a brief period in 1938. The more mature Hofstadter grew disenchanted with radical politics, indeed came to see it as hostile to scholarship. But SDAT, which revised his doctoral dissertation published in 1939, preserves Hofstadter's earlier world view, that of a precocious scholar, still much influenced by his mentors, Merle Curti and Charles Beard, who could say to close friends, "I hate capitalism and everything that goes with it" ... SDAT also bears the historiographic imprint of Beard's "rule" that historical interpretation must assume that "changes in the structure of social ideas wait on general changes in economic and social life" ... SDAT is thus sprinkled with unadorned Beardian claims, such as "Herbert Spencer and his philosophy were products of English Industrialism"..."

But let me return to Francis and his book. He sets his tone for the entire biography on p. 2 when

he writes:

"...the greatest source of popular confusion about Spencer does not arise from national prejudice, but from writers who have explained his theories by reference to those of Charles Darwin as if the former were a simple version of the latter. This misidentification has been so common that its correction would be an obligatory as well as unpleasant task for any Spencerian scholar. There are two reasons why it is painful. First it forces me to write about Darwin....also, it is slightly obtuse to explain an intellectual phenomenon such as Spencer's...by reference to something it is not."

This statement clearly lays forth the attitude of the author going forward, cumbersome as the use of the language is. First, there is the almost arrogant exposition of Spencerian evolution not being akin to Darwin and then the outcry of having to endure the unpleasant task of education of the reader, specifically what appears to be the less well educated readers who, frankly as per the author, should know better. Francis seems to bemoan the fact that he must tell the readers things that they should have know ab initio about Spencer. As such one wonders what audience Francis had in mind for his book. Perhaps it is meant for the small cadre of fellow Spencerian academics.

The last phrase in the above quote is at best condescending and at worst insulting to the readers since it implies that each reader should be approaching the biography already well educated in Spencer as well as in Darwin. This shrill tone of the author's style continues to resonate throughout the book.

The next interesting comment is on p 3 which frankly refutes the entire basis of the Hofstadter diatribe on Social Darwinists. In Hofstadter SDAT, he accuses Spencer of being a pure Darwinian and as such lacking in any human emotions. However Francis states:

"...First there was Graham Wallas....to him Spencer was merely an early and hasty generalize on the subject of evolution....secondly, there was Richard Leakey...he possessed the same information as Wallas except ...he was praising not condemning Spencer....After Darwin had explained his theory...Spencer quipped that it might as well be called "survival of the fittest"....if either Wallas or Leakey had read Spencer...(he) was unsympathetic to Darwin's theory..."

Thus Spencer was not a pure Darwinian. As Leonard states:

"Darwinian defenses of laissez-faire among scholars, who were more likely to have read Darwin, are not much easier to find. Bannister and other revisionists point out that even Hofstadter's social Darwinist exemplars, Herbert Spencer and William Graham Sumner, were not especially Darwinist. Spencer certainly invoked the evolutionary advantages of competition among men. And, Spencer's extraordinary intellectual prominence in the last third of the 19th century also made him a large target for reform scholars. But Spencer would have rejected the label of "Darwinist," in part because his own theory of evolution differed from and was published before Darwin's On the Origin of Species. The catch-phrase "survival of the fittest" was Spencer's and Darwin did not adopt it as a synonym for "natural selection" until Alfred Russell Wallace convinced him to do so in the fifth edition of the Origin (1869).

Importantly, Spencer was a Lamarckian with respect to human inheritance. He imagined that competition induced human beings to actively adapt themselves to their environments, improving their mental and physical skills - improved traits that would then be inherited by their descendants. Spencer's view was that, in the struggle for existence, self-improvement came from conscious, planned exertion, not from the chance variation and natural selection that are the heart of Darwinism. As a result, evolution is progressive in Spencer, whereas, for Darwin, at least the early Darwin, evolution means only non-teleological change. Spencer's fundamental belief in human progress via Lamarckian bootstrapping was at odds with Darwinian natural selection's randomness and its openness to non-progressive change.

Spencer, in fact, was not just a Lamarckian, he was a leading Lamarckian, taking up cudgels against the neo-Darwinians such as biologist August Weismann, whose watershed finding in 1889--that mice with their tails cut off do not bear short-tailed progeny--was seen by many as a crucial-experiment refutation of Lamarckism. Spencer's status as a defender of Lamarckism in the 1890s was such that that progressive Lamarckians, such as Lester Frank Ward, often found themselves in the awkward position defending Spencer, a man whose individualism and laissez-faire economics they loathed, and dedicated their lives to opposing."

Thus the fundamental basis of the Hofstadter argument against Spencer has no merit. Francis begins by throwing the cudgel down early on in the biography as to his apparent dislike of free markets and then continues to pound the cause home.

On p. 13 the author begins to position Spencer as a non-individualist, by redefining what he believed Spencer meant by his individualism. The author commences what appears to be his personal repositioning of Spencer as not the one lauded by many 21st century libertarians but as a mainstream 21st century liberal. Although he defines "individualist" as the "natural antonym" of the term "state" the author commences the rehabilitation of Spencer from his point of view.

The most published work of Spencer, his small but compelling book, "The Man Versus the State", is a well read treatise which clearly and unambiguously states the position of the individual against the state. Unfortunately the positioning by the author at this stage to marginalize this work of Spencer presages his attempt to reconstruct Spencer as a man who may not even have written that book.

Chapter 3 depicts Spencer and the problems he allegedly had with women. One of his alleged lovers was the writer George Eliot with whom he had an affair which lasted a brief while. The chapter is less a discussion of Spencer's problems with women than it is a presentation of conflicted Victorians in England.

Chapter 6 discuses Spencer's rather common eccentricities starting with his hypochondria. The author states:

"Spencer combined hypochondria with radical political opinions."

It appears that this was a common British trait not unique to Spencer. For if one looks at Lord Russell one see that he suffered from exactly the same set of problems. One may conjecture that

such a set of common characteristics were both common to the Victorian British as well as those holding extreme views.

The concept of the pervasiveness of evolution for Spencer is detailed by the author on p. 193 where he states:

"A constant refrain in Spencer's early scientific writings was that all phenomenon of the universe...were subject to evolution."

Further Francis states:

"Spencer's initial conception of life was not a cold and objective; he saw life as the general impulse towards goodness and perfection, evidenced everywhere one looked."

This is a teleological outlook towards evolution, the goal being the goodness and perfection as stated by Spencer. But was that indeed his view, and if so what drove this end point, since Spencer was not a truly religious man. Francis states that the intelligence was science in and of itself.

Spencer was a prolific writer and there are a continuing set of streams of an evolving set of views. Yet Francis states that the paper "A theory of Population" written in 1852 was the singular key to his early views. Francis argues on p 194 for Spencer's views, views which aligned with the expanding presence of Great Britain. Francis states:

"...Spencer perceived his own experience and that of nature generally as "the inherent tendency of things going towards good..." He called this vis medicatrix naturae...the progressive quality of nature even justified...suffering...necessary for benign progress...each conquered race or nation could acquire a liking for new modes of living...in the future Spencer saw new modes of evolution...(and) maintain a perfect and long lived existence for each individual."

In Chapter 15 Francis appears to get annoyed by the seminal work of Spencer, "The Man versus the State". He speaks of Spencer's anti-utilitarianism and his hostility towards Bentham like hedonism (see pp 248-249). Francis states:

"In "The Proper Sphere of Government" he (Spencer) wrote as a Christian utilitarian opposed to individualism and thus was hostile to those who construed happiness as if the collective did not matter."

On p. 249 he attacks "The Man versus the State" as being inconsistent with the true meaning of Spencer's views. This is a wandering and almost incoherent presentation in the text and Francis continually tries to say that "The Man versus The State" was an aberration of an old man rather than a culminating view developed by Spencer. In fact this was one of Spencer's clearest texts and the one which has had lasting influence. Moreover it is a text devoid of the Darwin and reflects an evolving and mature view of the individual versus the expanding nature of the State.

Francis on pp 250-251 then goes into the current position we find in Rawls with direct reference

to him. Francis speaks of the confusion Rawls has between liberalism and communitarianism, but no matter, both are counter individualism which is where Spencer had allegedly evolved to. Francis gets quiet complex and confusing as he attempts to draw together what he sees a conflicting views of Spencer while at the same time attempting to keep Spencer in what we would see today as a truly "liberal" player and not one dedicated to true individualism. He ends the discussion with the statement:

"For Spencer it was not that the individual and society operated in different spheres as they had for ...Mill. That distinction would have allowed for a principled discussion of when interference with the former was justified. Spencer's conceptualization of the individual and society places them on separate planes making it illegitimate to permit some restrictions on freedom while forbidding others."

This sentence makes little sense to me. On the one hand they are not in different spheres but on the other hand they are on different planes. Now the metaphor is not just weak it makes no sense. This chapter is rant with such non sequiturs!

Now Francis continues his attack against "The Man Versus the State" on pp 258-259. Here is states:

"Spencer's liberalism in particular is not usefully glossed over as a "bourgeois" individualistic ideology that was forged in opposition to the collective."

Indeed it was not. It was carefully thought out and predicated on the events that allowed him to detail fact by fact with the resulting impacts on individual freedom equally detailed. Also individualism had and continues to have evolving and complex expressions, from the one extreme of current day libertarian views to those which are socially more open.

In Chapter 18 Francis discusses Spencer's work on Sociology in political systems. On pp 304-305 he detailed the nexus between these topics and evolution. It is seen that Spencer continually winds the evolutionary elements into his work. To Spencer everything was continually in an ever changing evolutionary milieu. It was for him Lamarckian where the Darwinian step changes were Lamarck's slow changes which were absorbed.

In the Conclusion on p 334 he again returns to what seems to be the major conflict that Francis sees, that is that Spencer was at heart in his maturity a true individualist yet Francis does not seem to want to accept that. He states:

"When it is realized that Spencer was a corporate thinker rather than an individualist, then his argument for the need to give a paramount place for the emotions becomes more easily explicable."

This is apparently a total rejection by Francis of the facts that are evident in "The Man Versus the State". Francis fails to discuss the contents of this book in the slightest degree, he discusses in detail the early works but merely shouts against the latter. This book does provide valuable insight into Spencer and especially in view of the later invective by Hofstadter it would seem

most appropriate to have devoted some care an attention to it.

Thus this book is a good contribution to Spencer since it forces the reader to go back and read in detail what he said and see how all too often is counters Francis. Yet Francis knows Spencer and Spencer had and potentially continues to have made contributions to our thinking. Thus I recommend this book strongly for those interested in Spencer and just as importantly those interested in individualism as say a view in contrast to neo-progressivism.
Labels: Commentary, Politics

SATURDAY, APRIL 28, 2012

WILL THIS HAPPEN HERE?

The Guardian has an interesting piece on denial of health care under their socializes system.

They state:

A majority of doctors support measures to deny treatment to smokers and the obese, according to a survey that has sparked a row over the NHS's growing use of "lifestyle rationing".

Some 54% of doctors who took part said the NHS should have the right to withhold non-emergency treatment from patients who do not lose weight or stop smoking. Some medics believe unhealthy behaviour can make procedures less likely to work, and that the service is not obliged to devote scarce resources to them.

I can see this happening here. One just need look at the current crop of pols in DC and start to see who we can deny service to. A smoking Chief Executive, a morbidly obese Surgeon General, how about half of Congress, the SCOTUS, a few on the overweight side there I'd say. Think how much that would save!

Just a thought.
Labels: Health Care

A CALCULATOR: A SIGN OF AMERICAN INTELLECT IN DECLINE

Now one may wonder why I have spent more than a few seconds on this issue. The reason is that it is a metaphor for what is wrong with a few things. Here is the issue. Back in 1978 I believe I got the calculator on the left, a TI which may have been close to $100 at the time, a steep sum in today's world. Well designed, keys were colored to correspond to actions. Good human factors engineering. Bad packaging since it has not lasted this almost 30 years, neither did my first PC.

In the middle is a second unit about 10 years ago. Still good design, holds up, and the human factors is weakening, the blue keys should be of a more contrasting color.

Now today, I got the one on the right. The keys are all silver on silver and one cannot see them when using it in say a lab. Bad human factors design,

Now what makes the Apple products great are great human factors. I remember meeting Jobs back in the early 80's when I was at Warner, we had Atari and he had Apple, we had games and he had a dream. I always thought his idea was better and time tells out.

Now I bought one of these on the right and found it almost impossible to use. Bad human factors. So when I saw a comment on Amazon stating as such I just left my comment, using my real name which I believe is ethical and necessary to judge the remark, and then ZigZagJoe, whoever that may be, remarks:

"Fine tip black sharpie - problem solved."

Now that is when I asked what would Steve Jobs say to that remark? I suspect the good ZigZag would be leaving the parking lot for good before I finished this sentence!

But, and this is the observation, who is ZigZag and why should I listen to him. He has no real name, no bona fides, he lacks any engineering sense, just a snarky sense of humor, if that is what I sense. But more importantly the design flow is more critical, from a 1970s great design to something which is unusable. Perhaps that is one of the problems with American industry, people like ZigZag who may very well have been the designer!

The issue truly is as follows:

1. Form follows Function: This is a calculator, and using plus, minus, multiply and divide, are key functions, hidden by the form. This is by definition a design failure.

2. Yet the ZigZag character suggests a fix, use a marker, color in the key so that one can see them better, redesign the calculator. Only ZigZag misses the point, it is not the users role to design but to use. ZigZag is reflective of all that is wrong, he may suggest a suboptimal solution, if even that, but it is not the user but the designer who has the obligation. And TI clearly showed that decades ago, almost 40 years ago!

3. ZigZag has become a universal model for how not to act, his snarky attitude, his failure to understand the issue, his lack of appreciation of quality is an embodiment of what is wrong. Would a Japanese designer do this, doubtful.

4. The customer is key. One should never ask the customer to assemble the product, any moron should know that. I recall having this discussion in NYNEX (now Verizon) back in the 1980s when they were just getting out of being a monopoly. The customer, given a choice, will go with the provider who respects them, who anticipates their needs. ZigZag was and is clueless on this issue. He just seems to say that the customer should improvise and fix the fault, as if he has some divine insight.

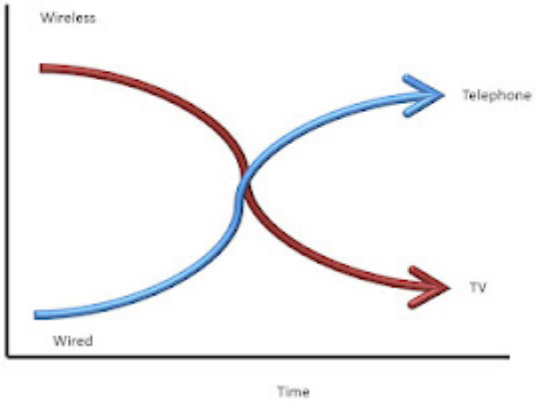
5. ZigZag is thus a representation for what I see more and more of in the US. Young arrogant people who have a modicum of knowledge and will push their arrogance on the customer. This is NOT Jobs, it is however much of what we see from the young developers. It is truly intellect in decline, it is the taking of the easy way out, namely they thought of this so it must be correct and you should use their simple idea or you are stupid. This is a product of our state run education systems.

6. The problem then is with TI and ZigZagJoe, each in their own way. TI, for no longer designing properly, it is truly a design flaw, and for that as an American company, a diminution of intellect. As for ZigZagJoe, he is unknown, and other than what appears to be youthful ignorance and arrogance, often telltale signs of American youth, he could frankly just be generationally representative.

It is a shame we do not have an overabundance of the perfectionists like Jobs, but we have all too many of the snarks like ZigZag!
Labels: Commentary

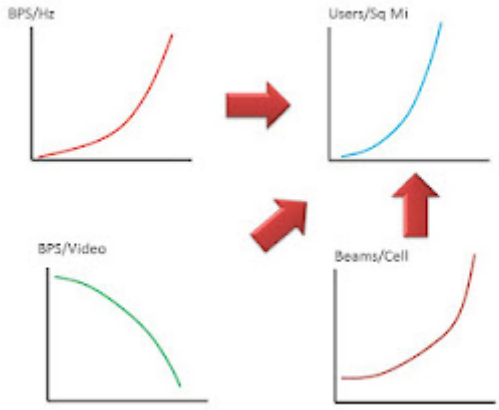
SATURDAY, APRIL 28, 2012

BANDWIDTH AND THE NEGROPONTE SWITCH



About 20 years ago Prof Negroponte published his switch concept: simply TV would go from wireless broadcast to fiber and telephony would go from copper wires to wireless. We show the idea above.

But what has happened. Twenty years ago I also proposed in an FCC Pioneer Preference Filing the extensive use of multi beam base station antennas, a technique I had worked on for thirty years by that time. Too early. Marty Cooper also started a company just after that which also was too early.



But what has happened since. The above graphic details some of the issues:

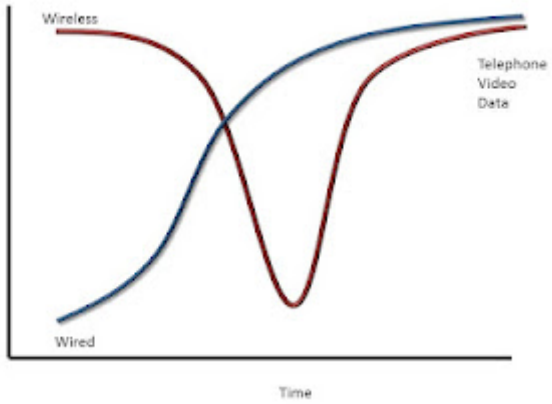
1. QPSK/CDMA led to OFDM, which is why Qualcomm bought Farinon, and we saw BPS/Hz gone from 1 to 10.

2. Video codecs have brought down HDTV from 200 Mbps to 2 Mbps.

3. Multi beam antennas have allowed beam pointing per subscriber.

The result, the number of instantaneous, yes I mean instantaneous, video channels per user can explode. How:

Stick fiber in the backbone and wireless at the edge, all IP. The we have the re-switch as below:

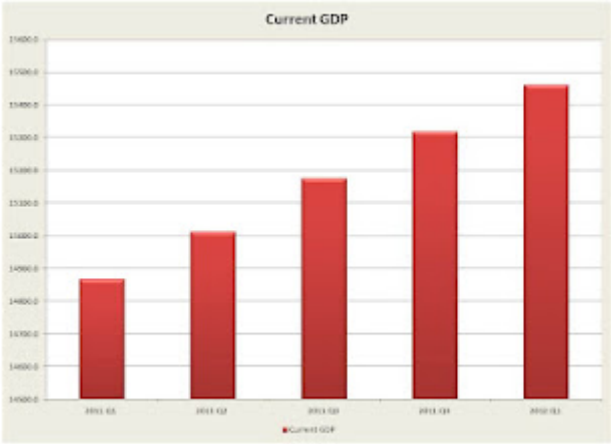


This shows the Negroponte switch goes back on video, namely video for the "last mile" can be all wireless, and yes with the same or even less spectrum.

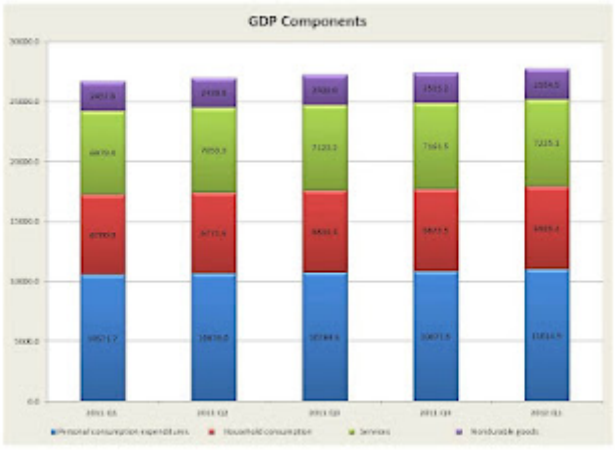
So why are the incumbent wireless carriers demanding more spectrum? Ever heard of monopoly? And the DoJ/FTC is chasing Google, while the foxes run rampant! Lawyers.
Labels: Wireless

FRIDAY, APRIL 27, 2012

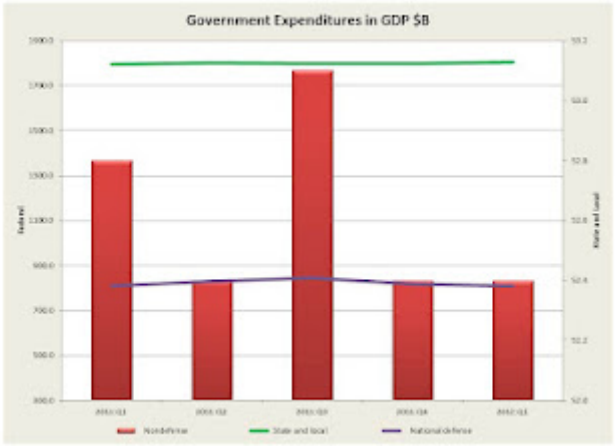
SOME GDP DETAILS Q1 2012



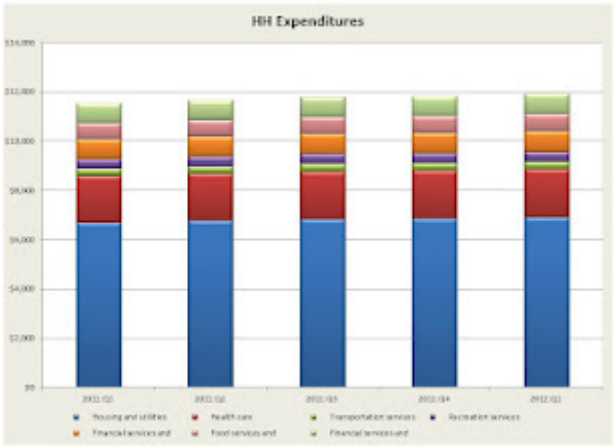
We have added some details on the recent GDP results. Above shows a close up of the unchained.



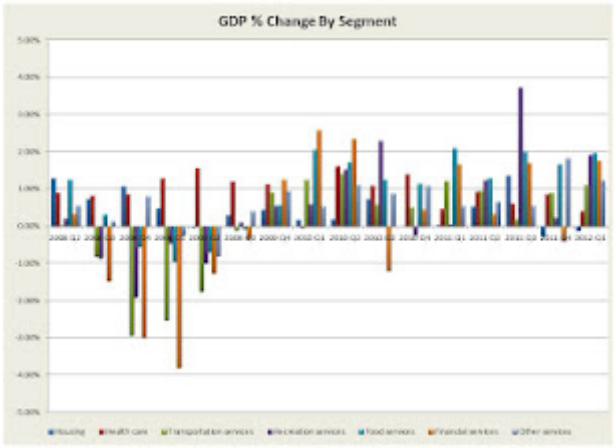
The above details the amounts by sector.



The above shows Government spending. Note the drop in non-defense. Defense still is half the amount! Frankly one could halve Defense and still have a strong base.



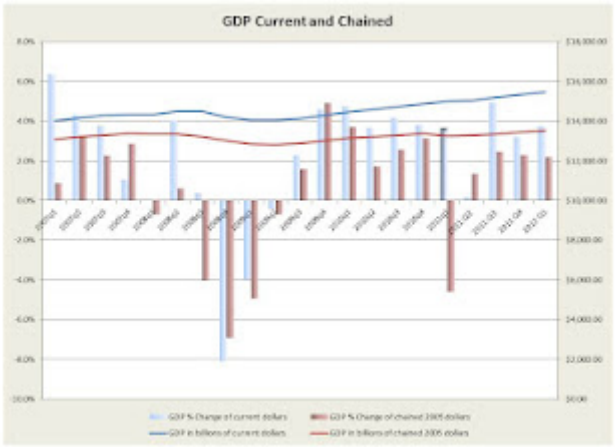
The above are the HH breakouts. There is a rise as we shall see below.



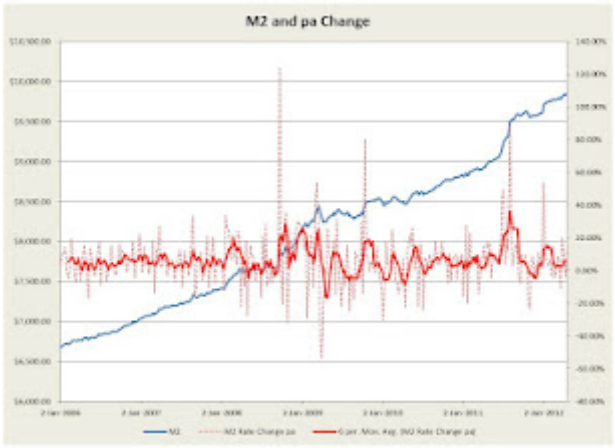
The above is the percent changes. Note the rise in all elements except housing. The spending seems to indicate some assurance that we will be better but not just yet.

Labels: Economy

GDP UPDATE

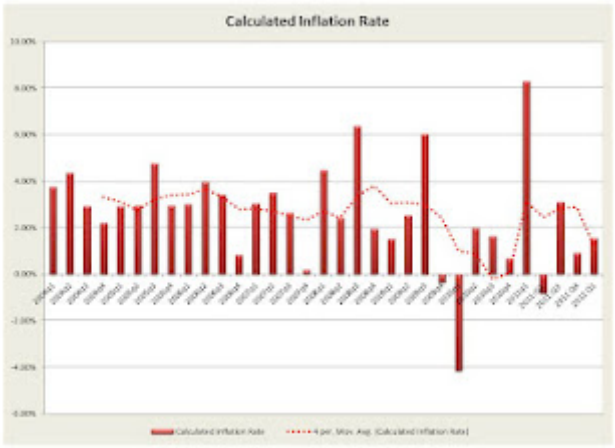


The GDP is still dragging as seen in the above based on latest release. There is slow growth in core numbers and only slow growth based on limited inflation which is controlled by the FED.

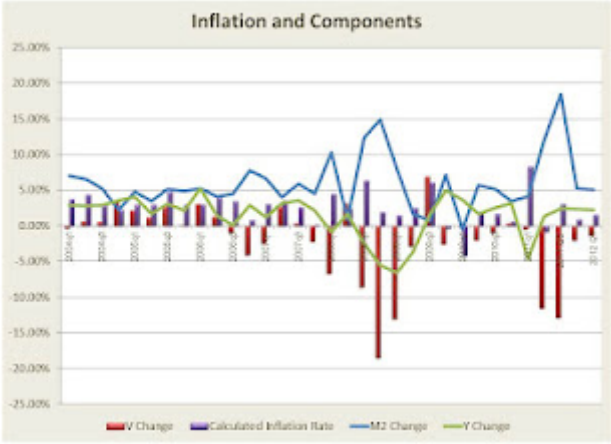


M2 is still increasing but slowly and thus limited risk of inflation if one looks at this classic measure. However:

The FED still has massive amounts of currency stored in banks who still are holding onto the cash making substantial spreads. With an all Democrat FOMC we do not expect a change for at least five years in this plan unless the current Chairman is replaced by a very strong and astute monetarist.



Current calculated inflation is still quite low and trending downward. This is monetary inflation as contrasted to real inflation at the consumer level which we estimate to be in excess of 10%. What drives this down is the housing collapse and the current Administrations pressure to allow stagnant foreclosable properties to become walking dead.



Non surprises in the above chart for inflation components.

Labels: Economy

WEDNESDAY, APRIL 25, 2012

SUBSIDIZE STUDENT LOANS? NOT THE PROBLEM

University Administrators are a class unto themselves. If they ran US corporations we would now be paying $5,000 for a gallon of milk. Why? Because they would have raised great amounts to construct massive barns for the cows, and massive cow support systems, but failed to figure in the life cycle costs or removing the cow manure. That is what would drive the costs of milk.

Now to the NY Times and Congress. Students have gotten hooked on ever escalating tuition. Part their fault. If you pay $250,000 for a BA in Roman Art or Byzantine History, then you have set yourself for a tragic economic crisis, unless you are a Trust Fund baby. If you are middle class you have demonstrated your total lack of understanding of our economy. And perhaps you are doomed to fail.

When I started tuition was about $1,200 per year, a small fraction of the average middle class salary, one may say 10%. Thus one could have parents pay, but equally one could work in summers and save and get by paying one's own tuition. Now tuition is $60,000 and it has become a multiple of average middle class salaries and unpayable by any summer job other than selling drugs or arms.

Why? Professors just do not get paid that much more and offices really are no better. Labs got more complex but alas the Administrative overhead has exploded and the buildings have life

cycle costs that have exploded. Namely University Presidents have expanded plants with no thought to their life cycle costs. Then as they costs kick in, yes buildings age, and need upgrading, the weakest link is fixed and the others go to disrepair. And as Administrators grow they suck up more buildings, more costs, and drive students and faculty away.

It is a deadly cycle. More Government subsidies will not solve the problem. Revolt against Administrators is the only solution.
Labels: Education

PLECKSTRIN HOMOLOGY: A SPY NOVEL OR A NEW TARGET FOR MELANOMA

There has been some recent work (see DeSemir et al) on the targeting of the Pleckstrin Homology, "PH", as an additional target for controlling melanomas. As DeSemir et al state regarding the Pleckstrin Homology Domain-Interacting Protein (PHIP) (slightly edited):

Given the important role of Akt in the IGF (Insulin Growth Factor) axis, we then assessed whether Phip was involved in Akt activation. …

Because of the uncharacterized role of PHIP in cancer, we performed cDNA microarray analysis to identify the global patterns of gene expression after suppression of Phip expression. Significance analysis of microarrays identified 51 down-regulated genes (including Igf2 and Tln1) and 184 overexpressed genes … Thus, PHIP can regulate the expression of upstream mediators of the IGF axis and downstream mediators of tumor cell invasion.

Having demonstrated Phip's functional role in promoting murine melanoma metastasis, we examined its impact on human melanoma progression.

We performed immunohistochemical analysis of PHIP expression on a tissue microarray cohort of 345 patients with primary cutaneous melanoma …

High levels of PHIP expression were found in each histological subtype of melanoma and accounted for almost one-third of the melanomas in this cohort.

High PHIP expression correlated significantly with the presence of ulceration, an adverse prognostic factor incorporated into the staging classification for melanoma whose biologic basis is poorly understood…

PHIP overexpression was significantly predictive of reduced distant metastasis-free survival … and disease-specific survival …

PHIP overexpression was an independent predictor of DMFS and DSS…

PHIP overexpression directly correlated with the progression of distant metastases, and with reduced survival, in both murine and human melanoma.

The human PHIP gene resides on the 6q14.1 locus. Deletions of the 6q arm have been shown in melanoma and have been suggested as a possible diagnostic marker. …

FISH analysis revealed that the PHIP locus was still present in all 78 melanomas examined.

Importantly, there was a significant correlation between PHIP copy number (assessed as a percentage of cells with three or more copies) and the corresponding PHIP immunohistochemical scores …

Melanomas with immunohistochemical scores of 1–3 had a significantly higher percentage of cells with increased copy number compared with melanomas with a PHIP score of 0 .. In addition, 80.6% of PHIP 3 melanomas had three or more copies of the PHIP locus.

Although we found no evidence of amplification, because PHIP copy number remains comparable with chromosome 6 centromeric copy number increased copy number of the PHIP melanomas for β-catenin mutations at six different sites (previously described in melanoma; COSMIC database) and found no mutations at any of these sites.

These results show that PHIP levels can be activated in a unique molecular subset of melanoma independent of mutations in these other four genes.

This brief summary of the work makes PHIP an interesting and attractive target. It presents a pathway element which is more a facilitator rather than a major participant (see Weinberg). As we shall note later from DeSemir et al, they contend that the PHIP target presents a more universal target especially for those melanomas which do not have well defined mutations in BRAF, NRAS or PTEN. As we have discussed previously, for example, PTEN mutations, loss of control in the Akt pathway, is often an end game in cancer progression, for example in prostate cancer and many others.

We will attempt to assemble some of the literature and present a brief summary of this area. In many ways it is distinct from the pathway targets themselves since the PH targets are smaller and often are found in many of the pathway elements. The PHD. Pleckstrin Homology Domain, has received significant interest by other researchers especially regarding its pathway control effects. For example Hirano et al have examined it in CML and Miyamoto et al in cardiology and the Akt pathway.

PLECKSTRIN AND THE HOMOLOGY

We first examine Pleckstrin then its homology and its function. We begin first with Pleckstrin. Pleckstrin is a specific protein which is found in blood platelets. The name is derived using the concatenation of the phrases: **P**latelet and **LE**ukocyte **C K**inase substrate and the KSTR string of amino acids. It is located on 2p13.3.

Now the Pleckstrin Homology is defined as:

Pleckstrin homology domain (PH domain) is a protein domain which consists of approximately 120 amino acids. The PH domain is present in various proteins which are key elements of intracellular signaling as well as constituents of the cytoskeleton.

This domain can bind phosphatidylinositol lipids within biological membranes (such as phosphatidylinositol (3,4,5)-trisphosphate and phosphatidylinositol (4,5)-bisphosphate. PIP3 and PIP2), and proteins such as the βγ-subunits of heterotrimeric G proteins, and protein kinase C.

Through these interactions, PH domains play a role in recruiting proteins to different membranes, thus targeting them to appropriate cellular compartments or enabling them to interact with other components of the signal transduction pathways.

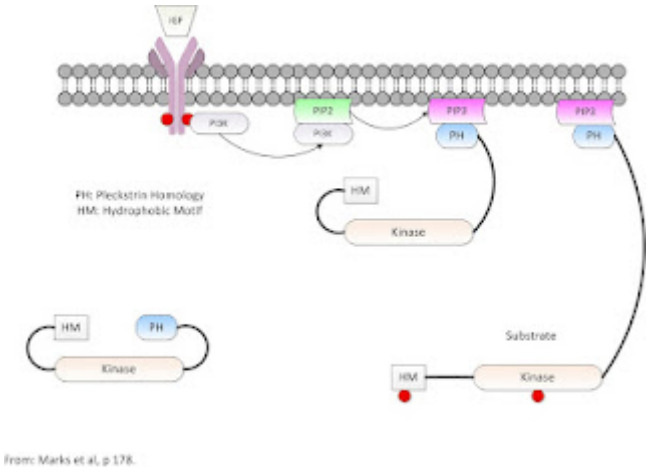
PH domains can be found in many different proteins, such as ARF. Recruitment to the Golgi in this case is dependent on both PtdIns and ARF. A large number of PH domains have poor affinity for phosphoinositides and are hypothesized to function as protein binding domains. Proteins reported to contain PH domains belong to the following families:

- Pleckstrin, the protein where this domain was first detected, is the major substrate of protein kinase C in platelets. Pleckstrin is one of the rare proteins to contain two PH domains.
- Ser/Thr protein kinases such as the Akt/Rac family, the beta-adrenergic receptor kinases, the mu isoform of PKC and the trypanosomal NrkA family.
- Tyrosine protein kinases belonging to the Btk/Itk/Tec subfamily.
- Insulin Receptor Substrate 1 (IRS-1).
- Regulators of small G-proteins like guanine nucleotide releasing factor GNRP (Ras-GRF) (which contains 2 PH domains), guanine nucleotide exchange proteins like vav, dbl, SoS and *S. cerevisiae* CDC24, GTPase activating proteins like rasGAP and BEM2/IPL2, and the human break point cluster protein bcr.
- Mammalian phosphatidylinositol-specific phospholipase C (PI-PLC) isoforms gamma

Discussion of PH in cancer is somewhat sparse and limited in detail. Bunz has a short reference (p 191) and Weinberg also has passing comments in several locations, and Schulz on p. 120.

PH and Pathways

The following is from Marks et al and shows how the PH domain can act as a binding and activating substrate in the overall pathway cascade process. It can unwrap from the complex protein of which it is a part, and then it can attach to a membrane protein and this allows activation, in the case below, by phosphorylating the resulting domain substrate. This simple model offers also a mechanism to block pathway activation as well.



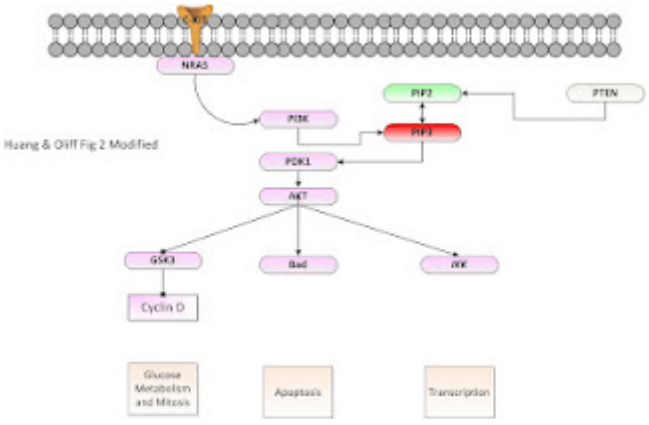
From: Marks et al, p 178.

As Huang and Oliff state regarding the PH domain:

There are three members of the AKT (PKB) family. They are widely expressed and implicated in apoptosis, insulin signalling and growth regulation. All three contain a pleckstrin lipid-binding domain (PH Domain)and are activated at the membrane by upstream kinases. Candidates for this upstream regulatory activity include integrin-linked kinase, PDK-1, and possibly AKT itself. In addition, AKT activity is regulated indirectly through modulation of lipid metabolism.

The loss of PTEN (a protein and lipid phosphatase) activity and the gain of PI3K (a protein and lipid kinase) activity correlate with AKT activity and binding of AKT to the membrane lipid, PI(3)P. The PI3K inhibitor wortmannin has already been shown to inhibit AKT signalling. Some proteins that have been shown to be substrates of AKT and relevant to apoptosis are listed. Antagonists of AKT kinase activity should inhibit signalling through these downstream effectors.

We demonstrate this pathway selectivity and control below. Here we have modified a Figure from Huang and Oliff to make the point that loss of PTEN control or over-activation of the Akt pathway can result in excess of proliferation and suppression of apoptosis. This is generalized below:



PTEN is a major control protein in pathway management. As Chow and Baker had stated in an earlier description of the effects of PTEN:

Soon after the discovery of its PIP3 phosphatase activity, PTEN was found to negatively regulate the PI3K/AKT pathway . Generation of PIP3 by growth factor-stimulated PI3K activity results in membrane recruitment of the serine–threonine kinase AKT via its pleckstrin homology (PH) domain, and activation by phosphoinositide-dependent kinases (PDK1 and 2) . Numerous AKT substrates have been identified affecting a broad range of cellular activities .

A few that have been implicated in oncogenic transformation include the Forkhead family of transcription factors (FOXO), p27KIP1, MDM2, GSK3, BAD, IKK-b, and tuberin (TSC2), a negative regulator of mTOR. The specific targets phosphorylated by AKT vary with physiological stimuli and cell context and the mechanism for this selection is unclear. The complexity of this pathway is further underscored by the recent finding that mTOR can act both upstream and downstream of AKT activation. The raptor–mTOR complex can phosphorylate and activate AKT while the raptor–mTOR complex, which regulates growth and protein translation, can be activated downstream of AKT .

PTEN-mediated regulation of the PI3K/AKT pathway results in cell context-dependent effects on cell size, proliferation and survival. A dominant-negative form of AKT rescues the lethality caused by PTEN deficiency in flies. This strongly suggests that AKT is the major critical downstream target of PTEN activity ..

The impact of Akt has been understood now for quite a while and the BRAF facilitation when mutated has become a focal element of the control mechanism. However PH also plays a significant role and this too has been understood. As Dehaia states:

PI3-kinase triggers signaling through multiple pathways, many of which are thought to associate with cell growth and survival. PTEN, working in opposition to PI3-kinase, is therefore associated with cell death or arrest signals. Phospholipid residues such as PtdIns(3,4,5)P3 are present in cells upon stimulation by several growth factors, such as platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and epidermal growth factor (EGF).

Upon activation by growth factor, proteins containing a pleckstrin-homology (PH) domain are recruited to the membrane 3 where they associate with phospholipids. One of the PH domain-containing proteins relevant in this pathway is the serine-threonine kinase, AKT, also known as PKB or RAC1*. AKT, in turn, and as a consequence of lipid binding, alters its conformation to allow two of its residues, threonine 308 and serine 473, to be phosphorylated and therefore become active.*

The kinase responsible for phosphorylation of threonine 308 is phosphonositide-dependent kinase 1 (PDK1), an enzyme which also contains a PH domain and is therefore dependent on lipid binding for its full activity. There is some preliminary evidence, predominantly from in vitro studies, that a second lipid-dependent, PH domain-containing enzyme, ILK (integrin-linked kinase), is responsible for phosphorylation of the serine 473.

Further, a recent paper has proposed that the kinase responsible for Ser 473 phosphorylation might in fact be PDK1, when it associates with certain specific proteins, such as PDK1

interacting fragment (PIF), as seen by in vitro studies. By dephosphorylating D3 residues on PtdIns(3,4,5)P3 and PtdIns(3,4)P2, PTEN works in opposition to the PI3K/AKT pathway and therefore counteracts cell survival mechanisms elicited by this signaling. The mechanisms of cell survival associated with AKT appear to involve multiple pathways, including growth factors, cytokines, c-myc overexpression, UV irradiation, and matrix detachment.

One of the known signals activated by AKT is its phosphorylation of the Bcl-2 family member, BAD: phosphorylation of BAD results in suppression of apoptosis. AKT has also been reported to counteract the apoptotic response of several cellular factors. Recently, the transcription factor NF-kappaB has been implicated in the apoptotic response antagonized by the PI3K/AKT pathway

Thus we have demonstrated that PH activateable proteins such as Akt can be deactivated if it were possible to focus on the PH Domain as a target sector. Recent work has demonstrated that in some detail.

Current Understanding

We now will examine some of the current understanding of PH and its implications in melanoma specifically. We examine the work of two other groups and then readdress that of DeSemir et al.

As Farang Fallah et al state:

As a major substrate of the insulin receptor, insulin receptor substrate 1 (IRS-1) plays a central role in transducing insulin-dependent signals that regulate biological processes such as cell growth and cellular uptake of glucose. IRS-1 is a modular protein comprised of an N-terminal region harboring a pleckstrin homology (PH) domain, followed by a phosphotyrosine binding (PTB) domain that cooperatively ensures selective recognition and efficient substrate phosphorylation by the activated insulin receptor (IR). The C-terminal portion contains multiple tyrosine phosphorylation motifs which serve as docking sites for the recruitment of various SH2 (Src-homology 2) domain containing signaling molecules, such as phosphatidylinositol 3-kinase (PI 3-kinase), Grb-2 adaptor protein, and SHP2 (SH2 containing phosphatase 2) tyrosine phosphatase, which in turn elicit the activation of biochemical cascades that promote the metabolic and growth responses to insulin….

In the present study we demonstrate that overexpression of either PHIP or IRS-1 alone in muscle cells was not sufficient in promoting transport of GLUT4 to plasma membrane surfaces This is consistent with other observations, indicating that activation of IRS-1-associated signaling effectors such as PI 3-kinase, although necessary, is not sufficient for GLUT4 activation.

Notably, growth factors such as platelet-derived growth factor and interleukin-4 can activate PI 3-kinase as efficiently as insulin and yet fail to stimulate glucose transport in insulinsensitive cells (17, 22).

One possible explanation is that additional PHIP/IRS-1/PI 3-kinase-independent pathways are required to coordinate GLUT4 intracellular routing. Indeed, recent evidence points to a novel

insulin-responsive pathway that recruits flotillin/CAP/CBL complexes to IR-associated lipid rafts in the plasma membrane, an event which is thought to potentiate GLUT4 docking to the cell surface after IR activation.

Our data, however, provide support for the involvement of PHIP/IRS-1 complexes in glucose transporter GLUT4 translocation in muscle cells. Specifically, the use of DN-PHIP or IRS-1 PH domain constructs known to interfere with efficient IR–IRS-1 protein interaction, and hence productive signal transduction from IRS-1 to PI 3-kinase, blocked the ability of insulin to stimulate GLUT4 mobilization in L6 myoblasts and inhibited insulin-stimulated actin cytoskeletal reorganization, a process required for the productive incorporation of GLUT4 vesicles at the cell surface. Moreover, this inhibition did not coincide with changes in the autophosphorylation status of the IR.

As Barnett et al state:

Akt/PKB (protein kinase B) is a serine/threonine kinase which has a key role in the regulation of survival and proliferation [1–8]. There are three isoforms of human Akt (Akt1, Akt2 and Akt3) and they all have an N-terminal PH (pleckstrin homology) domain and a kinase domain separated by a 39-amino-acid hinge region. The PH domains have approx. 60% identity and the kinase domains are >85% identical.

The hinge region is the least conserved at approx. 28% identity. The Akt active-site residues, described in a recent report on the crystal structure of Akt2 containing an ATP analogue and a peptide substrate , are the same in all three iso-enzymes. Based on the high degree of homology between the AGC protein kinase family members, the identification of specific active-site inhibitors has been predicted to be difficult. The identification of Akt iso-enzyme-specific inhibitors seemed to be an even greater challenge….

Two Akt inhibitors were identified that exhibited isoenzyme specificity. The first compound (Akt-I-1) inhibited only Akt1 while the second compound (Akt-I-1,2) inhibited both Akt1 and Akt2 with IC50 values of 2.7 and 21 μM respectively. Neither compound inhibited Akt3 nor mutants lacking the PH (pleckstrin homology) domain at concentrations up to 250 μM.

These compounds were reversible inhibitors, and exhibited a linear mixed-type inhibition against ATP and peptide substrate. In addition to inhibiting kinase activity of individual Akt isoforms, both inhibitors blocked the phosphorylation and activation of the corresponding Akt isoforms by PDK1 (phosphoinositide-dependent kinase 1).

A model is proposed in which these inhibitors bind to a site formed only in the presence of the PH domain. Binding of the inhibitor is postulated to promote the formation of an inactive conformation. In support of this model, antibodies to the Akt PH domain or hinge region blocked the inhibition of Akt by Akt-I-1 and Akt-I-1,2. These inhibitors were found to be cell-active and to block phosphorylation of Akt at Thr308 and Ser473, reduce the levels of active Akt in cells, block the phosphorylation of known Akt substrates and promote TRAIL (tumour-necrosis-factor-related apoptosis inducing ligand)-induced apoptosis in LNCap prostate cancer cells.

We can now return to the results of DeSemir et al. As they look to the usefulness of PHIP they state:

Although melanomas with mutant v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) can now be effectively targeted, there is no molecular target for most melanomas expressing wildtype BRAF. Here, we show that the activation of Pleckstrin homology domain-interacting protein (PHIP), promotes melanoma metastasis, can be used to classify a subset of primary melanomas, and is a prognostic biomarker for melanoma.

Systemic, plasmid based shRNA targeting of Phip inhibited the metastatic progression of melanoma, whereas stable suppression of Phip in melanoma cell lines suppressed metastatic potential and prolonged the survival of tumor-bearing mice.

The human PHIP gene resides on 6q14.1, and although 6q loss has been observed in melanoma, the PHIP locus was preserved in melanoma cell lines and patient samples, and its overexpression was an independent adverse predictor of survival in melanoma patients. In addition, a high proportion of PHIP-overexpressing melanomas harbored increased PHIP copy number.

PHIP-overexpressing melanomas include tumors with wild-type BRAF, neuroblastoma RAS viral (v-ras) oncogene homolog, and phosphatase and tensin homolog, demonstrating PHIP activation in triple-negative melanoma. These results describe previously unreported roles for PHIP in predicting and promoting melanoma metastasis, and in the molecular classification of melanoma.

This demonstrates the extended ability of PHIP to enhance the usefulness of other markers. They continue as follows:

As a result, "triple-negative melanoma" patients, whose tumors harbor wild-type v-Raf murine sarcoma viral oncogene homolog B1 (BRAF), neuroblastoma RAS viral (vras) oncogene homolog (NRAS), and phosphatase and tensin homolog (PTEN) (the most common mutations observed in melanoma), are not candidates for most targeted therapies developed to date.

This as we have noted before is one of the most significant findings. We know that BRAF mutations are currently targeted with some beneficial albeit temporally limited results. Perhaps PHIP may add an additional targeting.

They conclude:

Overexpression or mutation of genes that play important roles in tumor progression. A high proportion of melanomas are characterized by BRAF, NRAS, or PTEN mutations. However, the molecular basis of triple-negative melanomas lacking these mutations is poorly characterized. Our results suggest that PHIP levels may be used to classify some melanomas that lack these three mutations. It is likely that additional molecular aberrations will be identified to further characterize triple-negative melanomas.

Along with recent studies demonstrating that the IGF axis is activated in melanomas with acquired resistance to BRAF inhibition (23), these studies have identified IGF signaling as an important alternative pathway to promote melanoma progression. Overall, our studies identify PHIP as a molecular mediator of melanoma progression that also appears to function in the setting of a subset of triple-negative melanomas.

Clearly BRAF, NRAS and PTEN mutations are well defined targets, BRAF especially for melanoma and PTEN seems to span a wide number of cancers. However if they are not changed the PHIP mutation seems more in line with wit an reasonable target.

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Labels: Cancer

MONDAY, APRIL 23, 2012

MEDICARE REPORT

CMS has released the Medicare Trustee Report and we shall be looking into details.
Labels: Health Care

SATURDAY, APRIL 21, 2012

SOME THOUGHTS ON BANDWIDTH

The NY Times has recently reported on wireless that the carriers are seeking more bandwidth. They state:

The wireless carriers say that in the next few years they may not have enough of it to meet the exploding demands for mobile data. The result, they ominously warn, may be slower or spotty connections on smartphones and tablets. They imply in carefully couched language that, given the laws of supply and demand, the price of cellphone service will soar.

I would suggest several observations:

1. With the change from QPSK to OFDM we have gone from 1 bps/Hz to almost 10 bps/Hz.

2. With smart antennas we will go from 10 bps/Hz to over 100 bps/Hz.

3. At the same time data rates for video using MPEG X, 4 to 5, we see rates for HDTV dropping from 20 Mbps to 4 Mbps to 2 Mbps.

So as capacity increases and as demand decreases where is the gap?

Somehow this set of simple facts was missing from the article, and from the carriers as well.
Labels: FCC, Wireless

FAIRNESS: AND OTHERS WORDS

What really is fairness. In today's political debate it is about outcomes. In most other contexts it is about the rules. Fairness means following the rules, not what the winner or loser gets. In a NY Times piece there is a post hoc description of fairness.

The author states:

Economics, by contrast, hasn't traditionally been much concerned with fairness. Instead, economists have based their analysis on "Homo economicus," a model human being who is perfectly rational and perfectly guided by self-interest.

The financial crisis of 2008 made it hard to believe in a world of perfectly rational actors, even when they earn million-dollar salaries and have advanced degrees. Now, a growing body of research is challenging the second part of the definition of Homo economicus — that he is guided purely by self-interest.

The alternate view was advanced by Armin Falk, a Bonn University economist, at a recent economics conference in Berlin organized by the Institute for New Economic Thinking. It emphasizes the importance of fairness and trust to human behavior. This approach takes as its starting point the idea that we are social animals, driven powerfully by how we fit into our community.

The definition that they seem to be bringing out is fairness of outcomes and loss of individuality, and communalism. In contrast what has built a competitive entrepreneurial America is a fairness in rules, namely that one cannot steal or bribe to achieve a goal, one cannot steal or kill likewise, that there are rules and then let the players follow them to the end. The end may be quite disparate in results. That is the true nature of fairness.

Fairness is NOT ensuring that no matter how one functions that the end point is the same, that the community is more important than the individual. For it is the individual who takes the risk, who goes out bare into the playing field and attempts to seek a return. If Government will punish that efforts by redistributing what has been gained then why work at all, we should just sit back and watch the system collapse.

She continues:

Some of Dr. Falk's most recent work takes the question of fairness back into the medical laboratory. He and a team of colleagues asked what the physical impact of unfair pay was, this time as measured by our heart rate rather than brain waves. Experimental subjects who felt they were being unfairly paid showed higher heart rate variability, an indicator of stress that has been shown to predict heart disease.

Faulty tires and failing hearts are the grim consequences of unfairness suggested by Dr. Falk's talk. But the new vision he and like-minded researchers are developing of how human beings operate in the economy is actually rather uplifting. We aren't driven solely by self-interest; fairness and decency matter, too. Kindness and justice turn out to be useful concepts not just at the pulpit or among philosophers, but also as essential tools in the workplace.

If you feel you are poorly compensated, then quit and start your own company, this is America not Germany. You can readily do that, at least for a while. Life does not work in some 19th century Utopian commune, they are all failures. Success is driven by many factors and the ability to deal with risk is key. If you cannot do that then go work for the Government, it appears that it is impossible to get fired no matter how incompetent.
Labels: Economics

MEDICARE: A RELEASE TO WATCH

According to Medpage:

On Monday, the Medicare Board of Trustees releases its annual report, which will offer a long-term assessment of the solvency of Medicare.

This will be followed closely.
Labels: Health Care

TUESDAY, APRIL 17, 2012

MATHEMATICS, MODELS, REALITY AND GNOSTICS

Using mathematical models to understand and predict physical phenomenon has been around for a few centuries. The physical sciences is based upon them and engineering cannot function without them. However, there are other applications where we find that certain limitations may exist. Let me first start with a quote from Cassirer, The Philosophy of the Enlightenment, pp 108-109:

A survey of the special problems of eighteenth century epistemology and psychology shows that in all their variety and inner diversity they are grouped around a common center. The investigation of individual problems in all their abundance and apparent dispersion comes back again and again to a general theoretical problem in which all the threads of the study unite This is the problem which Molyneux first formulated in his Optics, *and which soon awakened the greatest philosophical interest.*

Is the experience derived from one field of sense perception a sufficient basis on which to construct another field of perception that is of qualitatively different content and of a specifically different structure? Is there an inner connection which permits us to make a direct transition from one such field to another, from the world of touch, for instance to that of vision? Will a person born blind, who has acquired an exact knowledge of certain corporeal forms by means of experience and so can distinguish accurately among them, have the same power to distinguish objects if, as a result of a successful operation, he gains possession of his visual faculties, and is required to judge concerning these forms on the basis of purely optical data without the aid of the sense of touch?

The point, perhaps one should be cautious in employing techniques which work well in one field but may have limits in others. Let me consider two recent efforts.

In Science there is a recent article on the use of models in understanding the operation of genetic pathways. Working in the field at this time I can fully understand the attraction. Yet I also understand the complexity and potential for misuse. The author states:

Four hundred years ago, Galileo observed that "Nature's great book is written in mathematical language." Since that time, physical phenomena have been described by mathematical equations, yet biology has remained qualitative. A possible explanation is that complex behavior in physics emerges from relatively simple interactions between many copies of few elements, whereas biological complexity results from nonlinear interactions of many heterogeneous species. In this sense, biological systems are similar to engineered machines: Inventories of both airplane parts and animal cell proteins consist of tens of thousands entries; cell interactomes look similar to machine blueprints; and performances of both engineering and biological structures are characterized by robustness and noise resistance. This analogy has limitations: Biological systems are built from stochastic and unreliable parts; are evolved rather than designed; and are subject to reverse, not direct, engineering. Nevertheless, in the last two decades, the mathematics usually applied to engineering and physics has been often used in cell biological studies where quantitative models serve as a guide for failing intuition.

Here I would agree and disagree. Mathematical models are embodiments of intuition, of understanding, not surrogates for them. The problem is that this is a very difficult problem. In addition there is "noise" in these systems which create uncertainty. Do we model the noise as random or is it necessary to understand its dynamics as well and push the noise level lower. Thus is miRNA a noise element or an element we must account for in detail.

The author continues:

The foundation for this surge was laid by two seminal papers that appeared 60 years ago. One was the biologically abstract and mathematically simple manuscript by Alan Turing proposing that a pattern can emerge in an initially homogeneous mixture of two chemicals. Turing used two linear partial differential equations (PDEs) with few parameters to demonstrate that two chemicals, a slowly diffusing "activator" and a rapidly diffusing "inhibitor," could concentrate in different regions of space. Untested and unsubstantiated at the time, this conceptual model has served as a basis for many studies of polarity, chemotaxis, and development. Another work by Hodgkin and Huxley was mathematically complex, grounded in experimental data and very detailed: Many ordinary differential equations (ODEs) with many parameters and nonlinearities were used to describe ion currents through voltage-gated channels in the axon membrane. The parameters and nonlinearities were measured, and the model reproduced the observed electric bursts in nerve cells, which revolutionized our understanding of excitable systems.

Here I have a true concern. The Turing paper is a true classic. It was intuition to the extreme. I have used it in modeling plant color patterning, and I am currently using it as a means to understand stem cells in melanoma. The problem is that despite the metaphor provided by Turing it may or may not be the correct one and the understanding to assure ourselves is still a bit distant. Let me consider cancer at a high level. It is characterized by:

1. Loss of control of the cell cycle. Namely we have ligands, then receptors, then pathways and then promoters, the cyclins, and then the cycle, and on and on. Control of the cell cycle will stop the multiplication of the malignant cell.

2. Loss of Location: Loss of E-cadherin attachment capacity results in melanocytes going where they should not. Why and is this a Turing effect?

3. Stem Cells: Are there some collection of control cells, the stem cells, which send out in a Turing like fashion in space control signals. If one removes the stem cell do the others die off? I have observed some of this in prostate neoplasia but it is at best anecdotal.

4. Mutations:How do they occur and why?

The authors continue:

These two papers symbolize the opposite ends of "modeling space". It is tempting to pronounce that we will be describing cells in ever more accurate terms and minute detail, moving from focused and conceptual (like ODEs describing three-node motifs in regulatory networks) to accurate and broad models, perhaps ending with a "whole-cell model" that completely recapitulates cell behavior on a computer, substitutes for wet laboratory experiments and makes personalized medicine possible. This is an appealing, if distant, goal. Meanwhile, this view subtly puts broad models above focused ones and suggests that there is a modeling "Road to Valhalla."

I doubt that we are near that "Road" yet but there is much superb work being done. If I had to bet I would bet on Turing. I have seen it function in plant patterning with secondary pathways, perhaps in cancer cells as well.

But the key question is: Are these models and methods reliable for this domain of knowledge. Have we managed to challenge the Cassirer model? I think they are worthwhile. I think they will function quite well but not as simply as many think. After all the control system for a B-2 bomber may be as complex as the pathways of a single cell organism, we just do not yet know enough. But it is worth a try.

Now to the other extreme, macroeconomics. A recent book, The Assumptions Economists Make, by Schlefer, is an interesting contribution to understanding the world of macroeconomists, from the perspective of an outsider. It also demonstrates the use and gross misuse of models, unlike the discussion above.

Let me start by commenting on a paper by Mankiw and Weinzierl, An Exploration of Optimal Stabilization Policy, which states in an opening set of assumptions (modified):

The economy is populated by a large number of identical households. The representative household has the following objective function:

$$max\{u(C1)+v(G1)+b[u(C2)+v(G2)]\}$$

where C, *is consumption in period* t, G *is government purchases, and* b *is the discount factor. Households choose consumption but take government purchases as given.*

Households derive all their income from their ownership of firms. Each household's consumption choices are limited by a present-value budget constraint:

P1(I1-T1-C1)+ P2(I2-T2-C2)/(1+i1)=0

where P is the price level, I is profits of the firm, T is tax payments, and i is the nominal interest rate between the first and second periods. Implicit in this budget constraint is the assumption of a bond market in which households can borrow or lend at the market interest rate.

Just what does this model have to do with reality? Why are households identical, is it not the real issue that they differ, and that their difference changes in time. and what objective function, is there not a psychological element as well and that often the choices are not logical or consistent. And what household owes its income from owning firms, very few. Thus, this statement, typical of almost all, assumes a world not in evidence. In contrast to my biological pathways, which we struggle so hard to understand with facts, the economists can easily say, "assume a spherical elephant". Yet none exists.

Unlike the problems in the world of genomics where we do not “assume” but base our models on “facts”, like science and engineering in general, this paper and this statement is the typical example of what Schlefer discusses, namely macroeconomists using equations to justify the total lack of reality. Schlefer goes through many of the absurd assumptions made by economists in their models and then he correctly articulates the arrogance many have in stating that they have knowledge that others lack. They have become the Gnostics of the twenty first century.
Labels: Cancer, Commentary, Economics

THURSDAY, APRIL 12, 2012

TREES: THE ISSUE OF CLIMATE CHANGE

I am a collector of trees, lots of trees. I collected dozens of Ginkgo seeds some twenty plus years ago from the New York Botanical Garden, ahead of an onslaught of Chinese nut pickers, and have planted and grown dozens of Ginkgo trees. I also have dozens of metasequoias. You see they are remnants of trees which have been around some hundred million years or more. No weak oak are these, they have seen massive climate changes and have more than prospered.

So when I read the op-ed today in the NY Times I was a bit surprised. They say:

Humans have cut down the biggest and best trees and left the runts behind. What does that mean for the genetic fitness of our forests? No one knows for sure, for trees and forests are poorly understood on almost all levels. "It's embarrassing how little we know," one eminent redwood researcher told me.

But what doe we have covering New York City streets? Ginkgoes. Why, they thrive on human pollution. They eat up CO2, the absorb all sorts of junk, they manage to thrive of the dogs and other mammals relieving themselves on their trunks. That have done this for hundreds of millions of years. The female shed seeds which smell putrid, although they roast to savory nuts. They are true survivors. And the Metasequoia, well it was down to its last legs in a valley in China when in the late 1940s someone brought out a few seed. Now it grows everywhere, humans have taken it to their heart and the things grows like a weed. Hundreds of feet tall, 3 feet or more per year!

So the problem with trees is the same as I guess Darwinism, there are the fittest which survive, survive independent of the human and survive with the help of the human. Redwoods are fragile, they will not grow anywhere. Ginkgoes will grow anywhere, literally. They will endure any extreme we throw at them. So what not reinforce that cycle, do away with wimpy trees, support the uber tree.
Labels: Climate Issues

SUNDAY, APRIL 8, 2012

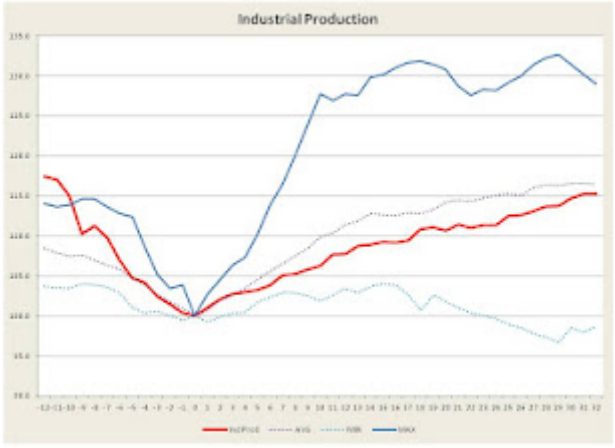
HAPPY EASTER

Una autem sabbati, Maria Magdalene venit mane, cum adhuc tenebræ essent, ad monumentum: et vidit lapidem sublatum a monumento. Cucurrit ergo, et venit ad Simonem Petrum, et ad alium discipulum, quem amabat Jesus, et dicit illis: Tulerunt Dominum de monumento, et nescimus ubi posuerunt eum. Exiit ergo Petrus, et ille alius discipulus, et venerunt ad monumentum. Currebant autem duo simul, et ille alius discipulus præcucurrit citius Petro, et venit primus ad monumentum. Et cum se inclinasset, vidit posita linteamina: non tamen introivit. Venit ergo Simon Petrus sequens eum, et introivit in monumentum, et vidit linteamina posita, et sudarium, quod fuerat super caput ejus, non cum linteaminibus positum, sed separatim involutum in unum locum. Tunc ergo introivit et ille discipulus qui venerat primus ad monumentum: et vidit, et credidit: nondum enim sciebant Scripturam, quia oportebat eum a mortuis resurgere. Abierunt ergo iterum discipuli ad semetipsos. Maria autem stabat ad monumentum foris, plorans. Dum ergo fleret, inclinavit se, et prospexit in monumentum: et vidit duos angelos in albis sedentes, unum ad caput, et unum ad pedes, ubi positum fuerat corpus Jesu. Dicunt ei illi: Mulier, quid ploras? Dicit eis: Quia tulerunt Dominum meum: et nescio ubi posuerunt eum. Hæc cum dixisset, conversa est retrorsum, et vidit Jesum stantem: et non sciebat quia Jesus est. Dicit ei Jesus: Mulier, quid ploras? quem quæris? Illa existimans quia hortulanus esset, dicit ei: Domine, si tu sustulisti eum, dicito mihi ubi posuisti eum, et ego eum tollam. Dicit ei Jesus: Maria. Conversa illa, dicit ei: Rabboni (quod dicitur Magister). Dicit ei Jesus: Noli me tangere, nondum enim ascendi ad Patrem meum: vade autem ad fratres meos, et dic eis: Ascendo ad Patrem meum, et Patrem vestrum, Deum meum, et Deum vestrum. Venit Maria Magdalene annuntians discipulis: Quia vidi Dominum, et hæc dixit mihi. Cum ergo sero esset die illo, una sabbatorum, et fores essent clausæ, ubi erant discipuli congregati propter metum Judæorum: venit Jesus, et stetit in medio, et dixit eis: Pax vobis. Et cum hoc dixisset, ostendit eis manus et latus. Gavisi sunt discipuli, viso Domino. Dixit ergo eis iterum: Pax vobis. Sicut misit me Pater, et ego mitto vos.

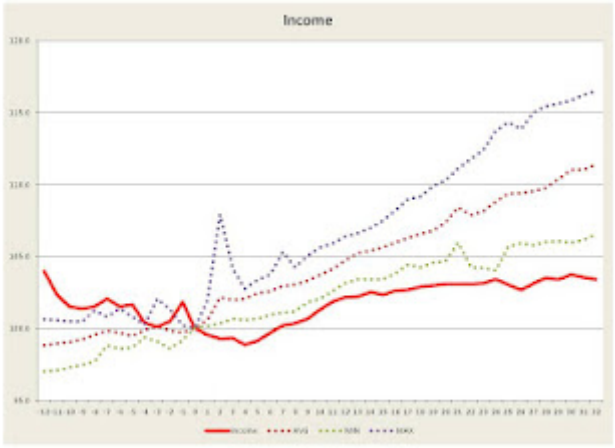
John 20 (Vulgate)
Labels: Commentary

FRIDAY, APRIL 6, 2012

RECESSION COMPARISONS



It is useful to look at the employment data as compared to other Recessions. From the St Louis FED we have the above and following charts. Industrial Production as shown above is still dragging. This indicates that as we have been saying there is a reticence on the part of companies to expand, and I would strongly argue that it is due to Washington.



The above chart shows Income Growth. In fact it is going no where. With the pent up inflation potential this is a terrifying statistic. We have the lowest Income Growth ever! And in fact it is decreasing. With the advent of the tax increase in January we anticipate a second dip recession, even if the Republicans win since the current Administration is on auto pilot and it is going no where fast.

We can see employment is also near the bottom, but when combined with Income we see that people are being moved down the salary scale and even though they are employed it is at a much lower paid job. This trend is expected to continue.

In our view the Recession is far from over and Washington is still making things worse.
Labels: Economy

VALUE DESTRUCTION: THE LESSON FOR AMAZON

I have been following a Customer Discussion on Amazon which I truly find amazing. You see I like Amazon, and they have been great over the past few years. They have great potential. Yet for some reason they are "snatching defeat from the jaws of victory". The issue is their delivery policies. The used UPS or Fed Ex or USPS as the standard delivery. Now these guys are generally reliable, vetted out, etc so one gets what one expects.

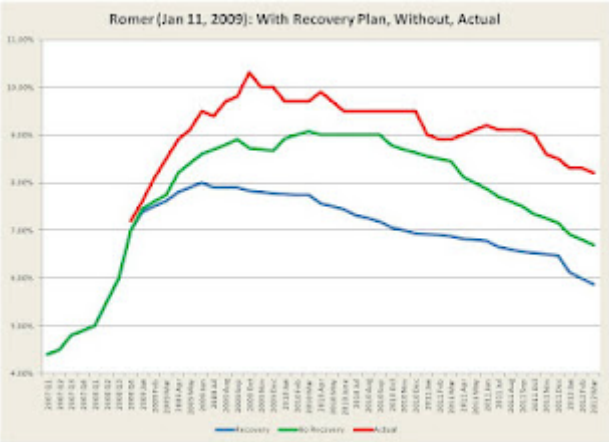
The Amazon changes its policy and for its Prime Customers, it decides to use low cost delivery services. Now this is a problem. I guess for gated communities they are not allowed in, I gather that they often fail to deliver and then outright lie about it, they threaten in a thug like manner etc. My solution is to pay for next day delivery, Amazon gets more money and I do not have to worry about the thug driving up my driveway, but since I live in that part of New Jersey where the thug is at more risk than the resident, yes think Sopranos, I have little problem.

But the issue is Amazon, why are they destroying their reputation, and with almost a hundred pages of complaints, not a word from Amazon. This is a classic example of value destruction. If they want more money, say so, if they want to charge more for UPS, then say so, if they want something, use customer loyalty, it was great. But not now. This is the most amazing example of self immolation in the corporate world I have ever seen.

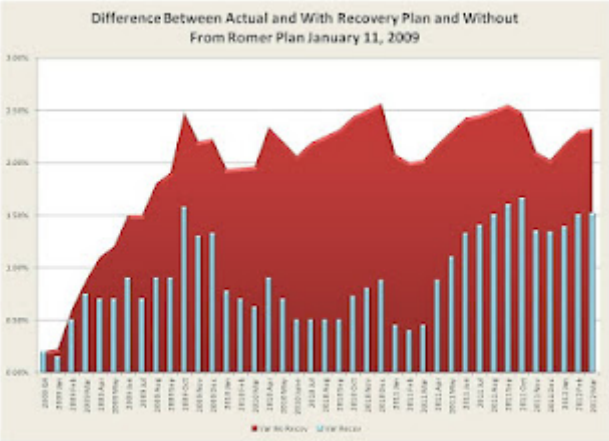
The risk to Amazon, lost customers, the real risks, a massive shareholder suit because they knowingly and willingly destroyed a market with malice aforethought! At least that could happen in today's world. I really wonder why they allow this to get so bad, just stupid

management? I doubt it, arrogance, possibly, or what? I keep recalling that sign behind my desk, "If all else fails listen to the customer!" Bezos seems to have slipped up on this one, why!
Labels: Books, Business

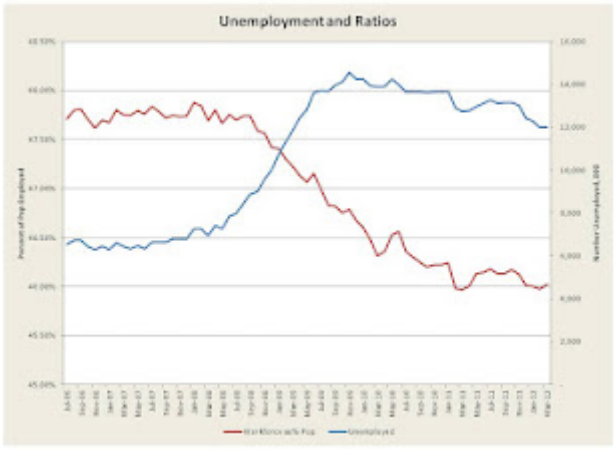
EMPLOYMENT: APRIL 2012



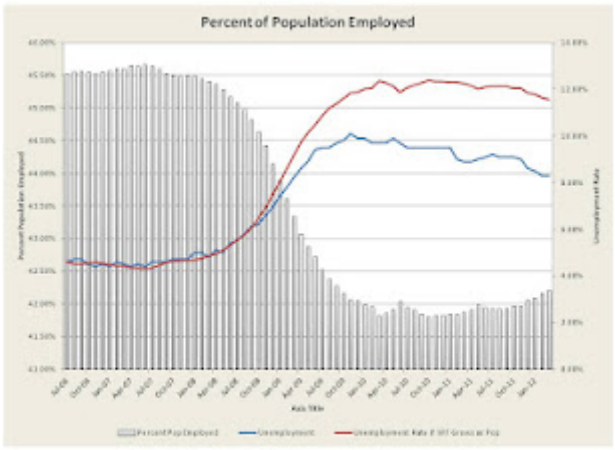
Let us start with the Romer Curve update. As expected she had predicted that we would be very well off by this time, in fact returning to normal, just spend a trillion! But somehow the economy did not follow her advice.



This chart shows the variance, and as we see it is again consistently growing. Not a surprise.



This is chart showing the denominator used to calculate the unemployment. Again it remains substantially below what it was before.



Finally we can see this in detail.Remember that with a growing population of well over 250,000 per month, and the baseline of having 45.5% of the population employed, just to keep unemployment fixed we need 45.5% of 250,000 new jobs, that is 120,000 new jobs to stand still! We allegedly got 120,000, or 0 above standing still. That means we effectively added nothing! Since we grow at 3 million per year and again 1.5 million new jobs per year would be required to stand still! The Administration claims 3 million plus new jobs in their 3+ years, if you deduct the stand still numbers you are still under water. So details count!
Labels: Economy

WHAT SIZE THE NAVY? WHAT WAR?

What is the right size for the Navy. What War are they planning for? I was at the Naval War College a few years back, 2009 I believe, and the CNO was proudly discussing the humanitarian role of the Navy, it most important missions. This was not Mahan, in fact it was almost an anti-Mahan. Now Mahan is a somewhat distant relative from Mohill, County Lietrim, Ireland, seem to be a fifth cousin, but perhaps the same Irish blood flows through the veins, and I too was a bit surprised. I thought the role of the Navy was to protect US interests abroad. But we do have a different administration.

Thus I was interested to read the update of the political battle over the new direction of the Navy's fleet, deploying coastal area vessels, Littorals, in the NY Times.

One of the two $700 million ships completed so far has had a major leak and crack in its hull, while the other is at sea, testing equipment that is failing to distinguish underwater mines from glints of light on the waves. More ominously, a report late last year by the Pentagon's top weapons tester said the ship "is not expected to be survivable in a hostile combat environment."...Able to operate on the high seas and along shallow coastlines (the "littorals"), the fast, maneuverable ship is central to President Obama's strategy of projecting American power in the Pacific and the Persian Gulf. It adds a relatively small and technologically advanced ship — part of what former Defense Secretary Donald H. Rumsfeld envisioned as a lean, proficient military — to America's traditional blue-water Navy of aircraft carriers and destroyers.

Now the issue is one of sea warfare tactics. I wrote a paper on an analysis of swarming tactics, using WW II Destroyer efforts in the Battle of Leyte, and noted that the use of low cost smaller ships, in this case WW II Destroyers, allowed for a successful attack against a superior fleet. The key however was tactics and integrated communications as I demonstrated in the analysis of the specific battle in my book on WW II Destroyers. The NY Times continues:

"If you use smart tactics, techniques and procedures, we believe the ship is survivable," Mr. Work said, making an argument that Mr. Hunter, the congressman, finds specious. If seven Iranian attack boats should come at the new ship, Mr. Hunter said, "it backs away, it can't take

any major hits." In short, he said, "it's not going to stand there and trade punches with anybody."But perhaps its appearance could frighten potential enemies. As Joseph J. Rella, the president of Austal USA, said in a recent interview: "If I was a pirate in a little boat, I'd be scared to death."

One should look at history here. $700 million is a lot to spend but the War possibilities are even greater. An integrated command, control, communications and intelligence backbone is critical as I had observed during WW II. In fact it can be argued that in WW II we were victorious due to that C3I backbone. We lost hundreds of destroyers, the past counterpart of the Littorals. That observation that numbers count is critical. The absurd, in my opinion, remark that the appearance will scare away an adversary is at face value ridiculous. It is also dangerous. Just look at the past, all of the past!

Thus the issue is what is the true mission of the Navy, what threats do we have, how far will we go to defend our interests? We need that discussion. Do we fear Iran more than China? What of Russia? What of the small terrorist group who could deliver a low yield nuke to a few locations, and we have but a few ships, then we may very well lose C3I. That is a real threat.
Labels: Military

CAN'T STOP TALKING: SOCIAL DARWINISM

It appears that the left has found a new word, or phrase if you will, even though they seem to have no clue about what they speak. That is Social Darwinism. Blame Herbert Spencer, perhaps, but not Darwin, he never really accepted it.

Now I suspect also that the commentators have no clue what Darwinism is no less Social Darwinism. Darwin is rather difficult to read, I have plodded through it, mid 19th century English prose, a bit self possessed and yet a struggle. You see Darwinism is simply a survival of the fittest, species that is, not just individuals. Gene expressions yield advantages. I have noted that in my hybridizing. I perform my intelligent design on plants, keep the attractive ones, and then throw the remainders on a hill in our New Hampshire home. They just get tossed. And guess what, some of them just take over, they thrive, reproduce, and do better than any of my pampered flowers, just look above. Social Darwinism for plants? No just Darwinism, human intervention not withstanding.

Thus I have been amused about the war between the left and the not so left, Chiat and Mankiw. I would assume from reading that neither has been near a copy of Darwin. But that is just a guess.

Now for Chiat. He states:

I happen to think "social Darwinist" captures the prevailing Republican philosophy pretty well. The point of the label, created by historian Richard Hoftsadter, is that a species of laissez-faire economics treated the market the way Darwinians treat natural selection — as the sole natural and correct mechanism for distributing rewards. You do not have to venture into the Republican fever swamps to find evidence of this belief. Greg Mankiw, an economist, adviser to Mitt Romney, and relative moderate within the party, has written: "People should get what they deserve. A person who contributes more to society deserves a higher income that reflects those greater contributions. Society permits him that higher income not just to incentivize him, as it does according to utilitarian theory, but because that income is rightfully his."

First, Hoftasdter, he was a reformed proto-communist, vile anti-Catholic, and typical extreme left wing Columbia academic, who thrived on attacking any form of American individualism. He was the source of a great deal of anti-American thought and a typical WW II draft dodger. Now let me tell you how I really feel ... But alas not enough room. Thus Chiat using Hofstadter as a baseline defines the argument, namely baseless. Hofstadter's book on Social Darwinism defined his position against the right and middle of the political spectrum. I have written extensively on him and find his overall views repugnant and unlikely to be accepted in polite society. Yet he was a reflection of Columbia then and now, a key fact to understand, because Columbia has always been ever so more anti-Catholic than Harvard.

Now Mankiw replies somewhat weakly in my view:

I think the answer is pretty clearly NO. But nonetheless, Jonathan Chait calls me a Social Darwinist, citing as evidence the paper from which the second passage above is taken. True, he quotes a different passage from that paper, but one would think a prominent journalist like Mr. Chait would read the entire paper and characterize the arguments fully before throwing around a pejorative like "Social Darwinist."

Mankiw is a far cry from being a Social Darwinist. He after all is a proponent and leader of the Pigou Club, the group which proposes taxing everyone and giving the money to the Government, a form of cap and trade, except the cap is a tax based cap with no quid pro quo. Pigou is hardly Darwinian and Mankiw in my opinion is so far distant from Social Darwinism that it is impossible how any one could make a connection. And Romney is also not even close. Just read Dickens, for in there we see Social Darwinism, the Irish Famine of 1846-48, that was Social Darwinism, and in fact the English treatment of any of their colonies, and Teddy Roosevelt's treatment of the Philippines is the same, and he was a Progressive.

The interesting fact is how has this concept spread. I thought we had buried Hofstadter, why is Croly when we need him.

On the other hand I am out today working on my fine hybrids in New Hampshire and as I look to the hill of Social Darwinistic Hemerocallis, I can see those plants which have survived and may very well take over in a millennium.
Labels: Politics

WEDNESDAY, APRIL 4, 2012

ROBOTS DON'T BUY MUCH, NEITHER DO BLACKSMITHS OR SCRIBES

In reading the NY Times one is often better informed by reading the comments to the article. The article was on Amazon, its purchase of a robot company, and the automating of its distribution sites. One comment from a Canadian was:

Robots don't buy much. Eventually, unless we come up with some form of guaranteed annual income, there won't be any customers for their output.

Now there is more insight here in this short comment than any of the long run on sentences. Perhaps because the writer is Canadian we may dismiss it as per se socialistic ramblings, but it does portray the views of many. No robots don't buy anything, yet the people who create them create value, the people who extract the minerals create value, the people who create the software create value. The value chain is a moving and living entity. To participate in it one must be prepared, educated, and willing to take a risk.

In contrast the solution is a guaranteed income. First where is the money coming from, second what are the unintended consequences. Had we kept our scribes busy, we would not have had a typewriter, and if we kept our typists busy we would not have had the word processor etc.

The logical disconnects in this single comment, two sentences, reflects the problem in our society, a culture of many who have neither the capabilities nor the insight to what has made America. Also the "demand" for those who are willing to risk and produce to fund those who are clueless is truly pathetic.
Labels: Commentary

TUESDAY, APRIL 3, 2012

HOW MANY PEOPLE CAN CONNECT SOCIAL DARWINISM AND SPENCER?

The more I thought of the tactic the more I wondered what type of person it would take to connect Spencer, Darwin, Social Darwinism and politics. Spencer had a good run at the end of the 1800s especially here in the US. Darwin ultimately dismissed him because he took Darwin's ideas and tried to apply them to society and not species. But I really wonder what it would take t understand this, given what little people really know about Darwin.

On the other hand as I have remarked many times, Hofstadter from Columbia was a proto-communist and an avid anti-Catholic, as was most of Columbia for quite a while, assuming they managed to have shed that now, so one may look more to Hofstadter for a definition rather than

Spencer. But still how many people watching MSNBC or Fox, or worse PBS or the Networks, even have a true intellectual clue? Have they read Darwin, Spencer, even Hofstadter? Unlikely, so why the reference? Perhaps there is some other agenda.....perhaps.
Labels: Political Analysis

SOCIAL DARWINISM

I know Herbert Spencer, and Paul Ryan is no Herbert Spencer. Now if you went to Columbia and had Hofstadter or his spawn as an instructor then they may very well see any non-socialist policy as Social Darwinism.

As I wrote in a review in Amazon regarding a bio on Spencer:

Spencer was well read from the time he started to write through the 1930s. Then he was attacked unjustly by the left wing in American academia, centered at the time at Columbia University, a hotbed of Communists and Marxists. For it was in the mid 1940s that Spencer was vilified by the one-time Communist history professor at Columbia University, one Richard Hofstadter.

Hofstadter in his book Social Darwinism uses Spencer's ideas on Darwin in a somewhat self serving and twisted manner to attack both Spencer and the free market capitalism as it evolved over the century from 1850 to 1950. Hofstadter was well known in leftist circles as one who could readily take a few apparently disconnected points and with what could be at best described as shabby research methods produce polemics against the conservatives and right wing advocates in the body politic.

Hofstadter was also well know to write "soft" history, what we would expect in a New Republic piece, rather than hard academic history. Hofstadter was polemical in his style and greatly deficient in primary sources. He was all too often just a recorder of old press clippings using these as the window to the world he wanted the reader to see rather than addressing the reality via primary sources.

In a recent work by Prof. T. Leonard at Princeton University (See Origins of the Myth of Social Darwinism: The Ambiguous Legacy of Richard Hofstadter's Social Darwinism in American Thought) Prof. Leonard states about Hofstadter and Spencer the following, while reviewing the issues in "Social Darwinism in American Thought", also called "SDAT":

"Richard Hofstadter, like many New York intellectuals in the 1930s, embraced radical reform. He joined Columbia University's Communist Party unit for a brief period in 1938. The more mature Hofstadter grew disenchanted with radical politics, indeed came to see it as hostile to scholarship. But SDAT, which revised his doctoral dissertation published in 1939, preserves Hofstadter's earlier world view, that of a precocious scholar, still much influenced by his mentors, Merle Curti and Charles Beard, who could say to close friends, "I hate capitalism and everything that goes with it" ... SDAT also bears the historiographic imprint of Beard's "rule" that historical interpretation must assume that "changes in the structure of social ideas wait on general changes in economic and social life" ... SDAT is thus sprinkled with unadorned Beardian claims, such as "Herbert Spencer and his philosophy were products of English Industrialism"..."

Thus Ryan is no Spencer, but one must look towards the source.
Labels: Political Analysis

SUNDAY, APRIL 1, 2012

MORSE CODE FOR THE NEWBIES

Google announced a new means of communicating, called TAP, also known as Morse Code! Even though it is April Fool's Day perhaps this is a good idea, it only requires a dot and dash. No letters!

For those of us who have an Amateur License from the old days, we actually had to learn this stuff.

KC2PMK
Labels: Google

FRIDAY, MARCH 30, 2012

SOMEWHAT TERRIFYING: LOSS OF IDENTITY

The Guardian has a frightful article on what is happening in the Internet, in my opinion the arrogance of the bot creators have a logic which one cannot follow.

As part of the Esc and Ctrl series, Jon Ronson recently published two videos on Comment is free in which he confronts a spambot version of himself and accuses it of stealing his identity.

These European Professors are in my opinion clearly cyber terrorists but also seem in my opinion to be grossly illogical. They seem to have the problem that in Twitter world the use of one's real name is verboten, yes they teach in Germany. Identity is a key element of existence but one must listen to these characters, they are truly unreal.

What do they have, they have bots which steal identities and then create cyber identities that are sent out into the Internet. It states:

We're at a turning point in the development of the internet. Bots, like any other scientific innovation, can be used for benign or malign purposes. The identity issues that Ronson raises are only the thin end of the wedge

The creators have a problem with the Wall Street algorithms which perform real time trades, and they allege are at the core of their lost earning, and this is the apparent underlying prime reason that they are sending bots out to destroy individual identities. For these creators they believe that attacking third parties is a way to make public their message. The logic is hardly compelling to say the least.

It is essential to listen to this interview. Ronson is clear and logical but the creators of the bots in my opinion seem totally incoherent. They jump from conclusion to conclusion with no logical connectives. The issue that by using Ronson's name and picture and creating a bot to tweet things that may make no sense to things which could be defamatory is their way of sending out a complaint about Wall Street. There is in my opinion a direct disconnect from reality here, something is truly wrong.

The fear is that our future may very well be in the hands, or worse, the minds of people like this. Ronson did a wonderful job by collecting their logic and lack thereof on video. It should be viewed by many because it establishes the mindset in my opinion of a total nihilism. The loss of logic in a world where anyone can go out and defame with impunity.

Of all the things which one could be concerned about, this is one of the most serious. Loss of identity. There are those stealers of our selves, thieves of the persona, who then take and contort and then present it to the world as if it were us. They take glee in such an act, and have applied a set of disconnected logic which can only in my opinion be called bizarre!
Labels: Commentary, Internet

THURSDAY, MARCH 29, 2012

KEEN INSIGHT INTO THE OBVIOUS

I am always amazed that studies are done, and done again, demonstrating the obvious. Being obese will almost always result in Type 2 Diabetes. Loosing weight and moving will almost always mitigate against Type 2 Diabetes.

Now in a NEJM article the authors conclude:

Weight loss and improved fitness slowed the decline in mobility in overweight adults with type 2 diabetes.

So what is new here? Nothing really. They conclude:

Among overweight and obese adults with type 2 diabetes, an intensive lifestyle intervention led to a relative reduction of 48% in the severity of mobility related disability, as compared with diabetes support and education. This effect was mediated by both weight loss and improvement in fitness. Group differences that favored the lifestyle-intervention group were most striking in the severe- disability category. However, as shown by prevalence rates in the good-mobility category during all 4 years of the study, participants in the lifestyle-intervention group also retained higher levels of healthy functioning than those in the support group. The proportion of participants with the highest level of functioning at baseline in the support group was generally stable until year 3 and then declined. By contrast, in the lifestyle-intervention group, there was an increase in the prevalence in the good mobility category by year 2, and rates never fell below baseline.

Reuters also published a piece on this result:

The lifestyle changes helped mobile people stay that way and eased severe mobility problems in others, at least over the short term. Lead author .... , said the trends show the importance of encouraging people to get their weight down and exercise sooner, rather than waiting until they develop problems getting around.

But all of this was clinically well known. Perhaps another study is supposed to demonstrate something. The only way to stop the obesity epidemic is to do what was done with cigarettes, tax it. Unfortunately none of the Republican advisors want to do that; one wants to tax gasoline out of existence and the other wants to have the Government mandate all health care, none of which addresses this issue! And the Democrats, well they seem to be even worse. Just watch the costs explode.

Labels: Diabetes, Health Care

ENGINEERING HEALTH CARE: AND A BIRD!

What the Supreme Court arguments show is that Washington is NOT Cambridge and neither is New York. In Cambridge one can go back and forth from the Academy to the home in the suburbs and rarely see reality. In Washington it is a continuous political battle. In New York, for better or worse, it is just money, nothing person, and you win or lose, at least until Washington stuck its head in. You see New York is still driven by Dutch individuality and capitalism, Cambridge by Puritan aloofness and exceptionalism, and Washington by the slime of politics.

Now the NY Times has a piece on one of the MIT Profs who spent his career pushing for a dream, a theoretical dream for health care. Now dreaming up a scheme with models is a far cry from designing a system and assuring it works. It is ivory tower economics versus engineering. This is why we are in such a mess, economists and the ivory tower. Their "ideas" just fails to meet reality.

As I have argued, universal coverage is essential, but the devil is in the details. We have models which work, auto insurance and even home insurance. The characteristics are simple:

1. Universal, yes one just can't seem to get around it. There should be an uninsured pool just in case.

2. Individually procured, NOT through an employer or third party.

3. Minimal required coverage primarily for catastrophes, and of a form where an individual can then add on.

4. Rates determined solely by variation of life style choices, you smoke you pay, you are fat you pay, but no variance for those with hereditary and the like diseases.

5. Skin in the game, you can have even oil change covered but it costs, otherwise you pay out of pocket.

6. Regulation, yes regulation, of the insurers.

7. Government support if incomes are too low. Cannot seem to get around this.

Now I had done a detailed financial model showing how this would efficiently work. I also argued along the line of changes in the means and methods of health care. As did hundreds or thousands of others. Yet the Times believes that there was a single voice. Pity they so all too often neglect the facts.
Labels: Health Care

WEDNESDAY, MARCH 28, 2012

REDUCTION IN CANCER DEATHS AND POLITICS

The CDC issued a new release summarizing a published report, requiring what appears to be a substantial fee, strange for a taxpayer funded work. Yet the conclusions indicated a significant reduction in both incidence and mortality.

Specifically it states:

The Report to the Nation was first issued in 1998. In addition to drops in overall cancer mortality and incidence, this year's report also documents the second consecutive year of decreasing lung cancer mortality rates among women. Lung cancer death rates in men have been decreasing since the early 1990s.

Colorectal cancer incidence rates also decreased among men and women from 1999 through 2008. Breast cancer incidence rates among women declined from 1999 through 2004 and plateaued from 2004 through 2008. Incidence rates of some cancers, including pancreas, kidney, thyroid, liver, and melanoma, increased from 1999 through 2008.

Melanoma has a long tail since most cases are sun induced but take substantial time to progress so that is not unexpected. Pancreas may very well be linked to obesity and the inflammatory response that results. What was once a rare form of cancer has seen a rate of increase paralleling the increase in obesity. The same may be true for renal carcinomas since they are well established as having linkages to Type 2 Diabetes as well as obesity. Thus the increases are most likely obesity linked.

The release continues:

"In the United States, 2 in 3 adults are overweight or obese and fewer than half get enough physical activity," said John R. Seffrin, Ph.D., chief executive officer of the American Cancer Society. "Between children and youth, 1 in 3 is overweight or obese, and fewer than 1 in 4 high school students get recommended levels of physical activity. Obesity and physical inactivity are

critical problems facing all states. For people who do not smoke, excess weight and lack of sufficient physical activity may be among the most important risk factors for cancer."

We have been arguing this for years. We indicated the scope in our book on Health Care and our book on Obesity. The irony is that one of Romney's senior economic advisors rejected any Government attempts to control this epidemic while at the same time recommending a $1.00 a gallon added tax on gasoline. That approach is as bad as or worse than the current Administration's mess. But then again they are all filled with Harvard economists.

The fact is that technology can fix the gas problem but that people's behavior must be controlled to fix the cancer and other obesity related problems, just as those smoking related have been shown to have been fixed. We now have almost banned smoking everywhere, why not try that with obesity?
Labels: Cancer

MONDAY, MARCH 26, 2012

GENES AND PATENTS

This case is interesting and now very much worth following. The Washington Post states:

The Supreme Court on Monday threw out a lower court ruling allowing human genes to be patented, a topic of enormous interest to cancer researchers, patients and drug makers. The court overturned patents belonging to Myriad Genetics Inc. of Salt Lake City on two genes linked to increased risk of breast and ovarian cancer. ... The case is Association for Molecular Pathology v. Myriad Genetics, 11-725.

It will be interesting to see if pathways will have similar standing since in many ways they are the next step in creating ways to control cancers. Just a thought.
Labels: Law, Technology

SUNDAY, MARCH 25, 2012

WOULD YOU BUY A USED CAR FROM THIS MAN?

In the FT an opinion writer states:

Economic forecasters divide into two groups. There are those who cannot know the future but think they can – and then there are those who recognize their inability to know the future. Major shifts in the economy are rarely forecast and often not fully recognized until they have been under way for some time. So judgments about the US economy have to be tentative.

Now I read his paper which he and a west coast academic are circulating and it is one of those if and if and if documents with models which would not pass muster in any good engineering school, but read the words. The conclusion, no forecaster ever has a good forecast. Yet then he asks us to believe his recommendation of what will make the future better ... is that not a forecast, and has he not already denied any valid forecast, thus why should we believe him now.

That is the problem with academics, especially economists, the write all too often as if they understand reality and then in the next breath ask us to suspend it.
Labels: Economics, Economy

AMERICA'S FIRST SOCIALIST: TR

Recall that TR made the following in Osawatomie, Kansas on August 31, 1910:

Nothing is more true than that excess of every kind is followed by reaction; a fact which should be pondered by reformer and reactionary alike. We are face to face with new conceptions of the relations of property to human welfare, chiefly because certain advocates of the rights of property as against the rights of men have been pushing their claims too far. The man who wrongly holds that every human right is secondary to his profit must now give way to the advocate of human welfare, who rightly maintains that every man holds his property subject to the general right of the community to regulate its use to whatever degree the public welfare may require it.

The New Nationalism, inspired by Croly, a founder of the Progressive The New Republic, assisted TR in this speech. TR truly believed that property rights were no longer there, they were destroyed by his contention that the community can regulate them, whoever the "community" is, and for TR it was him and his followers. This was a decade before Lenin, before Stalin, this was the basis of the election of 1912.

Now a hundred years later we reflect on the same issues as the case before the Supreme Court in many ways resonates with the philosophy of TR. Just a thought!

Labels: Commentary, Politics

THE REPUBLICAN'S LEFT WINGER:PIGOU

Energy Policy has become a euphemism for back door tax increases. The Pigou Tax is its leader. Tax the poor, let the rich ride. It is the most regressive tax ever and it make cap and trade look tame. Cap and Trade is a Democrat creation, typical, a Rube Goldberg Government controlled means to reduce gas consumption. Pigou is pure taxation in its intent and execution, tax the life out of it.

But as I have indicated before, the tax takes money from the open economy and places it in the hands of Government, read waste. That is the major concern. Taxing something out of existence does work, painfully, and at times usefully, look at smoking. But it destroys individual wealth at the benefit to politicians. They redistribute. But also gasoline consumption is highly inelastic. Even more so for those on the low end of the economic spectrum.

But the left wingers always see Government as the proper beneficiary of peoples hard work As is stated in Barrons:

Harvard University economist Greg Mankiw, currently an advisor to GOP presidential hopeful Mitt Romney, has long been an advocate of a $1-per-gallon gas-tax hike phased in over 10 years (Romney won't countenance the tax). Absent the tax, politicians resort to crazy, Obama-like schemes to achieve the same end of reducing our dependence on foreign oil supplies.

Yes the same Republican that brought you health care by law in Massachusetts has an advisor bringing you not cap and trade but a simple $1.00 a gallon INCREASE in your transportation, and just where does that $1.00 go, to the coffers of the same folks in DC that caused the mess. This is a solution? So now where is the difference in these candidates? Harvard Law, mandated health care, taxing the poor for energy .... ? They are starting to look an awful lot alike.

The key problem is defining the issue and then seeking a solution. An economics based solution is but one of many, and that usually entails a tax. On the other hand if the problem is using too much foreign oil, then there are two technical solutions; get more energy from the US itself and/or improve efficiency. These are engineering solutions. Having the Government choose winners or losers in this domain is insane as we again see with the current Administration. However using the heavy hand of economic solutions, mandated taxes, is based upon belief and not facts. The Chinese leadership is dominated by engineers, almost to the extent of banning economists. Perhaps they know something we do not. And oh yes, they have no lawyers.
Labels: Economy

FRIDAY, MARCH 23, 2012

COMMUNITY COLLEGES

Science has an interesting Editorial on Community Colleges. Having just attended one, I retook Organic Chemistry 50 years later, I thought my comments might have some weight.

The author states:

In the 2009 American graduation initiative, President Obama enthusiastically highlighted the importance of community colleges—publicly funded 2-year institutions—for meeting the projected growth in jobs requiring a college degree. Increasing the number of college graduates earning science- and math-related degrees depends on these institutions increasing workforce preparation through science, technology, engineering, and mathematics (STEM) education. Community colleges are accessible, affordable, diverse, and flexible, and thus well positioned to meet this need. However, the current demand for courses far exceeds capacity, thereby calling for more government, business, and local resources to support these institutions.

and she then continues:

Community colleges can play a pivotal role in preparing under-represented students for STEM careers. People of color will make up 45% of the working-age population in the United States by 2030, up from 18% in 1980. According to the U.S. National Academies, they "embody a vastly underused resource and a lost opportunity for meeting our nation's technology needs." Community colleges currently enroll more than 50% of undergraduate Hispanic students and about 45% of African American and Asian undergraduates. Among those currently holding a

baccalaureate or master's degree in science or engineering, 55% of Hispanics and 50% of African Americans attended a community college. For immigrants pursuing the American dream, community colleges are a vital resource. They provide English language instruction, citizenship preparation, job skills, and assistance in navigating American bureaucracy.

My observations are somewhat in line but with some variance. I speak of a New Jersey CC and one in a somewhat upscale county. The students were a real mix, about 50% female, about 25% minority, Asian and Hispanic, and many returning to college or seeking a low cost path to their last two years. Thus this was an alternative path and a valuable one. It allowed them to attend college near their residences at a fraction of what it would cost.

The teaching was good, albeit at a High School level, the instructor always "warning" students, and yet he was competent and engaged. Yet he lacked what one would find at a first class university, namely engagement with the students. But he was not at a first class university, yet the material paralleled the MIT class material. Thus basically the student would have the book exposures. The Labs were twenty years old or older, the equipment was quite aged, computers ran Windows 95 in the Lab, and the techniques were also at best High School. Yet the resources were limited.

The students were for the most part intelligent, motivated, accomplished. Yet they lacked the vision that would be necessary. It was not their problem, the school did not provide it. What was missing was the nexus with what a professional does. At MIT a Freshman can do research with a top class researcher. At CC there is no such opportunity. Instructors are competent but they just teach, and try to seek other income as possible. The mindset of what real research is one cannot find.

The students learn technique not technology, and especially no science. Science is the art of asking questions having the expertise to frame the answers. The CC provides technique, and that is the shame. It clearly is a step above High School, but it is run as a High School. I do not blame them, yet the opportunity is there to expand the plane to provide the insight, namely seek stronger industry ties, seek out retired researchers and academics as adjunct advisers, and open the doors to those who are accomplished. The Administration of the CC is more politically oriented than academically, that to me is the challenge. The students are fertile ground, it should not remain fallow.
Labels: Academy

FRIDAY, MARCH 23, 2012

CANCER: AN EVOLVING PUZZLE

Several recent papers have been published on the details of cancer genetics which make the understanding a continuous process of complexity. Let me first provide a brief précis of how we have progressed to this point:

1. The clone. It has been asserted that almost all cancers begin with a single aberrant cell, the clonal source. From this one cell we have generate everything else. One single cell then replicates in an uncontrolled manner.

2. The Vogelstein Paradigm: The Vogelstein Paradigm (VP) states that the clone is created in some predictable sequence of gene changes and that these changes can be detected and perhaps blocked.

3. The genetic profile: This concept uses the wealth, also excess, of gene mutation data available from microarray analysis to determine "profiles" for various cancers attempting to gain prognostic information as well as "individual" profiling for treatment. In many ways the micro array tool provides "too much data", akin to the comment in Amadeus when the Emperor was asked about Mozart's music, and he remarked "too many notes". Namely the wealth of data is essential but the ability of the human processor is not quite up to it yet.

4. The pathway model: In this case we use pathways as a means to understand what is going wrong in a cell by cell basis. Then we try to block aberrant pathways to have the tumor no longer function as it has to that point. We have argued that this approach has a strong core, namely a model which can be verified and improved, but at the same time it lacks two major factors; (i) is does not deal with intercellular communications well enough, (ii) it does not deal with the issues of what causes the loss of gene activity and homeostasis well enough.

Now there have been several papers in NEJM discussing results on several cancers, kidney and AML, acute myeloid leukemia. Combined they tell and interesting tale. I have already commented on the kidney paper by Gerlinger et al but will add to it in this analysis.

As Gerlinger et al state:

Multiregion genetic analysis of four consecutive tumors provided evidence of intratumor heterogeneity in every tumor, with spatially separated heterogeneous somatic mutations and chromosomal imbalances leading to phenotypic intratumor diversity (activating mutation in MTOR*) and uniformity (loss-of-function mutation in* SETD2 *and* PTEN*). Of all somatic mutations found on multiregion sequencing, 63 to 69% were heterogeneous and thus not detectable in every sequenced region. Heterogeneous patterns of allelic imbalance were found in all tumors, and ploidy heterogeneity was found in two tumors. Therefore, we found that a single tumor-biopsy specimen reveals a minority of genetic aberrations (including mutations, allelic imbalance, and ploidy) that are present in an entire tumor.*

Thus with this study we see significant genetic variability. The sequencing of genetic changes and the expectation of clonal consistency seems to be at variance.

In contrast, to justify the clonal progression, as Walter etal state regarding AML:

A unique aspect of the biology of leukemia is that hematopoietic cells freely mix and recirculate between the peripheral blood and the bone marrow. Clones that persist and grow over time must retain the capacity for self-renewal. Mutations in new clones must confer a growth advantage for

them to successfully compete with ancestral clones. The result is that these secondary-AML samples are not monoclonal but are instead a mosaic of several genomes with unique sets of mutations; this mosaic is shaped by the acquisition of serial mutations and clonal diversification. Similarly, recent analysis of de novo AML samples with the use of whole-genome sequencing showed that relapse after chemotherapy is associated with clonal evolution and acquisition of new mutations. Analysis of individual cancer cells may reveal additional layers of genetic complexity. Recent studies of B-cell acute lymphoblastic leukemia have shown that serial acquisition of cytogenetic abnormalities in that disease most often occurs through a branching hierarchy and only rarely follows a simple linear path…. Our study has several clinical implications. First, the distinction between the myelodysplastic syndromes and secondary AML currently relies on manual enumeration of bone marrow myeloblasts, a standard that is subject to interobserver bias but nonetheless drives major decisions about treatment for patients with small differences in myeloblast counts. Ultimately, identifying the patterns of pathogenic mutations and their clonality in bone marrow samples from patients with myelodysplastic syndromes should lead to greater diagnostic certainty and improved prognostic algorithms.

Neither studies presented intracellular pathways models which could be verified as state machines leading to malignant processes nor did they provide any basis for the genetic variations observed. These two factors will be essential in a better understanding of these diseases. However we see strong hematopoietic clonality and non-hematopoietic non-clonality.

The question one may ask is: does the cancer cells as they progress in a metastatic manner do so in a random ever changing manner unconnected from one another or is there some rational basis for the changes in a manner in which the cancer has become an alter-organism in the human host? Is cancer a “slime mold” atop the human?
Labels: Cancer

ACA, MEDICARE, AND THE STUPIDITY OF GOVERNMENT

It is always useful to see the provision of Government controlled health care through one's own lens. Now I am one of the few who try not to get sick, and to that point I watch diet and exercise especially watching blood glucose. To wit, I record each day for the past ten years fasting and post prandial glucose, weight, food intake, etc. Ten years of daily data, never a miss, truly. It is plotted, managed, watched, just to be certain we keep from getting Type 2 Diabetes. You see I am my own petri dish.

CMS stated to me in their correspondence:

A claim for blood glucose test strips was filed with NHIC, Corp. (NHIC) and an initial determination was performed on January 7, 2011. The clEiim was found unfavorable because similar items were already provided...The reconsideration case file included a Reconsideration Request Form, re-determination Request Form, Medicare remittance, physician's order, delivery ticket, and clinical documentation...

*Our Medical Review Panel, consisting of a **nurse and a physician**, has reviewed the submitted documentation and decided that payment cannot be allowed for blood glucose test strips....*

In addition, there was no progress notes submitted for review current to the date of service. The one submitted establish progress note is after the date of sen/ice in review and cannot be used ... Medicare, the patient's medical record must contain sufficient documentation of the patient's medical condition to substantiate the necessity for the type and quantity of items ordered and for the frequency of use or replacement (if applicable). The information should include the patient's diagnosis and other pertinent information including,

When I turned 65 the Government took over control of my glucose monitoring. I could not buy the tabs anymore, the Government, some physician and nurse, yes some unknown nurse, said my 10 years of daily data were not proof that prevention works. I even sent them my book on Obesity and Type 2 Diabetes! For CMS, it appears, I must gain 50 or more pounds and have HbA1c in excess of 7.0 before they would allow me to buy it myself. Well thank God for Amazon, they sell them and I buy them, and I stay well! And thank you Government, for the ACA, you really created a monster. Happy Second Birthday.

But to the most strange part is the recent NIH News, stating that intervention and prevention works, namely I am doing the right thing.

They NIH state:

Prevention programs that apply interventions tested in the landmark Diabetes Prevention Program (DPP) clinical trial would also improve quality of life for people who would otherwise develop type 2 diabetes. The analysis of costs and outcomes in the DPP and its follow-up study is published in the April 2012 issue of Diabetes Care and online March 22 at http://diabetes.org/diabetescare.

The DPP showed that lifestyle changes (reduced fat and calories in the diet and increased physical activity) leading to modest weight loss reduced the rate of type 2 diabetes in high-risk adults by 58 percent, compared with placebo. Metformin reduced diabetes by 31 percent. These initial results were published in 2002. As researchers monitored participants for seven more years in the DPP Outcomes Study (DPPOS), they continued to see lower rates of diabetes in the lifestyle and metformin groups compared with placebo (www.nih.gov/news/health/oct2009/niddk-29.htm). Lifestyle changes were especially beneficial for people age 60 and older.

The economic analysis of the DPP/DPPOS found that metformin treatment led to a small savings in health care costs over 10 years, compared with placebo. (At present, metformin, an oral drug used to treat type 2 diabetes, is not approved by the Food and Drug Administration for diabetes prevention.) The lifestyle intervention as applied in the study was cost-effective, or justified by the benefits of diabetes prevention and improved health over 10 years, compared with placebo.

So NIH wants prevention but CMS, that is Medicare prohibits prevention, or at least that nurse in Tennessee says so. Remember my fear of some bloated GS 9 denying coverage! Well she is in Tennessee. And she is a contractor!

The stupidity of CMS, the intent should be prevention, not waiting until the disease takes over. I

even wanted to pay out of my own pocket, denied. Back to Amazon! Thank you Dr. Bezos! Perhaps Amazon could open a full service Medical practice as well. The of course DC would send in the thugs and shut it down, perhaps even send in EPA!

Thus with the new ACA, on one hand they deny prevention and on the other hand they praise the need for prevention. In case anyone has noted this happens all the time with big Government. And we are only 2 years into this mess!
Labels: Health Care

RESEARCH PUBLICATIONS: A COMING EVOLUTION OR REVOLUTION

We have been commenting on the many new outlets for publishing technical results as the Internet expands. The old Academic world of peer reviewed articles may in many ways be creating its own demise for a variety of reasons.

Let me remark on a few. First why have peer reviewed journals:

1. Credibility: These journals were created to ensure credible results by having them reviewed by peers. Namely the reader had some semblance of safety that what was presented was correct. However we know that often that is not the case. Fraud is as bad in professional journals as in many other outlets so that safety net is not really effective.

2. Dissemination: Having a professional journal published and available at a library meant that one could access it. Even some almost 50 years ago I did searches, handed in cards and in a week or so got copies of the articles. I rarely ever sat with the journal itself. Today of course it is rare if I even know where they are. I used to keep my old NEJM, but they are all on line and all I get to look at are the ads. Same with JAMA, Science etc. Where possible I use on line access.

3. Citation and Credit: In the academic world your rank is based often on how many times you have been cited. Go to Google Scholar, look at your publications, add up the citations, and that is a measure of your rank. But not so fast. Today almost 90% of the articles say in IEEE publications are many authored, and I mean many, a dozen is not uncommon. So who did the work. Fifty years ago they were single authors so we knew who did the work.

4. Critique: Journals allowed professionals to write comments and have them published thus serving as an ex post facto means of vetting the results. Today we have instant comments on line, albeit in some cases from unknown individuals whose remarks we have not value of.

Thus the reasons for having journals may be fast disappearing. There are a few recent articles in the Scientist regarding this issue. The first looks at open access papers, journals such as PLOS PLOS is an online fee to publish not fee to subscribe journal. No paper, peer reviewed and the author pays to publish, a nominal amount. This in many ways is the road to the future.

Second, the other issue is that Academies are making faculty research available on line. Again the Scientist states:

Academic publishers are currently up in arms about the Federal Research Public Access Act (FRPAA)—a bill that has the perfectly reasonable goal of making publicly funded research available to the public that funded it. Tom Allen, president of the American Association of Publishers, described it rather hysterically as "intellectual eminent domain, but without fair compensation." Why are he and his colleagues so desperate to retain the current business model? By any objective standard, academic publishing is a very strange business indeed. It became established at a time when all publishing was on paper, when duplication and delivery were demanding problems, and when publishers provided an important service to researchers. Now, as the Internet is dramatically changing other forms of publishing, academic journals seem stuck in the 1980s, with results both comical and disastrous.

The extreme costs of journals may force many to seek PLOS type approaches. Moreover providing White Paper works in progress, rather than the full peer review process is also a trend which I have used. If people know you, they can judge, in addition they can understand the work in progress model and at the same time one establishes precedence.

Thus perhaps there will be a transition from the old form journal, through an on line journal and with an real time work in progress approach as well.
Labels: Academy, Commentary

SUNDAY, MARCH 18, 2012

REINVENTING HISTORY

The recent book extolling the old Bell Labs has had a few reviews on Amazon and I was interested to see what folks said. As I had noted in an analysis of the work, namely that Bell Labs was and is a bit over rated, I noted a review on Amazon which stated:

This led to the greenest of recruits learning at the feet of masters like Bardeen or Shannon. Most importantly, you were free to pursue any idea or research project that you wanted, free to ask anyone for advice, free to be led where the evidence pointed. Of course this extraordinary freedom was made possible by the immense profits generated by the monopolistic AT&T, but the heart of the matter is that Bell's founders recognized the importance of focusing on long-term goals rather than short-term profits. They did this by gathering bright minds under one roof and giving them the freedom to pursue their ideas. And as history makes clear, this policy led not only to fundamental discoveries but to practical inventions greatly benefiting humanity. Perhaps some of today's profitable companies like Google can lift a page from AT&T and channel more of their profits into basic, broadly defined, curiosity-driven research.

Gertner's highly readable book leaves us with a key message. As America struggles to stay competitive in science and technology, Bell Labs still provides the best example of what productive industrial research can accomplish. There are many lessons that modern scientific organizations can learn from it. One interesting lesson arising from the cohabitation of research and manufacturing under the same roof is that it might not be healthy beyond a point to isolate one from the other, a caveat that bears directly on current offshoring policies. It is important to have people involved in all aspects of R&D talking to each other. But the greatest message of all

from the story of this remarkable institution is simple and should not be lost in this era of short-term profits, layoffs and declining investment in fundamental research: the best way to generate ideas still is to hire the best minds, put them all in one place and give them the freedom and money to explore, think and innovate. You will be surprised how much long-term benefit you get from that policy. As they say, mighty trees from little acorns grow, and it's imperative to nurture those little seeds.

Let me examine the facts which the reviewer so nimbly ignores:

1. *Google can lift a page from AT&T and channel more of their profits into basic, broadly defined, curiosity-driven research* Now as I have shown many times ATT charged its customers for the Labs, and profits had nothing to do with it. Profit was a return on invested capital plant. The more inefficient and costly the plant the more profit. It would help if the reviewer had some basic knowledge of whence he spoke on this point.

2. *greenest of recruits learning at the feet of masters like Bardeen or Shannon. Most importantly, you were free to pursue any idea or research project that you wanted, free to ask anyone for advice, free to be led where the evidence pointed* Shannon worked almost alone and the hallowed halls of Murray Hill were off limits to almost all. As freedom, most staff had projects and were limited strictly.

3. *Bell Labs still provides the best example of what productive industrial research can accomplish* Bell Labs is an example for no reality that exists. It was an artifact of a monopoly. The productive research leads to products that are economically viable in a competitive domain. That was never a Bell Labs concern. Just look at the black dial telephone.

4. *One interesting lesson arising from the cohabitation of research and manufacturing under the same roof is that it might not be healthy beyond a point to isolate one from the other, a caveat that bears directly on current offshoring policies* Let me consider the Andover wireless plan as an example. The system engineering was done at Holmdel, and some at Whippany but manufacturing was done at Andover. The Bell Labs staff there supported manufacturing.

5. *the best way to generate ideas still is to hire the best minds, put them all in one place and give them the freedom and money to explore, think and innovate* The best way to generate new and innovative products, things people will buy and use, it to get the best people but in an open and competitive market where abject terror from competitors drives results, results which generate cash flow, positive cash flow. It also destroys bad ideas and bad management. The suggestion made by the reviewer is one found in a dream world lacking any foundation in reality.

Frankly as I had discussed based upon my experience the intent was to spend as much as possible because it went into the costs which were paid to the monopoly and in addition to lock up patents to ensure the monopoly. And it was Government sanctioned. There was no Darwinian survival of the fittest as we find in the venture and real world. It was a monopolist political world driven by maintaining control and killing off any potential competition. But I suspect the author of this review has no knowledge of the facts, just some idealistic view of what they think reality should have been.

In contrast, Bob Metcalfe writes in the WSJ an interesting contrast and somewhat balanced. Metcalfe states:

Mr. Gertner, besides celebrating forgotten figures and seminal discoveries, wants us to re-evaluate our contemporary assumption that innovation can only be brought about by "small groups of nimble, profit-seeking entrepreneurs." Think big, the author urges. "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."

Mr. Gertner grew up in the glow of Bell Labs headquarters in Murray Hill, N.J., and certainly romanticizes the place. Like many before him, he exaggerates the numerator of Bell Labs while ignoring the denominator. With almost limitless support from its monopoly benefactor, Bell Labs grew to employ more than 25,000 people. So was Bell Labs cost-effective? You will not find the answer in Mr. Gertner's eulogy.

The author also makes the common mistake of confusing invention with innovation. Mr. Gertner credits Bell Labs with inventing the silicon solar cell in the 1950s. If only they had finished the job. Solar energy remains uneconomic today, more than half a century later—invented but not innovated. Likewise, Bell Labs in the 1960s poured its money and reputation into an early form of videoconferencing, PicturePhone, which flopped when deployed.

Brilliantly stated. They never finished any job I saw them attempt. The solar cell is a great example. They wanted the patents and the rights to keep others out! The idea that one should look at numerator and denominator is critical. There were a few brilliant producers but then again the Bell Labs as the only game in town for those working in telecom sucked up the best talent it could find and in many ways warehoused them so that nothing could be created. It was not until 1982 and the AT&T breakup that the dam broke!

Bob continues:

Mr. Gertner suggests that society would do well to re-create more Bell Labs. But trusting research to corporate monopolies is problematic in two ways. First, their money comes from overcharging customers by using monopoly power. (If you doubt that AT&T was overcharging, ask some old-timers how our mothers urged us to phone home after we arrived safely up at college—"Call, but hang up after letting the phone ring three times"; actually completing the call was too expensive.) Second, a corporate monopoly has little motivation to disrupt a market that it already dominates. AT&T had to be forced, starting in 1968, to let the nascent Internet connect to its telephone network; "Ma Bell" resisted every step of the way.

So true! The Internet screw up, the modem, and the list goes on. Bell Labs was in my opinion based upon my experience a bloated machine designed to suck money from rate payers and to block any and all innovation.

The irony of the Metcalfe review is that when one scans through the comments most of those

opposing Bob do so based on the assumption Bob is an academic. Bob invented the Ethernet and started and grew 3 Com. Bob is the example of good R&D, not Bell Labs. Those who commented without knowing this just exposed in my opinion based upon my direct experience their gross incompetence in understanding the entrepreneurial world.

But even more chilling is the thread that large centralized R&R, such as Government sponsored R&D is the best way to go. In reality it is the worst. Just look at DoD. For years they had all home brewed designs until the industry outpaced them. The typical cell phone of today is better than any DoD design over the years and at one millionth the cost. It is a shame that so few understand the entrepreneur. It is more of a shame that the often run the country!
Labels: Telecom

MORE ON PSA

The recent NEJM article purporting to show that PSA screening saves lives has all sorts of issues, as do almost all of these. I noted some of this in an earlier posting but let me continue:

They state:

The principal screening test was measurement of the serum PSA level with the use of the Tandem-R/Tandem-E/Access assay (Hybritech). A positive test result, defined as a PSA value of 3.0 ng per milliliter or higher, was an indication for biopsy in most centers. Sextant prostatic biopsies were recommended for all men with positive test results; lateralized sextant biopsies4 were adopted in June 1996. Some exceptions to these procedures have been described previously.

That level of 3.0 is better than most, it is lower and has a higher false alarm rate and also higher detection probability on the ROC.

They continue:

The median screening interval was 4.02 years. A total of 6963 prostate cancers were diagnosed in the screening group (cumulative incidence, 9.6%) and 5396 in the control group (cumulative incidence, 6.0%), with approximately 1000 additional cases of prostate cancer in each study group, as compared with our earlier analysis

Here is a problem if one reads this correctly, namely it was too long a screening period.

Again the question to be asked is what PSA level and what screening interval yields the best if any survival. Then one can check the costs.

The issue is really also one of looking at PSA as a progression over time including % Free as well.

Now a Reuters report has some interesting comments:

Dr. Otis Brawley, chief medical officer of the American Cancer Society, said the European study is actually eight studies in eight countries, and only in Sweden and the Netherlands did PSA testing significantly reduce the risk of death from prostate cancer. "Screening saves lives if you live in the Netherlands and Sweden, but not the other six places," he told Reuters Health in a telephone interview. One factor that may have skewed the Swedish data, he said, is that men who were screened were treated at an academic medical center, while men in the control group who developed cancer were treated elsewhere in the community. That alone might account for the lower mortality rate in the PSA population. In all, there were 299 prostate cancer deaths in the screening group compared to 462 in the control group that was not screened. Brawley said PSA testing is being widely promoted because "there's a huge profit in screening and treatment" for prostate cancer, even though most studies have failed to show that screening saves lives.

Strange in my opinion for ACS to advocate against screening, as they seem to be saying above.
Labels: Cancer

TYPE 2 DIABETES OR JUST THE FLU?

In a recent Cell article the senior researcher argues that he has identified that he has a gene for Type 2 Diabetes and after such a discovery he finds that after a year of monitoring he has actually shown signs of Type 2 Diabetes. Then after dieting it goes away. Really?

The details on the subject were:

Monitoring of glucose levels and HbA1c revealed the onset of T2D as diagnosed by the subject's physician (day 369, Figures 2A and 2C). The subject lacked many known factors associated with diabetes (nonsmoker; BMI = 23.9 and 21.7 on day 0 and day 511, respectively) and glucose levels were normal for the first part of the study. However, glucose levels elevated shortly after the RSV infection (after day 301) extending for several months (Figure 2D). High levels of glucose were further confirmed using glycated HbA1c measurements at two time points (days 329, 369) during this period (6.4% and 6.7%, respectively). After a dramatic change in diet, exercise and ingestion of low doses of acetylsalicylic acid a gradual decrease in glucose (to 93 mg/dl at day 602) and HbA1c levels to 4.7% was observed. Insulin resistance was not evident at day 322. The patient was negative for anti-GAD and anti-islet antibodies, and insulin levels correlated well with the fasted and nonfasted states (Figure S2C), consistent with T2D. These results indicate that a genome sequence can be used to estimate disease risk in a healthy individual, and by monitoring traits associated with that disease, disease markers can be detected and the phenotype treated.

Now the patient did not have a high BMI but did have two viral attacks. As is well known obesity effects an immune like inflammatory response, chronically, and a viral attack has an acute response, yet both will effect an increase in blood glucose, often not suppressed by insulin in those with the potential for Type 2 Diabetes.

The problem with this patient is shown in Figure 2D where the blood glucose is measured, in somewhat of a random manner and where HbA1c is also shown. The problem is as follows. HbA1c reflects red cell glucose uptake and red cells last for 90 days and thus to reflect an elevated HbA1c one would expect an elevated level for 90 days, or at least for 45. That is not the

case for this patient on the upside or on the down side. Also the glucose spikes as one would expect to find in acute inflammatory diseases or use of steroids and the like. In addition to do this properly one should be measuring fasting blood sugar and two hour post prandial and accounting for such exogenous factors as travel, stress, and excess carb intake. None of this was done.

The author and patient in question was interviewed and he states:

"I was not aware of any type-2 diabetes in my family and had no significant risk factors," said Snyder, "but we learned through genomic sequencing that I have a genetic predisposition to the condition. Therefore, we measured my blood glucose levels and were able to watch them shoot up after a nasty viral infection during the course of the study."

As a result, he was able to immediately modify his diet and exercise to gradually bring his levels back into the normal range and prevent the ongoing tissue damage that would have occurred had the disease gone undiagnosed.

The question is was this Type 2 Diabetes or the flare seen in those with low insulin control when in an acute inflammatory state. Could one use a steroid to induce this and then watch blood sugar rise equally as well, and perhaps use that as a diagnostic. After all we use a classic glucose tolerance test to measure insulin response.

How does one define Type 2 Diabetes? Is it low insulin response? Or is it HbA1c above say 6.0? Is it the "potential" for the disease or the disease. The problem here in my opinion is that the author and patient in question may have crossed the line by saying if you have a genetic predisposition then you have the disease. A very slippery slope in my opinion.

Labels: Diabetes, Health Care

SATURDAY, MARCH 17, 2012

THE IMPACT OF FULL GENE TESTING ON HEALTH CARE COSTS

In a recent JAMA article the author attempts to show the potential for genetic analysis on a per patient basis as a means to reduce health care costs.

We have argued that advances in genetic tests and analysis can result in advances in three areas:

1. Determining predispositions and the attempt to mitigate the disease states.

2. Determining the specific abnormality or malignancies and assessing treatment protocols accordingly.

3. The establishment of genetically oriented treatment methodologies.

However we are looking at two extreme situations:

First the understanding of basic genetic causes of disease inherited or set as a predisposition state. For example the heritability of Marfan or Huntington's. Also the predisposition for certain cancers.

Second, genetic changes in somatic cells to assess the state of a malignancy, such as breast cancer or prostate cancer.

The problem is twofold:

First we know some but hardly all genetically inheritable traits. In fact we are just starting to understand them. In a sense we are in year 1 of say a Framingham study for these issues and the time to determine what they are is lengthy.

Second, in the case of cancers, we need to understand the dynamics, and as recently shown in an earlier post from a NEJM article, the complexity of cancer genes from cell to cell is not understood.

The JAMA article states:

Several steps are needed to realize any potential beneficial effect of genomics on the cost of health care. First, the development of effective clinical decision support is needed so that patients and clinicians use genomic test results appropriately. Such decision support already is available for several tests and should become a US Food and Drug Administration requirement for the introduction of new targeted therapy with a companion diagnostic test. Second, information systems need to be adapted so that genomic information can be stored efficiently and accessed indefinitely. Given its rapidly declining cost, whole-genome sequencing is likely to become the dominant model for germline genetic testing and can provide substantial efficiency assuming that test results can be stored and reliably accessed in the future. Third, professional and patient advocacy organizations need to develop guidelines about how to manage genomic information unrelated to the clinical question of interest, in order to minimize the evaluation of clinically irrelevant genetic variation and wasted health care dollars. Fourth, genomics can only reduce costs if the aggregate cost of testing is lower than the cost of the health care interventions that are used.

I would argue that there are many steps needed beyond these. First, most physicians lack a true understanding of these issues. For example as I have indicated a urologist may perform a prostate biopsy and find highly disseminate HGPIN and then 9 months later perform a saturation biopsy in anticipation of a malignancy and find none. Why? Surgeons generally do not ask those questions, for them the patient has become a lucky end point. But why? What has genetically reversed what is assumed to be irreversible?

We need to establish large data bases readily accessible by professionals to be worked upon an jointly shared. Leverage of this type is essential. Closed data will result in slow progress, open and shared data is essential.
Labels: Health Care

CHINA AND THE US DEBT

China Daily provides insight into China's current and near term dealings with US Debt.

It states:

China increased its holdings of US Treasury securities by a slight $8 billion to a total of $1.16 trillion in January after cutting the purchase for five consecutive months, according to data released by the US Treasury Department on Friday. But analysts suggested the move doesn't signal a reversal of China's efforts to diversify its foreign exchange holdings and reduce its exposure to dollar assets. China remained the largest foreign creditor of the United States among the overall foreign net buyers of US financial assets in January. But Japan, as the second-largest holder of US Treasuries, is closing in on China after boosting its holdings by $21 billion to $1.08 trillion in January. China had been moving away from US Treasury bonds since July, continuously cutting its holdings by a total of $163 billion by December. By the end of last year, China had reduced its holdings of US debt by $8.2 billion compared with the previous year, the first time it had reduced the amount year-on-year since 2001.

Now China has over $1 T in US debt which is a substantial sum. The slowing down of their purchases reflects two things. First internal stress within China. Second concern over the US debt situation in general.

This will be a careful issue to watch in the next six months as we approach the election.
Labels: China, Economy

HAPPY SAINT PATRICK'S DAY

Come and tell me Sean O'Farrell tell me why you hurry so
Hush me buachaill hush and listen and his cheeks were all a glow
I bear orders from the captain get you ready quick and soon
For the pikes must be together by the rising of the moon

By the rising of the moon, by the rising of the moon
For the pikes must be together by the rising of the moon

Come now tell me Sean O'Farrell where the gath'rin is to be
At the old spot by the river right well known to you and me
One more word for signal token whistle out the marchin' tune
With your pike upon your shoulder by the rising of the moon

By the rising of the moon, by the rising of the moon
With your pike upon your shoulder by the rising of the moon

Out from many a mud wall cabin eyes were watching through the night
Many a manly heart was throbbing for the blessed warning light
Murmurs rang along the valleys like the banshees lonely croon

And a thousand blades were flashing by the rising of the moon

By the rising of the moon, by the rising of the moon
And a thousand blades were flashing by the rising of the moon

There beside that singing river that dark mass of men was seen
For above their shining weapons hung their own beloved green
Death to every foe and traitor! Forward strike the marching tune
And hurrah, me boys, for freedom, 'tis the rising of the moon

'Tis the rising of the moon, 'tis the rising of the moon
And hurrah, me boys, for freedom, 'tis the rising of the moon

Well they fought for poor old Ireland
And for bitter was their fate
Oh what glorious pride and sorrow fills the name of â€™98
Yes thank god instill our beating hearts in manhoods burning loom
Who would follow in their footsteps at the rising of the moon

At the rising of the moon, at the rising of the moon
Who would follow in their footsteps at the rising of the moon
Labels: Commentary

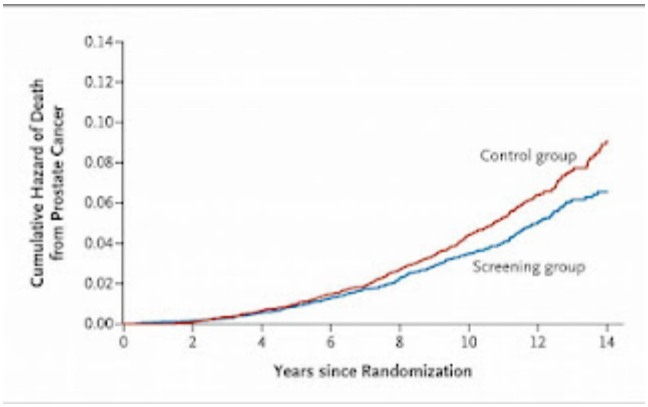
WEDNESDAY, MARCH 14, 2012

PSA DEBATE CONTINUES

We all remember the discussion that the Government declared PSA tests as not effective. It was the same group which wanted to do away with mammograms. Most likely the same group which wants to do away with health care for anyone over 65, the current team in Washington that is.

Well NEJM just reported a different tale.

Here it is:



Namely it does save lives! Eureka, that is what we have been saying for the past four years, and now we have the data in spades.

Here is the test:

The principal screening test was measurement of the serum PSA level with the use of the Tandem-R/Tandem-E/Access assay (Hybritech). A positive test result, defined as a PSA value of 3.0 ng per milliliter or higher, was an indication for biopsy in most centers. Sextant prostatic biopsies were recommended for all men with positive test results; lateralized sextant biopsies were adopted in June 1996. Some exceptions to these procedures have been described previously.

Yes a PSA cutoff of 3.0, not 4.0, and sextant biopsies. Today we would use 14 cores at a minimum, and saturation in many cases, say 24 cores, although it increases morbidity to a degree.

The end point was:

The primary end point of the trial was prostate-cancer mortality. We evaluated deaths among men in both the screening group and the control group in whom prostate cancer was diagnosed (including cases that were first diagnosed at autopsy), regardless of the official cause of death, as described previously. Data on overall mortality were collected by linkage to the national registries. Each trial center followed the common core protocol and provided key data to the joint independent data center every 6 months. The independent data monitoring committee received updates every 6 months according to a predefined monitoring and evaluation plan.

They conclude:

The controversy regarding screening for prostate cancer has been renewed by the publication of the draft report of the U.S. Preventive Services Task Force, which after a literature-based analysis of benefits and harms recommended against the use of PSA testing in asymptomatic men. The report has been discussed in several Perspective articles in the Journal. ***Clearly, the issue can be resolved only on the basis of evidence that considers both the advantages and disadvantages of screening, data that are not available at this time.*** *Our study* ***shows that the absolute effect of screening on the risk of death from prostate cancer increased in the intention-to-screen analysis from 0.71 to 1.07 deaths per 1000 men at a median of 11 years of follow-up, as compared with the initial results with a shorter follow-up period.***

Clearly there is a benefit but clearly as I have previously stated they did not ask the correct question, which is:

"What should the PSA level be by age, race etc so as to have a decrease in survivability by some factor x?"

Notwithstanding, there is a clear benefit. The details of the benefit are yet to be determined but

the conclusion is that the USPSTF conclusion is in error. The "Death Panel"'s conclusion is just that. And we have just begun!
Labels: Cancer, Health Care

TUESDAY, MARCH 13, 2012

CHINA TO RAISE PRICES ON RARE EARTHS

The rare earths are major ingredients in our high tech society and China is the worlds major supplier, mainly because the US decided to shut down its production for environmental reasons. Now China is going to charge for their environmental costs as reported in China Daily:

The era of cheap rare earth supplies from China is doomed to end as the country tightens control over the precious resources out of environmental concerns, Chinese lawmakers said on the sidelines of the parliamentary session. China has been supplying enormous quantities of rare earth products to the world. However, environmental costs were not included in the pricing of the commodities, said Liao Jinqiu, an economist at Jiangxi University of Finance and Economics. "The exploitation of rare earths should be further integrated, and a rare earth industry chain must be forged so as to ease the environmental pressure created by excessive extraction," said Liao, also a deputy to the National People's Congress. China is believed to have abundant reserves of rare earth metals, a group of 17 elements that are vital for manufacturing an array of high-tech products, including cell phones, wind turbines, electric car batteries and missiles. China now produces more than 90 percent of the world's rare earth products, but its reserves only account for about one-third of the world's total.

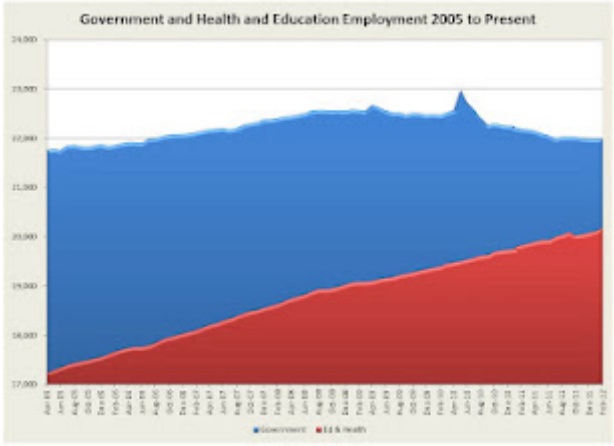
China is being both prudent and controlling in this action. However the use of rare earths is increasing in our high tech society and total costs should be reflected but at the same time this may open the window for the US to reconsider the fact that we have an equal amount of rare earth reserves as does China.

In many ways the rare earth issue is a microcosm of the oil issue, we have both, but we refuse to prudently use them and place the burden on others, yet at an ever increasing cost.

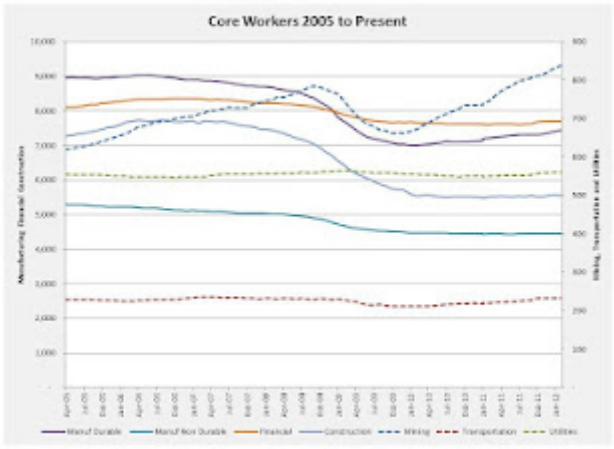
Labels: China, Economy

MONDAY, MARCH 12, 2012

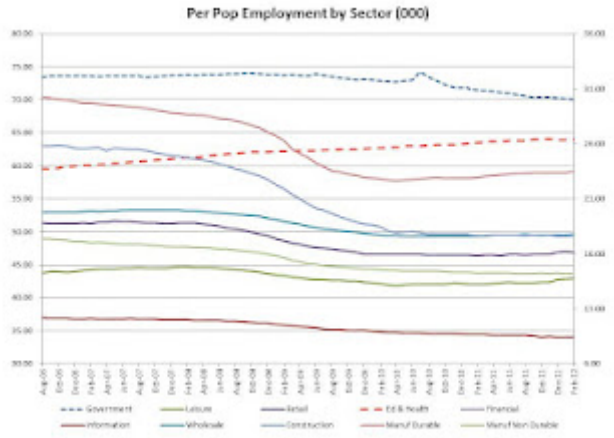
MORE DETAILS ON EMPLOYMENT



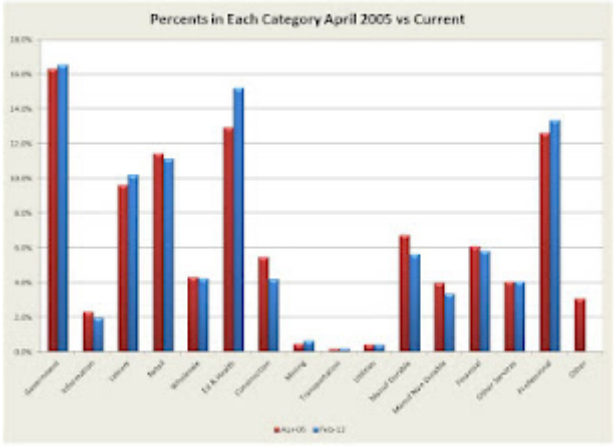
Let's start with the two publicly supported elements; Government and Health and Education. State and Local Govt have declined, with the blip back in 2010 due to the Census and H&E continues to explode. This frankly is a bad omen, these are not "productive" elements in the sense that they are paid from true productive elements.



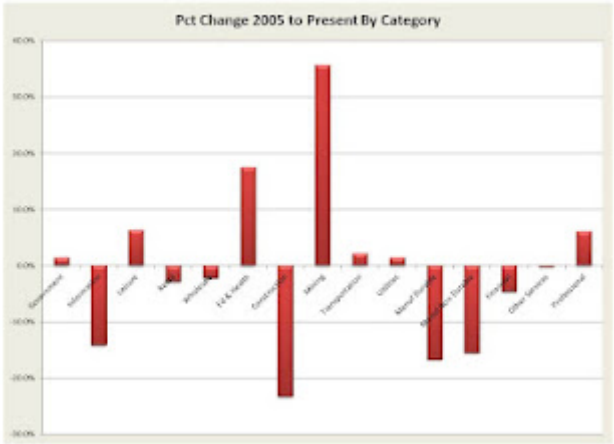
The above are the actual productive worker force and we see a true depression across the boar with recovery in mining and Durable Manufacturing.



On a per Pop basis we show the above which demonstrates the reduction. Namely we normalize all jobs by the total population and this shows growth only in H&E. That is an upsetting trend.



We show the percents by category from April 2005 to the present by sector. Government, H&E and professional show increase. All others declined.



The above demonstrates the actual percent changes. Mining is a small sector so we can disregard it. In summary things are really getting worse.
Labels: Economy

SATURDAY, MARCH 10, 2012

MIT AND NUMBERS

In a recent post by the MIT News group the author quotes a speaker at an MIT conference as follows:

"There is a huge disenfranchisement going on, due to our voting laws," .... said. "And I think to fight that we have to build a conversation with Latino leaders, because we're both being disenfranchised." .... students, he noted, have found in studies that in Los Angeles, Miami and New York, "at least 30 percent of the taxpaying adult voting-age population can't vote because of immigrant status. If you add in ex-felons who can't vote … you're at nearly 50 percent of the [urban] population."

Now if I do a back of the envelope calculation what is being said is as follows:

1. Take New York City...

2. The 30% of the voting age population is an illegal alien

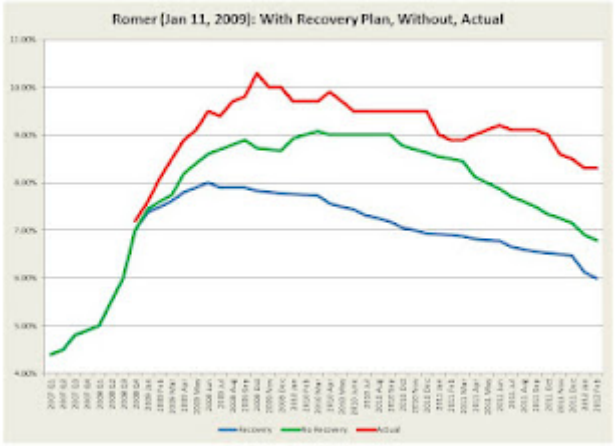
3. 20% of the voting population is a convicted felon.

Yikes, that means that every other person is either a convicted felon or illegal! I have lived here for 70 years, yes I know of a few convicted felons, a few, and I grew up on Staten Island, home to the Genovese family, nice folks but some convicted felons amongst them, and my father and grandfather were police officers, but 20%, that means in an 8 million population we have with us 1.6 million felons! It just does not add up. We just do not have that many prisons. As for illegals, that would be 2.4 million, and there I have another problem. 200,000, maybe 500,000 but not 2.4 million! Where do these numbers come from? And this is MIT, and an MIT Press Release. Would someone at MIT check the facts?

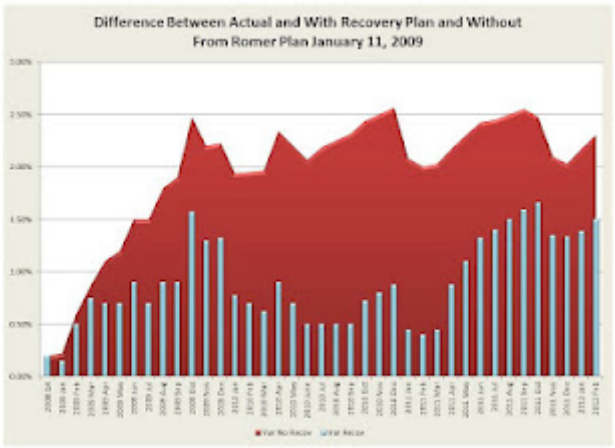
Labels: Commentary

FRIDAY, MARCH 9, 2012

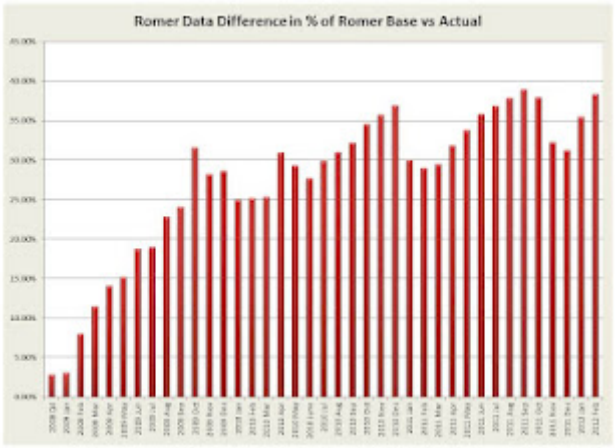
EMPLOYMENT: GOOD NEWS AND BAD



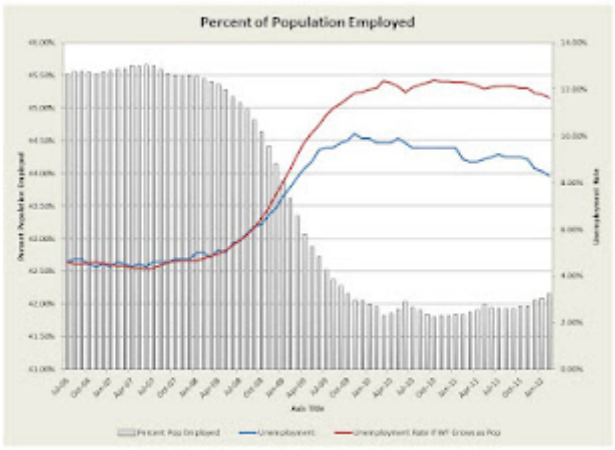
The ghost of Romer still haunts the halls of power. The above is the current unemployment, 8.3%, as announced, and her predictions from January 11, 2009. As we have argued for more than three years now our friendly economist seems as if she could not hit the side of a barn with her predictions. But back to California.



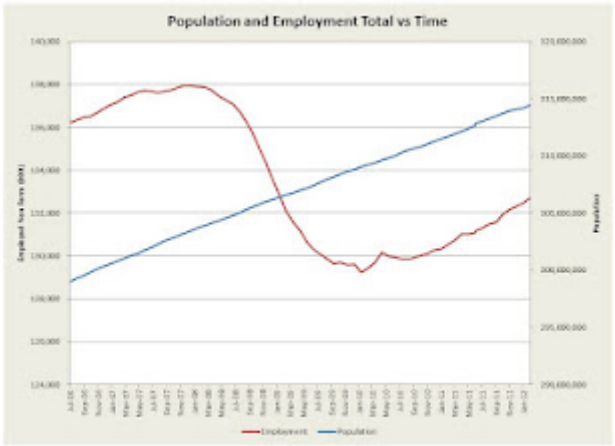
The above shows the level of variance which is clearly growing.



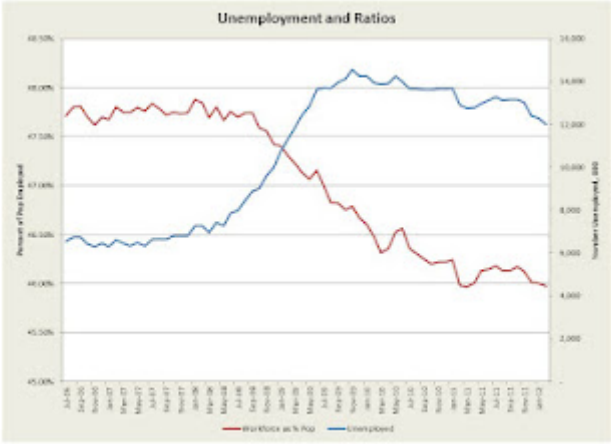
This details the growing variance in some detail. Now to the overall stats. We use the SA non-farm stats.



The good news seems to be an increase in percent employed albeit at best a small amount and at worst an anomaly. Secondly the unemployment using the 2006 base has dropped below 12% for the first time. This should be the true measure.



Employment and population seem now to be in lock step. This curve above shows the loss of the 2008 recession but it also shows no recovery.



Unemployed seems to be decreasing bu the concern is still the workforce as a percent of population, a slight dip again.
Labels: Economy

WEDNESDAY, MARCH 7, 2012

THE CHALLENGE OF CANCER GENETICS

In the current NEJM there is an interesting article on the heterogeneous nature of cancer cells. Namely in examining renal carcinoma the authors clearly demonstrate the genetic complexity of cancer cells, namely that the cells express a wide variation in genetic changes, the focus being on mTOR.

The authors state:

Multiregion genetic analysis of four consecutive tumors provided evidence of intratumor heterogeneity in every tumor, with spatially separated heterogeneous geneous somatic mutations and chromosomal imbalances leading to phenotypic intratumor diversity (activating mutation in MTOR) and uniformity (loss-of-function mutation in SETD2 and PTEN). Of all somatic mutations found on multiregion sequencing, 63 to 69% were heterogeneous and thus not detectable in every sequenced region. Heterogeneous patterns of allelic imbalance were found in all tumors, and ploidy heterogeneity was found in two tumors. Therefore, we found that a single tumor-biopsy specimen reveals a minority of genetic aberrations (including mutations, allelic imbalance, and ploidy) that are present in an entire tumor.

This is a very powerful conclusion. Namely just sampling a single cell is inadequate. Moreover it will become essential to have a dynamic system model which can project the nature of the changes, namely what comes first and then what causes the progression.

The optimism of finding genetic markers which can be used for treatment are made more

complex by this somewhat obvious finding. It is obvious from the models of cancer as a complex system, but not obvious from what was known before. That challenge will be to establish models for explaining these changes. The challenge will also be to explain what role the cancer stem cell plays here as well.
Labels: Cancer

MONDAY, MARCH 5, 2012

A VERY INTERESTING EXPERIMENT

In the late 1960s I taught 6.02 at MIT which was the core electronics course for incoming EE students. I had some 350 students and many sections which were handled by Instructors, some were even Associate Profs. So we had a high power group. Now each lecture was planned to the micro second, better than any Shakespeare play.

Now MIT is offering 6.002x, an on line version of this course almost 50 years later! So I enrolled. What the heck, can I still do this stuff, it is a bit of an FCC exam as well. But what is more interesting is the questions from the students! I am amazed, the flow of misunderstanding from across the world! Since it is free I would suggest that one enroll if for no other reason than reading the real time commentary.

Now for me some comments:

1. The lectures are a bit shaky, not fully structured as we did those 50 years ago, but I guess things change.

2. The lab is cumbersome at best. It finally works but not ready for prime time.

3. The problem sets are trivial, but unless you really pay attention you get killed in sloppy addition and subtraction. Here 50 years does make a difference, we are so dependent upon spread sheets.

4. The text is in my view overly verbose and lacks motivation, but that is style.

It will be interesting to follow along. Great idea any way!

SUNDAY, FEBRUARY 26, 2012

BELL LABS: ANOTHER VIEW

The NY Times had a piece praising the way Bell Labs innovated. I beg to differ. First I was at Bell Labs from 1964 thru 1972, at various times and at multiple locations. I was there from undergrad days until just after my PhD from MIT. From 1986 through 1989 I was also Head of R&D for what was then NYNEX and is now Verizon. Thus I speak from firsthand experience, more than anything the author of the piece can do.

The author states:

Why study Bell Labs? It offers a number of lessons about how our country's technology companies — and our country's longstanding innovative edge — actually came about. Yet Bell Labs also presents a more encompassing and ambitious approach to innovation than what prevails today. Its staff worked on the incremental improvements necessary for a complex national communications network while simultaneously thinking far ahead, toward the most revolutionary inventions imaginable.

I could not disagree more. In my opinion based upon a decade of direct presence and exposure I contend that Bell Labs is the antithesis of how research and technology development in a corporate world should be done! In fact if one follows that model one will fall into a world which we no longer live in. It is a world devoid of creative destruction, a world devoid of any truly competitive innovation, a world where we would have a very small fraction of what we have today.

The author also states:

He personally helped design a building in Murray Hill, N.J., opened in 1941, where everyone would interact with one another. Some of the hallways in the building were designed to be so long that to look down their length was to see the end disappear at a vanishing point. Traveling the hall's length without encountering a number of acquaintances, problems, diversions and ideas was almost impossible. A physicist on his way to lunch in the cafeteria was like a magnet rolling past iron filings.

Now I spent time at Murray Hill, Whippany, Holmdel, and Indian Hill, I also was at the West Street office on my first days. In reality it was all too often a 9-5 location with Chess Clubs, model airplane clubs, amateur radio clubs, bridge clubs, which occupied many hours in excess of lunch. In my ten years of exposure I failed to see much of what the author contends. My conclusion is a generality, but one based upon a broad exposure.

Now to the facts. Bell Labs was set up to support Western Electric, the manufacturing arm of AT&T. Western was the sole supplier to the Bell Operating companies, BOCs. ATT was a Government sponsored monopoly exempt under the law from antitrust restraints along with baseball. Bell Labs was thus a way to develop technology for the operating companies and also to create patent rights to prevent any other entrant into the business. It was a Government sanctioned monopoly which effectively insured telecommunications related technology development was suppressed everywhere except in Bell. Somehow the author seems to miss that point.

Now a second fact, the BOCs and ATT had a different profit making rule. Unlike the normal market where the price is set in an open free market place by supply and demand, and profit was revenue less expenses, the Bell equation was materially different. They, namely the BOCs and ATT, set rates, actually the Government claimed to do so but in reality, in my opinion, ATT told

the Government what to do, and there were times of some disagreement, but eventually in my opinion ATT got what they wanted.

The rates and economics of the business from my perspective generally worked as follows:

1. Revenue was set based upon rates.
2. Revenue equaled costs, operating and depreciation, plus a return on the capital plant investment.
3. Profit then was the rate of return on capital, usually somewhere between 12-18%.
4. Costs had nothing to do with profit, and profit was maximized by designing the least efficient means of production, namely the more capital per customer the more profit.
5. There was no incentive to reduce costs or improve technology.
6. It was a monopoly.

Thus Bell Labs was motivated to get as big as possible and to be as inefficient as possible. However the PR issues were at the fore, so to keep the Government at arms-length they publicized what they did in research and did a great deal of Government development work. For example they did work on undersea sub detection and the Nike anti-missile program.

The author of the article praises all of the Labs development. Let me make a few corrections:

1. Internet: According to Bob Kahn, as I recall having discussed with him, when he was head of IPTO at ARPA he went to Bell Labs to seek their help to deploy packet switching by utilizing some of their modem designs and networks. Bell Labs management, there were a great number at the meeting, which was all too common, informed him that they would take an exclusive contract from ARPA and design and build what Bell thought was right and that Kahn could watch the results. Fortunately Kahn rejected the exclusive deal and in his brilliant way created the core group who “invented” the Internet, despite Bell Labs! I was fortunate enough to play a small part in that effort when I was at Comsat, getting the first satellite connections operating.

2. Satellites: John Pierce boldly published a design for dozens of satellites as necessary to perform as a communications net of limited capacity. He stated that it was technically impossible to have a synchronous satellite. Believing Pierce Comsat was funded assuming dozens of satellites and launches. Hughes soon thereafter launched the first synchronous orbit satellite and only 3 were need for all the world! Pierce was proven wrong as was Bell Labs. Perhaps the Pierce design was consistent with the massive capex overspending as was pandemic at Bell. Harold Rosen at Hughes was the driving force of this new world and he rather than Pierce should have the recognition. Again the author seems to have missed this point. Bell launched Telstar, and then just withdrew as competition arose.

3. Digital Switches: Bell Labs refused to move to digital switches, they had developed the No 1 ESS, a project I had worked on, and wanted to allow a "normal progression" as I recall. They thus stalled. The Chairman of ATT at the time, as I was told, was frustrated and he went to Bell Northern Research, the Bell Canada arm, which AT&T at the time owned, and asked them to

build a digital switch. That switch became the basis for Northern Telecom, one of the most advanced switches for a few decades.

4. Modems: In the early 1980s, with the advent of PCs, companies such as Telenet and Tymnet grew and modems were need. Bell refused to do this because it would reduce costs. Instead a small company called Hayes built one of the first digital modems to work on these separate networks. It allowed what became the Internet to grow.

5. IP Networks: The IP based networks came from small companies such as Cisco, and wireless came first from Motorola and then new entrants such as Qualcomm. Telecom as we know it today grew despite of Bell Labs not due to it.

The author, in my opinion, is totally blind to where true progress was made, it was made with the entrepreneur, not the massive corporate research center. I would argue that Bell Labs was a major drag on inventive elements in telecom. It was Codex and modems, Cisco and routers, and many other entrepreneurial companies which lead the way. Entrepreneurial companies work in a Darwinian fashion, success is rewarded and failure falls away. Bell Labs, for many generations, in my opinion, and based upon my experience, actually thwarted development. Perhaps that story may someday be told, not the one sided tale contrived, in my opinion, from some PR machine.

Labels: Commentary, Telecom

THURSDAY, FEBRUARY 23, 2012

OBVIOUS OR NOT

In Science in 1991 Vogelstein et al published one of their many results on colon cancer and its related genes and a Science writer presented the above picture in a summary article. The above paradigm has become common place amongst a wide class of cancers. Namely we see a set of well defined genetic changes that lead to intermediate steps in a cell and eventually to a cancer.

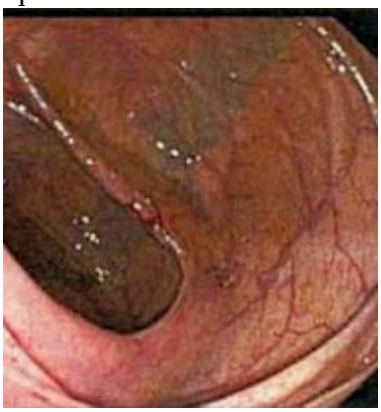
In this weeks NEJM the authors have concluded that colonoscopies with the removal of adenomas actually improves survival.

The authors state:

We previously found that polypectomy reduced the incidence of colorectal cancer in the NPS cohort.The present study suggests that adenoma removal significantly reduced the risk of death from colorectal cancer, as compared with that in the general population, and in the first 10 years after polypectomy, reduced the risk to a level similar to that in an internal concurrent control group of patients with no adenomas.

Our comparison of observed deaths in the adenoma cohort with expected deaths in the general population, based on SEER data that were specific for age, sex, race, and calendar year, may have underestimated the reduction in mortality that may be achieved with colonoscopic polypectomy in screening populations. Because all the patients in the adenoma cohort had adenomas, including 57.3% with advanced adenomas, they represented a higher-risk group than the general population

Now this is no surprise, namely that survival is better. However what is a surprise is that there should be any deaths at all for those being closely watched with polyp removal. Namely if colon cancer, adenoma type, are following the Vogelstein paradigm, then careful colonoscopies would in almost all cases catch and remove a polyp before going to a final stage, especially one of metastatic potential. Thus one should have assumed that zero mortality was expected and anything but would and should be questioned.



The authors state:

This prospective study has some limitations. First, a small number of trained endoscopists performed the colonoscopies according to a study protocol that required examination to the cecum, adequate preparation, careful inspection of the colon, and removal of all identified polyps, features that are consistent with reports of high-quality performance. Consequently, the NPS observations may not be generalizable to present community practice, for which reported incidence rates of colorectal cancer after polypectomy are higher than those reported in the NPS

Indeed there are concerns, for why were there any mortalities if the colonoscopies were done as we would expect.

You see, if we believe Vogelstein, and after 21 years the belief is fact, that when we remove an adenoma we are removing the pre-malignant cells, that is those cells which will eventually become the cancer stem cell, and their progeny, then we remove any future malignancy from that source. Thus what then is the source for the cancer which consumes the patient.

Perhaps looking at the data may provide some evidence but then again perhaps not. The paper qua report does not offer that detail. Thus one wonders if the Vogelstein model is in error or that there may be some secondary but highly significant issues in the patient pool.

One should have concluded total removal of any colon cancer, not a 50% reduction in death from that cause. This should in my opinion be the conclusion of this report, instead the press seems to

laud the reduction in death rate by 50%, not the fact that it really should be 100%! Was the adenoma the cause, where else did the cell come from, had it metastasized already, where was the resulting stem cell hiding, is the Vogelstein model wrong, does this effect happen elsewhere, such as in melanoma in situ? What of the presence and then absence of HGPIN, was that a removal of a CSC?

This result raises many questions from the aspect of a systems model for cancer. Unfortunately few seem to be considering them. Hopefully it will instigate a few.
Labels: Cancer

TUESDAY, FEBRUARY 21, 2012

OBESITY

The OECD issued a report on obesity and their projections are as we had predicted, the US is just plain fat!

They state:

Governments can help people change their lifestyle by making new healthy options available or by making existing ones more accessible and affordable. Alternatively, they can use persuasion, education and information to make healthy options more attractive. This gentle approach is more expensive, hard to deliver and hard to monitor. A tougher approach, through regulation and fiscal measures, is more
transparent but it hits all consumers indiscriminately, so can have high political and welfare costs. It may also be difficult to organise and enforce and have regressive effects.

There is motivation and there is punishment. There also is the Department of Agriculture which is the dominant culprit in the US, just look at school meals, that is one of the problems. In the old days, you brought lunch or better went home for lunch. Now there is no home to go to and the law demands you consume the junk the DoA serves up. Recall that the DoA budget is doubled under the current Administration's Budget proposal, instead it should be eliminated!

They continue:

Denmark introduced a tax on foods containing more than 2.3% saturated fats (meat, cheese, butter,
edible oils, margarine, spreads, snacks, etc.) in 2011. Consumers pay 16 kroner (EUR 2.15) per kilogram of saturated fat on domestic and imported food, which is equivalent to up to 30% more for a pack of butter, 8% more for a bag of chips, and 7% more for a litre of olive oil. Tax revenues are expected to be over EUR 200 million per year, and saturated fat consumption is expected to decrease by 4%. Denmark had also increased its excise taxes on chocolate, ice cream, sugary drinks and confectionery by 25% in 2010. Also in 2011, Hungary introduced a tax on selected manufactured foods with high sugar, salt or caffeine content. Carbonated sugary drinks are among the products targeted by the new measures. The tax does not concern basic food stuffs and only affects products that have healthier alternatives. The Hungarian government

is reportedly expecting to raise in excess of EUR 70 million per year from the tax. 2011 was also the year that Finland introduced a tax on confectionery products, while biscuits, buns and pastries remained exempt. The tax, originally intended to be set at almost one euro per kilogram of product, was subsequently dropped to EUR 0.75 per kilogram. At the same time, the existing excise tax on soft drinks was raised from 4.5 cents to 7.5 cents per litre.

These are actions which have merit. But as I have noted it is the very Government which decries this that at the same time not only supports it but denies options, just look at the recent case of the child who brought lunch from home having to eat fried chicken nuggets! The problem is not obesity it is the Government.
Labels: Health Care

MONDAY, FEBRUARY 20, 2012

PCA3 AND PROSTATE CANCER

The FDA has recently approved a PCA3 test assay which is owned by a Canadian company, Gen-Probe. This opens up a whole new avenue for examining PCa amongst men. I examine some of the issue here at a fairly high level.

There has been a great deal of discussion regarding PSA and its lack of sufficient specificity and sensitivity to PCa and there is some evidence that PCA3 will improve the situation. This is yet to be determined in extensive clinical trials. One of the problems with PSA is that it is reflective of total prostate volume and it also naturally increases with age. Thus a male of say 70 years of age and with a 70 cc prostate may easily have a PSA of 2.5 just based upon the size and age factors.

Likewise if the male were 40 and had a 35 cc prostate then this may be indicative of PCa. In a recent paper by McGarty, we detailed the issue of PSA sampling and the percent change, ie velocity, as a means to assess the nature of the underlying cause. Namely the more prostate basal cells and luminal cells the higher the PSA. As we shall see there is better correlation with PCA3 but the underlying molecular and cellular dynamics do not appear as well defined at this time, namely we have a marker with no clear underlying genomics cause.

The PCA3 measurement is define as follows:

PCA3 Score = 1000 [mRNA PCA3]/[mRNA PSA]

where [mRNA PCA3] is the concentration of mRNA of PCA3 and the same for the denominator. The range is such that a PCA3 score of less than 5 gives a very low likelihood of PCa and >35 gives a very high probability. The issue here often is repeat biopsy. The suggestion then is that one use PCA3 as a test for repeat biopsy indication (see Gen-Probe PCA3 documentation). Details on ROC for PCA3 are not broadly available and repeatable at this time.

PCA3 was first discussed in 1999 in a paper by Bussemakers et al, at which time it was called DD3. In their abstract the authors stated at the time:

The DD3 gene was mapped to chromosome 9q21–22, and no homology of DD3 to any gene present in the computer databases was found. Our data indicate that DD3 is one of the most prostate cancer-specific genes yet described, and this makes DD3 a promising marker for the early diagnosis of prostate cancer and provides a powerful tool for the development of new treatment strategies for prostate cancer patients.

It further turns out that PCA3 is a noncoding mRNA and thus there is no protein resultant. This was speculated by Bussemakers et al when they published their work in 1999. The key question seems to be why does PCA3 increase when there is a PCa and what is the details of the mechanism. Furthermore where does PCA3 fit within the context of the many pathways we know exist in PCa development.

As Cao an Yao report:

The DD3PCA3 encoding gene is located on chromosome 9 (9q2122). The gene includes four exons and three introns. In PCa, the most frequent mutation is the selective splicing of the second exon. At present, there is a vast body of ongoing studies on PCA3. Hopefully they can further confirm the role of PCA3 in the occurrence and the development of PCa and provide new treatment targets for patients with PCa. Hessels suggested that using quantitative reverse transcriptase polymerase chain reaction (RTPCR) for the detection of urine DD3PCA3 was a valuable molecular detection method in patients with PCa and could help reduce unnecessary biopsies.

In a multicenter study designed to examine the diagnostic capacity of urine PCA3 detection, the AUC of urine PCA3 detection was 0.66, while the AUC of serum PCA3 detection was merely 0.57. The sensitivity and specificity of PCA3 detection were 65% and 66% , respectively . Recently, researchers have suggested that serum PSA level plus PCA3 detection was the most promising diagnostic method for PCa . All these studies show that PCA3 is probably an important urine marker for PCa. It also provides a new clue for developing noninvasive detection methods for PCa. Hence, PCA3 may have considerable significance in multiple tumor marker screening of patients for PCa in the future.

Thus one of the questions is what is PCA3 and why does it reflect PCa presence. We know that we are measuring mRNA concentrations, and we know that in measuring them we have experimental evidence that PSA reflects total cell concentration. But what of PCA3, what does that reflect.

In a recent paper by Clarke et al the authors attempt to clarify what the role of PCA3 is.

In order to understand further the importance of the PCA3 gene in PCa we undertook a more detailed investigation of this gene and its chromosomal locus. This investigation points to a considerably more complex transcriptional unit for PCA3 than originally reported including additional novel exons. We describe a number of novel PCA3 splice variants with more specific expression in PCa tissues and metastases. We also demonstrate that PCA3 is embedded in the intron of a second gene, BMCC1, a gene implicated in controlling oncogenic transformation and that both genes showed increased expression in PCa and metastases. The absence of a TATA box

element within a human gene promoter has been associated with promiscuous transcriptional initiation. The PCA3 gene does not contain an upstream TATA sequence and it was therefore of interest to determine whether any additional transcription initiation sites existed for PCA3

Perhaps this relationship to BMCC1 may lead to some insight. They continue:

BMCC1 is upregulated in PCa and androgen inducible Since PCA3 is upregulated in PCa and since we showed here that this gene is embedded in a second gene BMCC1, implicated in cellular proliferation, we determined whether BMCC1 was also differentially regulated in PCa. We used a set of RT-PCR primers that span that region of the BMCC1 gene (exons 6 and 7), specific for the full-length BMCC1-1 transcript. Expression of BMCC1-1 was evident in normal prostate and BPH specimens and was upregulated in PCa and metastases. This was confirmed using primers corresponding to the BCH C-terminal region of BMCC1 and for BMCC1-2.

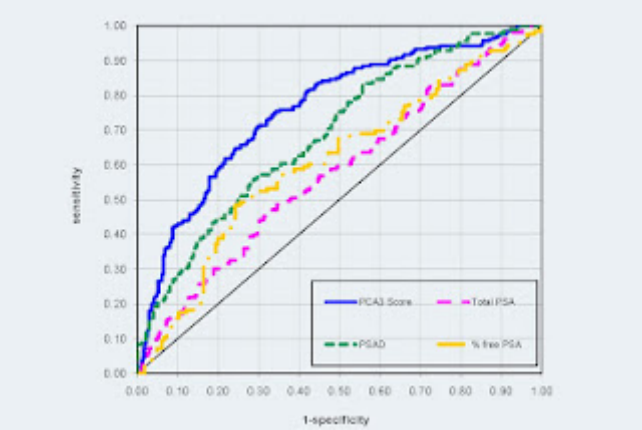
Indeed amplification of this isoform gave better discrimination between PCa and BPH. Extending these experiments to PCa and other cell lines revealed that both genes were highly expressed, specifically in the PCa cell line LNCaP. In addition BMCC1-1 was detected in a second PCa cell line DU145 but at lower levels. PCA3 is also expressed in DU145 but required further rounds of amplification for detection. The shorter BMCC1 isoforms (BMCC1-3 and/or BMCC1-4) were also detected (using primers specific for the BCH region) in an EBV-transformed lymphoblastoid cell line (JHP), but the longer BMCC1-1 isoform was not detected. Previous data have shown that the level of PCA3 can be induced in LNCaP cells after treatment with dihydrotestosterone, which mimics the effects of binding of the androgen receptor (DHT). We determined whether BMCC1- 1 was also responsive to hormonal induction. The results …. demonstrate that both PCA3 and BMCC1 are maximally induced in the LNCaP cell line at a concentration of 0.5 mM DHT.

Thus there seems to be some means of related induction but again no definitive relationship to well defined pathways.

The following is the PCA3 and PSA ROC for comparison. Note the following (see de la Taille):

The area under the curve of the receiver operating characteristics (AUC ROC) of the PCA3 Score was compared with that of serum total PSA, PSAD and % free PSA. The diagnostic accuracy of the PCA3 Score was statistically significantly better than that of serum total PSA, PSAD and % free PSA. The greatest diagnostic accuracy of the PCA3 Score was obtained at a cut-off of 35: specificity 76% and sensitivity 64% . At a sensitivity of 80%, the PCA3 Score specificity of 58% was higher than the 44% for PSAD and 27% for serum total PSA and % free PSA.

The following from de la Taille is the comparative ROC. It appears that from the limited data available that the ROC curve is substantially better with PCA3 than PSA alone.



The key questions remaining in my mind are:

1. What pathway elements does PCA3 reflect. What genetically is happening and what is the underlying system model. This is always an issue. As with primary medicine we have underlying physiology, here we must have some underlying genomics.

2. What are the cellular mechanism which control PCA3. Again this is a pathways issue.

3. How sustainable is PCA3 ROC for this assay. Many tests have been done and FDA approval is merely acceptance of some limited tests.

4. How does one relate PSA and PCA3. Note that the PCA3 measure does reflect PSA concentration, so we have not abandoned PSA.

5. Why do we normalize PCA3 on PSA? If PSA has such a variability are we normalizing on something which is inherently unpredictable?

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Labels: Cancer

SUNDAY, FEBRUARY 19, 2012

OIL, IRAN AND THE ECONOMY

Iran has terminated oil sales to England and France. This is of course all over the European Press and the Guardian states:

Iran announced on Sunday that it had stopped selling crude oil to British and French companies, in a move that may put further pressure on the price of oil amid heightening political tensions. The price of Brent crude – the benchmark for oil – had been rising last week because of tensions with Tehran, which had warned it might cut oil supplies to the Netherlands, Greece, France, Portugal, Spain and Italy in retaliation for Europe's latest sanctions. On Sunday, a spokesman was quoted on the Iranian oil ministry's website as saying: "Exporting crude to British and French companies has been stopped … we will sell our oil to new customers. We have our own customers … The replacements for these companies have been considered by Iran."

And Les Echos states:

L'Iran a cessé de vendre du pétrole aux compagnies pétrolières françaises et britanniques, a déclaré dimanche le porte-parole du ministère iranien du Pétrole, Alireza Nikzad, cité par le site officiel du ministère.« Les ventes de pétrole aux compagnies britanniques et françaises ont cessé », a déclaré M. Nikzad.Mercredi dernier, un autre responsable iranien avait déjà annoncé la suspension des exportations de pétrole vers plusieurs pays européens. Cette annonce avait alors été démentie dans la journée.Cette suspension des exportations intervient avec quatre mois d'avance sur l'embargo mis en oeuvre par l'Europe. Les Vingt-sept ont décidé de ne plus importer de brut iranien à compter du 1er juillet afin de sanctionner Téhéran au sujet de son programme nucléaire.

Le Monde states:

L'Iran a cessé de vendre du pétrole aux compagnies pétrolières françaises et britanniques, a déclaré dimanche 19 février le porte-parole du ministère iranien du pétrole, Alireza Nikzad, cité par le site officiel du ministère. "A la suite de la décision officiellement annoncée par le ministère des affaires étrangères, le ministère du pétrole a cessé ses ventes de pétrole aux compagnies britanniques et françaises", a précisé M. Nikzad. "Nous avons prévu de livrer notre pétrole à d'autres clients", a-t-il ajouté. Cette décision ne devrait pas impacter dans une grande mesure les importations françaises de brut, qui se sont élevées en 2011 à 58 000 barils/jour de brut iranien, soit 3 % de ses besoins d'or noir. "La décision iranienne n'a pas de conséquences pratiques directes", a expliqué Jean-Louis Schilansky, président de l'Union française des industries pétrolières (Ufip). Dans les faits, souligne-t-il, "la France a pratiquement cessé d'importer du pétrole iranien" depuis 2011 et ces livraisons "représentaient une très faible part

de l'approvisionnement" hexagonal, de l'ordre de 3 à 4 %. Le Royaume-Uni est lui aussi dans la même situation.

Even China Daily has covered this as follows:

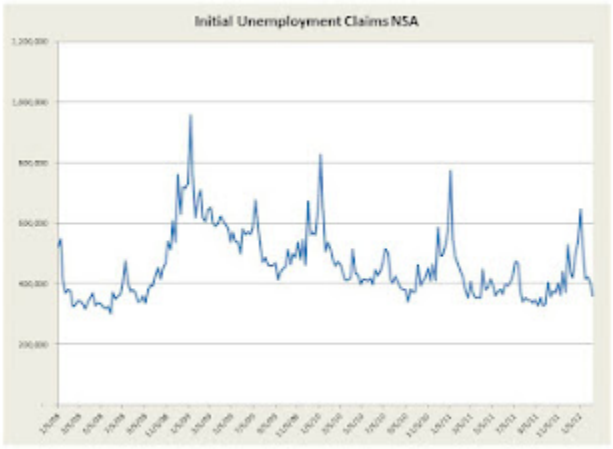
Oil ministry spokesman Alireza Nikzad-Rahbar said as the oil minister had earlier announced about the probability of halting oil exports to some European Union (EU) countries, "the Oil Ministry has stopped oil sales to British and French companies." The Islamic Republic has no problem in selling its crude oil to its customers, Nikzad-Rahbar said. "We have our own oil customers and the replacements for these (British and French) companies have already been considered and we will sell the crude oil to new customers instead of the British and French companies." The spokesman's remarks, which did not specify the time of the sales' cut to the British and French companies, were posted on the website of Energy and Oil Information Network affiliated to the Iranian Oil Ministry.

The irony is that the NY Times has yet to reference the event.

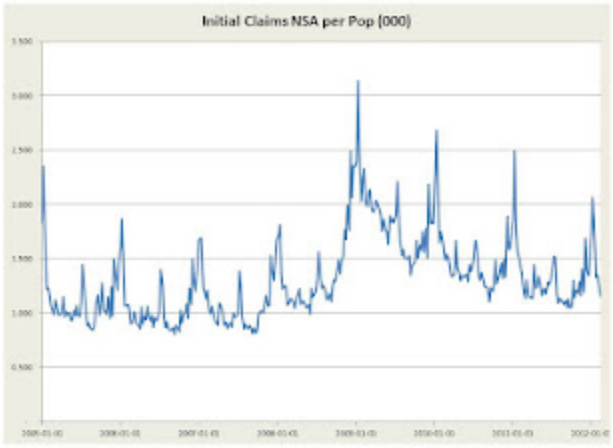
This will be a major event this week as oil prices are likely to explode. Needless to say it will further dampen Europe in the midst of the Greek mess and then filter to the US. Unfortunately no one seems to be focusing on this here.
Labels: Economy

THURSDAY, FEBRUARY 16, 2012

UNEMPLOYMENT CLAIMS DOWN



Unemployment claims are down again, yet still a bit high as shown above on NSA basis. The chart below normalizes per Pop and provides a better view:



Note that we are still above the lower level of 1 per 1,000 seen in 2005. Yet we are well below the 3.25 in late 2008.

Labels: Economy

WEDNESDAY, FEBRUARY 15, 2012

HYPOCHONDRIA IN THE AGE OF PERSONAL GENETICS

One of the things a young medical school student often experiences as they study new and oftentimes dire diseases is that they too soon sense the symptoms of some of them. Dengue Fever is often a common complaint in Boston, despite the fact that there never was any known such case.

Then there are CAT and MRI scans. One can guarantee that if one has one that the radiologist will find something, often something totally independent of any symptom you may have and that something will result in more tests. Most of which eventually will result in nothing too serious, for after all we all age.

Now for personal genomics, and Bloomberg provides and interesting piece on the discovery of genetic defects which may possibly at some future time result possibly in some disease which may possibly be serious.

The author states:

Then my eyes were drawn back to the top of the report and a variant called JAK2-V617F. I realized then that the list was ranked in order of medical importance. Clicking on an entry brought me to a few pages of medical information, and those pages were linked to published scientific and medical studies. I began reading about JAK2 more closely.

This wasn't good. The report classified the JAK2 variant's clinical importance as "high," and its impact as "well- established pathogenic," meaning harmful. It's seen frequently in people with

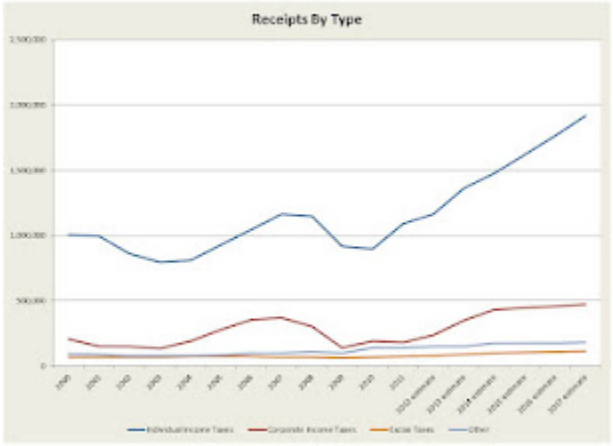
rare "cancer-like" blood diseases. Indeed, as the report said, doctors test for the JAK2 variant to confirm cases of these diseases, called myeloproliferative disorders.

Well, what does this mean? Knowing this can one do something to mitigate the downside? What value is this knowledge? As one reads on it seems that there is nothing to do other than wait. So do we want to know this? Genetic diseases are often a small class of diseases and all too often we cannot do much. Take Marfan's syndrome, the enlargement of the aorta which often could rupture. On can diagnose it by looking at the patient, sunken chest, thin, long fingers etc. But so what, just watch, tell the patient, replace the aorta? How much, what cost, what risk?

The article raises a plethora of questions which it does not answer. It is more a personal journey into the hypochondria of disease awareness, which often is of little value.
Labels: Health Care, Medicine

TUESDAY, FEBRUARY 14, 2012

BUDGET 2012: SOME THOUGHTS

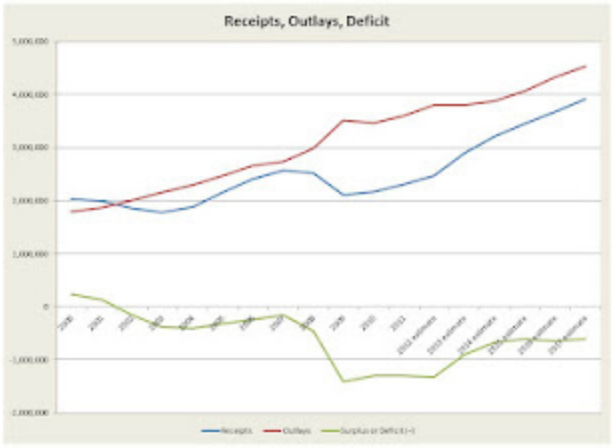


The Administration issued its budget for 2012 and following years. It is worth a look. First note above the explosion of anticipated income taxes from individuals. This can only be achieved if the Government increases taxes on a massive scale. All other elements rely on this drastic assumption. It is unrealistic but it necessary to justify the budget.

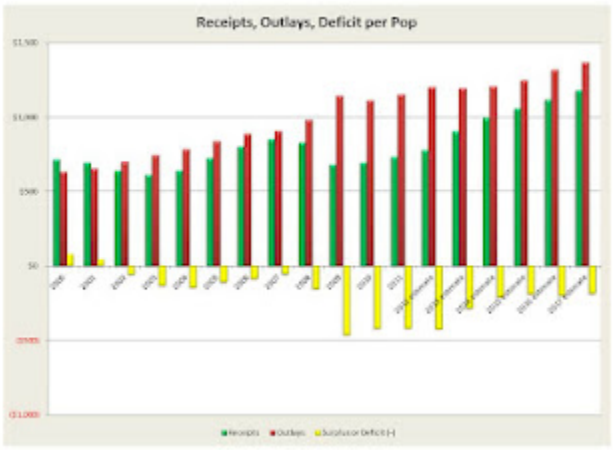
I have used 2000 as a baseline year. Why:

1. No wars
2. Stock Market up and down
3. Balanced Budget

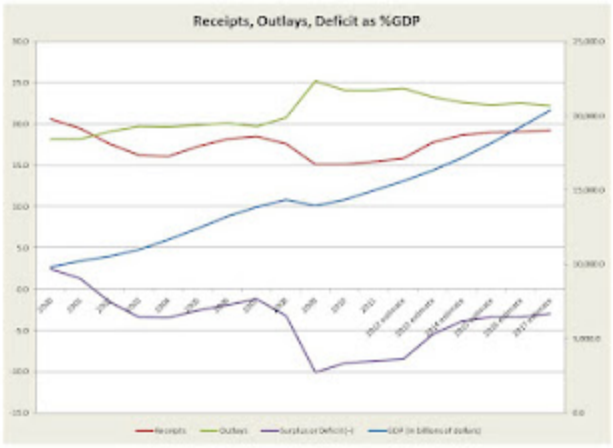
I will provide six images which I fell tell a story.



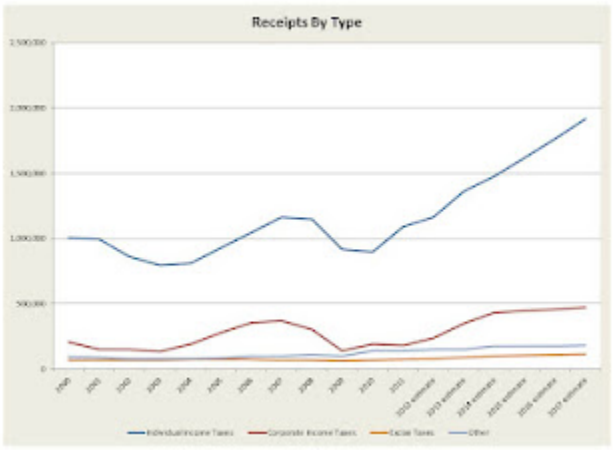
First receipts and outlays. The outlays had jumped in 2009 with the new administration and then ramped up from there. Why? One reason was stimulus etc bu frankly that does not show as a large bump of almost a trillion so one wonders where it went. Second receipts dropped, unemployed and no taxes collected and then not even SSI taxes. But long term there is no attempt to correct expenditures. With little inflation one wonders why the increase, just SSI and Medicare, not really as we shall see.



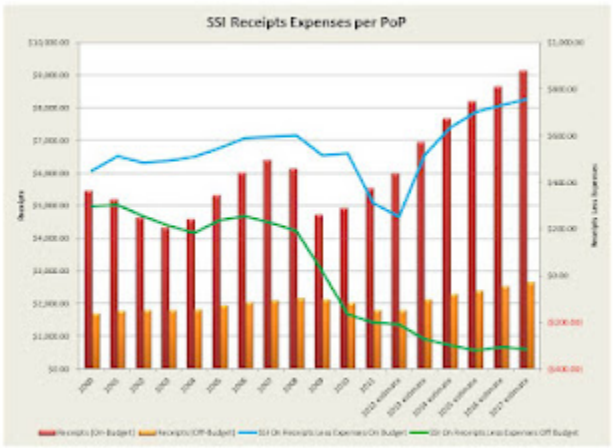
This shows the same but with a per Pop, per person, ratio. Here we should not see the impact of a growing population, but we do. So why? Too much expenditures.



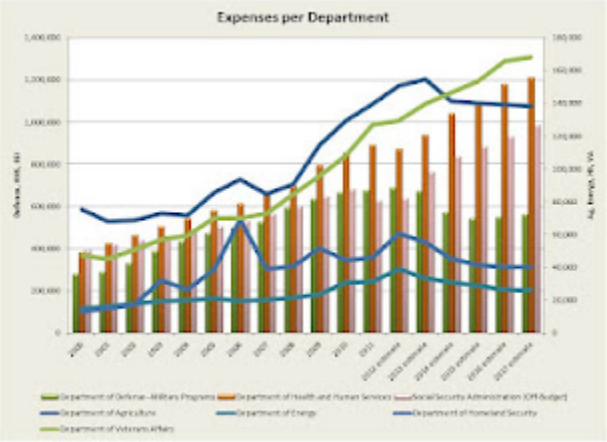
This is the same but as a % of GDP. Outlays were 25% of GDP! And they are not going below 22.5%! This is a problem.



This is receipts by type showing the major increase is by income taxes, and only and the middle and upper class.



This is SSI. Focus on On Budget numbers and we see they are growing as more people go back to work, hopefully. The on budget has no deficit. The off budget does!



Finally some select departments. HHS is the major grower due to Medicare, Medicaid and ACA! Remember ACA kicks in for 40 million more people! SSI continues to grow but no surprise there. Defense declines.

Why in God's name has Agriculture exploded! DHS is also high but Ag! What do they do...It has more than doubled, and it is not salaries.

One should ask, why should we increase any expenditures from a 2000 level, exclusive of the mild to zero inflation during this period. Second, we must handle Medicare and SSI, mainly through adjustments of eligibility age and increasing rates for Medicare as well as caps based on income. That is critical. SSI can and will take care of itself if and only if that is all it is used for. But there is a catch, the SSI stats were predicated on Fed interest rates well above 5%. Since the Fed drove those rates down the SSI fund will run short. This is but one example of how the Feds actions are harming the overall economy. One need go no further than these few charts to lay out a course for the future. If we do not then we face collapse.
Labels: Economy

CHINA AND ITS LEADERS

The NY Times has a brief commentary on technically trained national leaders and it states:

China has even more scientists in key positions in the government. President Hu Jintao was trained as a hydraulic engineer and Premier Wen Jiabao as a geomechanical engineer. In fact, eight out of the nine top government officials in China have scientific backgrounds. There is a scattering of scientist-politicians in high government positions in other countries as well. German Chancellor Angela Merkel has a doctorate in physical chemistry, and, going back a bit, Margaret Thatcher earned a degree in chemistry.

The BBC (also see BBC) also has an interesting piece on the putative next head of China:

Who is Xi Jinping? It's not an easy question to answer. The man the Communist Party is busy grooming to be China's next leader can be read in so many ways. He is a communist "princeling," the equivalent of royalty in the Party, born into power and privilege but who then lived in a cave. He is a man who has spent his life in the Communist Party but who knows what it is like to be outcast. He has convinced businessmen he is their champion, while overseeing a system where the state controls huge chunks of the economy. He has shown himself to be irritated with foreign criticism of China but has sent his daughter to study at Harvard under a false name to hide her identity. His wife, Peng Liyuan, a singer, has, for most of his career, been far more famous than he has. When he was first announced as China's next leader-in-waiting, he was already vice-president, but people still joked: "Who is Xi Jinping? He is Peng Liyuan's husband."

And yes he is a Chemical Engineer from Tsinghua University. In many ways we have lawyers and Harvard and China has engineers and Tsinghua. What would happen if we had EEs and MIT?

These combinations and contrasts will be interesting to watch especially in light of the chaos currently in Washington.The problem is that they come from two different worlds, and I do not mean China versus the US, I mean engineers and lawyers, two different planets. I doubt that anyone in the Administration could even interpret, mindsets and world views not languages.

Labels: China

SUNDAY, FEBRUARY 12, 2012

MIT ADMISSIONS HACK

Now I do not want to be too old a curmudgeon but I saw this MIT new admission "hack" where a balloon was sent with the admissions letter to some tremendous altitude, 91,000 feet. Admirable but I wonder what if this got sucked into an engine on a 737 or entangled in the prop of a single engine aircraft. Just a thought. Prior planning prevents poor performance.
Labels: Commentary

FRIDAY, FEBRUARY 10, 2012

WHERE IS MY FREE $50 BILL?

Today the Administration in its Solomon like manner agreed to not force Catholic institutions to violate their religious beliefs but at the same time provide "free contraception" to those insured. Now the Government is not providing the free stuff, the Insurance carriers are. Let me see, can I get some of those free $50 from the printing house, I now use them instead of $20s, they buy the same at the gas pump and the grocery store.

Better yet, if you made a bad real estate decision the Government will give you free $20,000, well not directly, they made the bad banks do that, that is after they gave the bad banks billions.

Does anyone start to see a theme here somewhere.

There is no free lunch. Someone must pay, and that someone is those of us paying taxes. As I indicated before the current administration is spending $1,000 per month per person, up from $650 under the prior set of folks. And the new budget just gets worse! Any suggestions from out there?

POST NOTE: Again Greg Mankiw has keen insight into the obvious, a rare trait amongst many. As he states:

Yet it seems that the White House yesterday switched from A to B, and that change is being viewed by some as a significant accommodation to those who objected to policy A. The whole thing leaves me scratching my head.

My conspiratorial mind says that the Administration orchestrated this whole mess to get what they wanted in the first place. Did the Insurance industry have a hand here. As usual one must ask if anything is really as it appears, or is Mankiw's head scratching a true sign that is was not stupidity but a strategy. Then again perhaps I spent too much time in Russia.
Labels: Commentary, Economy, Politics

FRIDAY, FEBRUARY 10, 2012

CATHOLICS NEED NOT APPLY

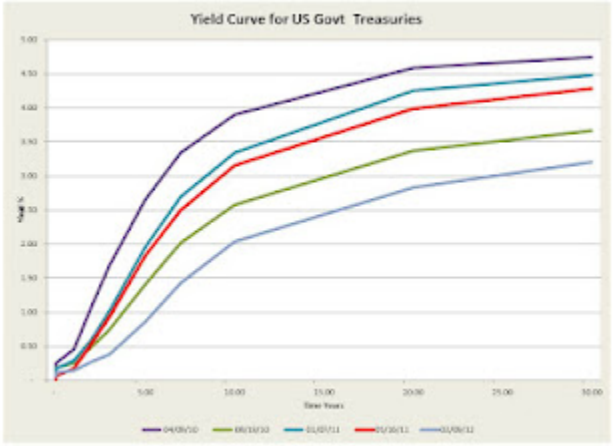
In reading the comments in the NY Times regarding the Administration accommodation to the HHS mandate, I am amazed by the near abject hatred on the part of those writing towards Catholics. I wonder if they ever read what they write. They make the Brits seem to be an accommodating and accepting group. We may all be safer with the Penal Laws, at least we knew where we stood.

This issue can be divided simply: (i) for the Individualists, the individual makes choices and Government should not mandate except when life and limb are at stake, ie murder, (ii) the Progressives, who firmly believe that there exists a select group to which they belong this group has been granted truth by some non-Kantian manner and that those not so endowed must obey them, since they lack the gift of truth. Fundamentally it is hubris, a group believes that they are correct and all must follow and the individual be damned.

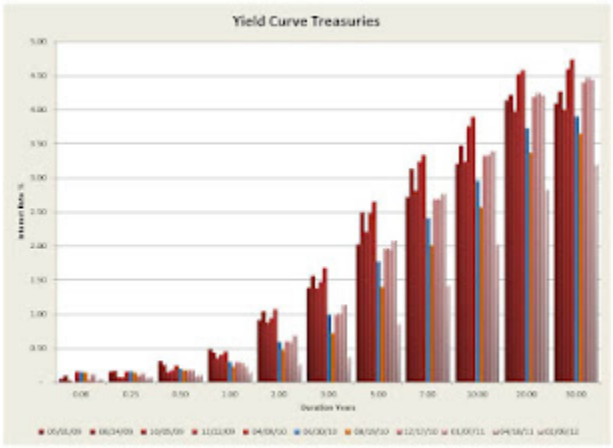
This exercise was a brilliant move by the Administration, they feint to the left, then "accommodate" to the right, get what they want, and move on. A classic Russian chess move. But it has drawn out the vitriol of the left against Catholics. What group is next. Perhaps some of the left leaning bishops will see that they have been in error, so much for guitars in church!

As Camus and Dostoevsky said, we all die alone.
Labels: Politics

YIELD CURVE AT ALL TIME LOWS

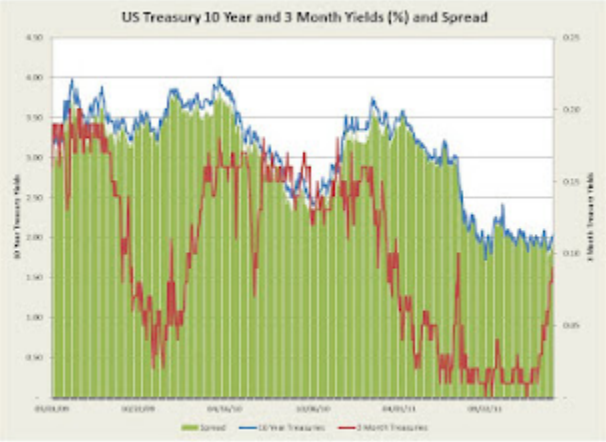


The above shows the lowest yield curve seen. Note the tremendous drop in the 30 year. It is like selling vodka at a penny per bottle. That was the case in Russia before the collapse.



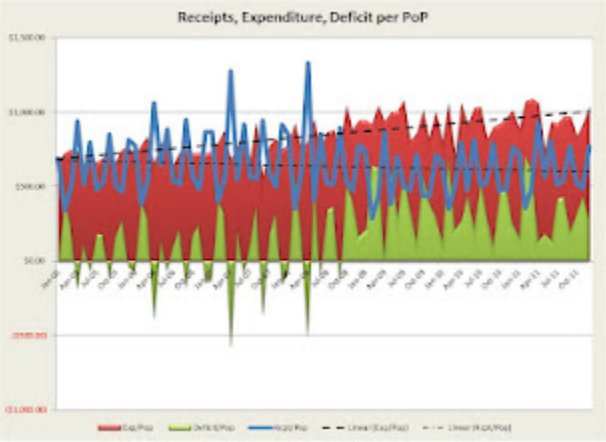
The above shows the same but at other spots. Look at the 30 year drop.

The above is the spread. It also has been locked at all time lows. Money seems frozen in the banks and not much has changed.



Finally above shows the curve in some detail but the 90 day Treasuries are rising sharply, the reason for the spread drop, not the 30 year alone.
Labels: Economy

UNEMPLOYMENT AND DEBT



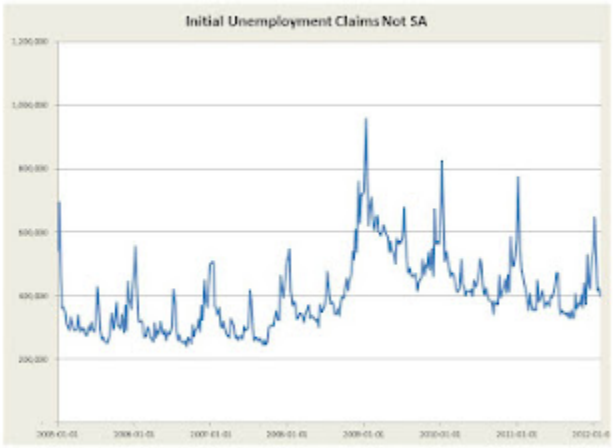
The above chart is chilling. It plots Treasury Receipts, Expenditures and Deficit per person per month for the past seven years. Initially Receipts and Expenditures were close, not bad. Then things start to fall off the cliff. We now spend more than $1,000 per month per person for Federal services and collect just over $500. We used to spend and collect close to $650.

Now use a bit of logic. If we had a 5% unemployment and we went to 10% then we lost about 5% of the revenue stream. That is 5% of $650 or about $40. So where did the other $110 get lost? Maybe it is the 1%? I don't think so. So that is the first question.

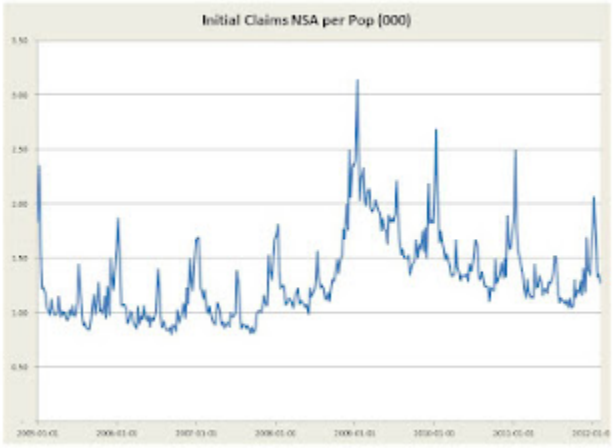
Second, we are now spending $1,000 per person, up from $650. Where are we spending that. If we are paying unemployment, so be it but that is a relatively small amount per person, not enough to get there. Also we stopped collecting SSI, dumb but that would be in Receipts not expenditures.

So should we worry, I suspect so since no one seems to have discussed this and we have gotten sidetracked by the current slam on freedom and rights to choose, namely the birth control issue. That is just fodder added to the mess.

Just to collect more data we show below the new unemployment claims, raw and per Pop.



And per Pop:



We typically run at 0.1% but as of last month we are still at 1.3-1.4%. That is not as good as the Administration spins it to be.

But back to the first curve, it is essential to watch this one, it is the Table of Doom!

Labels: Economy

THURSDAY, FEBRUARY 9, 2012

LAWS AGAINST CATHOLICS

The Penal Laws in England stated the following as regards to the Irish Catholics (See Duff, Six Days to Shake an Empire, 1966, pp 59-60):

No Catholic permitted to vote in parliamentary, county, borough or corporation elections.
No Catholic permitted to stand for parliament, or for a county or borough or corporation.
No Catholic permitted to hold a commission in the army or navy, or a post in the civil service.
No Catholic permitted to be a member of a learned profession, except medicine, and in that only a chosen few.
No Catholic permitted to open or administer a school.
No Catholic permitted to teach.
No Catholic permitted to carry a firearm without a licence, seldom granted.
No Catholic permitted to own a horse worth more than £5.
No Catholic in trade or industry permitted to have more than two apprentices (except in the linen industry, which was to the Ascendancy's advantage).
No Catholic permitted to manufacture or sell books or newspapers. (This included all printing.)
No Catholics permitted to marry a Protestant
No Catholic estates permitted to be entailed.
No Catholic permitted to take or grant mortgages.
No Catholic permitted to take a lease for more than 31 years, and then at two-thirds the annual value.
No Catholic priest permitted to enter the country from abroad.
All Catholic archbishops and bishops must leave Ireland under the penalties for high treason.
One priest only permitted to each parish, however large.
All Catholics were made to pay special taxes. All Catholic owners of land were subjected to special restraints and disabilities.
All of any Catholic's estates must at death be divided among all his children.

No Catholic priest permitted to move one step outside his own parish.

We may have had of laws like this before, and perhaps again, even here in the US. And by the way, many of these are still on the books in England! Is the current HHS ruling the first new "Penal Law" for the US?
Labels: Politics

INDIVIDUALISM, PROGRESSIVES AND CONTRACEPTION

The current flap over the demand by the Federal Government that Catholic institutions provide birth control in direct violation of their beliefs has been framed in two ways. By the Individualists it is what right does the Government have to tell me what to do when it violates my faith. To the Progressives this is women's health.

Now women often spend hundreds if not thousands on makeup and skin creams, not yet covered by ACA but perhaps not far away, and likewise thousands on iPhones and other stuff but the law demands that all employers fund certain types of medication. On the other hand the law seems to be creeping along so that it will refuse PSA tests and prostate biopsies while funding birth control. Logic? Hardly.

But it does go to the heart of one's world view. To the Right it is the right to be left alone and make individual choices. To the Left it is that there is a central authority that deems what is best and we then all MUST follow it. Just read the comments in the NY Times and other outlets as to public views.

This is a true core issue, not the contraception issue, but who tells whom what to do and at whose costs. I had major problems with the current health care bill from the start. I imagined a morbidly obese GS 9 telling me what I can and cannot do, even with my own money. I was told the fear was unfounded. Yet we have a head of HHS doing just that to a Church, well "First they came for the Catholics .... and then they came for me, and there was no one left..."

One should remember that the current President was educated at Columbia University, a school which has had a long standing dislike, to say the least, of Catholics. I personally experienced that in 1960 when I was denied admission to Columbia expressly because I was Catholic, in writing,

from a Dead! Thus perhaps we should not expect any different treatment from alumni. But as for the Individualists this is just another nail in the coffin of our freedoms, the creation of a country that De Tocqueville would hardly recognize.

The Progressives fundamentally believe that their truth is a universal truth, the only truth, and despite the belief of others they must all follow this humanly discovered truth. This, more than any other issue, is and must be the core of the discussion in the upcoming election. Do we have individual liberty and rights or is there some elite group whose ideas we all must follow, or else.

One is not forced to work at a Catholic Hospital, or University, and although I support universal health care, it is primarily for those tragic moments when survival is at the fore, not for runny noses, wrinkles, or even contraception. There must be a point when the individual makes a choice, and not the Government.

What of the employers who will fire someone who smokes, someone overweight, why are they free to do that. I agree they should but then why this flap over contraception. It is not cancer surgery, it is not testing for breast cancer, prostate cancer, it is in many ways akin to decongestants.

The problem is that we have empowered HHS and the hundreds of new agencies under ACA with powers we could never imagined. Remember, "you will see what is in the Bill after you pass it..." We are just beginning to see. The future looks terrifying.

POST NOTE: Just after posting this Greg Mankiw linked to a Cochrane Opinion in the WSJ which adds to the argument. Now Cochrane has a great economic argument but I further believe that the real issue is a battle of world views, Individualism versus Progressives, liberty versus Government control. When reading comments the Progressives write, they have a fervent religious belief, albeit ungodly, in the sole correctness of their conclusions and opinions. The Individualist says that anyone may hold any opinion, the Progressive demands that everyone comply with theirs. The issue is not what the Catholic Church says but that the Government believes that it is sine qua non, above all. The Progressive believes in a Government which has become a usurper of liberty. The question is; what world do you want your grandchildren to live in, unless of course you are consuming all those free contraceptives. In which case you may not really care.
Labels: Politics

WEDNESDAY, FEBRUARY 8, 2012

CHINA, CANADA, OIL, AND THE ELECTION

China Daily rep[orts on the completion of the agreements between China and Canada giving China access to most of Canada's oil reserves. They state:

Wen Jiabao on Wednesday urged the forging of a long-term, stable and diversified partnership with Canada in the energy and resource sector.

"The negotiation on China-Canada investment protection agreement has concluded. We hope to sign the important document as soon as possible to facilitate two-way investment," Wen told visiting Canadian Prime Minister Stephen Harper in the Great Hall of the People.

Harper came to Beijing Tuesday for his second China visit since taking office in 2006.

Calling the two economies highly compatible, Wen proposed to draw up an all-round plan on boosting bilateral economic cooperation based on joint research on economic complementarities.

One wonders what the current Administration may think regarding their decisions to thwart the US relationship here. It will drive costs sky high while playing into the hands of a potential global competitor or possibly even worse.
Labels: Political Analysis

LAW OF UNINTENDED CONSEQUENCES

Some tax lawyer wrote a piece in the NY Times today suggesting that the IRS get taxes from shares held at a then market valuation of some sort. He states:

This tax would not affect the middle class, or even most wealthy Americans. Nor would it affect small-business owners. It would affect only individuals who were undeniably, extraordinarily rich. Only publicly traded stock would be marked to market.

Some would argue that it is inherently unfair to tax "paper gains" before they are realized — Mr. Zuckerberg won't receive $28 billion in cash; he holds only paper. Moreover, markets are inherently volatile; one year's paper gains is another's real losses. However, these arguments are far less credible when paper losses give rise to real tax refunds. Moreover, in a downturn, the mark-to-market tax would act as a fiscal stimulus — the cash refunds would offset a declining stock market.

This proposal follows the Ronald Reagan model by broadening the "base" of tax without increasing rates. In fact, Reagan was responsible for the last major reform of our antiquated realization system when he signed a law requiring taxpayers to pay a tax on interest that accrued on bonds but was not paid.

The most profound effect of a mark-to-market tax would be to level the playing field between wage earners, on one hand, and founders and investors on the other. Superwealthy holders of publicly traded securities could no longer escape tax on their vast wealth.

Now leaving aside the sanity of this scheme one should examine the unintended consequences.

Let us assume I start a company. I put say $1 million of my money in it. It gets going. I need more money, and I get a first round of financing at a $9 million pre money valuation and raise say $9 million. My one million is now worth $9 million and I must pay 35% tax on this $8 million gain even though I never saw a penny and am still out $1 million.

So why would I start the business? And if I do a second round at say a $40 million pre money, my first round investor must pay tax on $11 million and of course so do I. Why would he want to invest, his rate of return is destroyed just then and there!

So what will happen, well we will find ways to do start ups in say Mauritania or some other place that does not have this strange way of taxing.

It seems clear to me that this fellow is clueless about the entrepreneur. The money was meant to grow the company, employ people, pay taxes, not give money to the Government. I guess it is now clear why we will be in this mess for a real long time.
Labels: Commentary

TUESDAY, FEBRUARY 7, 2012

WHY I HATE DICKENS

When I was quite young my grandmother handed me the above set of Dickens. She had been the head of the Socialist Party in New York and ran for Senate and NY State Treasurer. Never won. Yet I had to read Dickens so that understood the problems of the underclass. Now at the time I did not know that I was the underclass but by reading Dickens I was to see that there were those who were oppressed by the rich. Kind of the Occupy folks of today, but they are not really underclass.

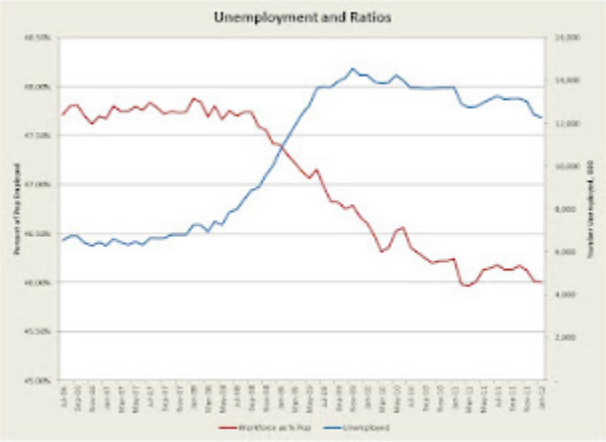
Now I read all of these, and trying to see how they related to New York in the early 1950s was a bit of a stretch. You see Dickens understood the British class society, and we in the US, at least then, had a somewhat classless society. Or at least none of us saw any limitations on what we could achieve. For Dickens and the Brits class and your position in society defined your very existence. For me it made no sense. Thus book by book I read understanding that this world made no sense and even if it did as an American I could change it, I was not set in concrete. After many conversations even my grandmother was a believer.

I never made my grand children read this nonsense, yes nonsense. And today is Dickens' 200th anniversary of his birth. Perhaps for some he presents a world of meaning but for others he

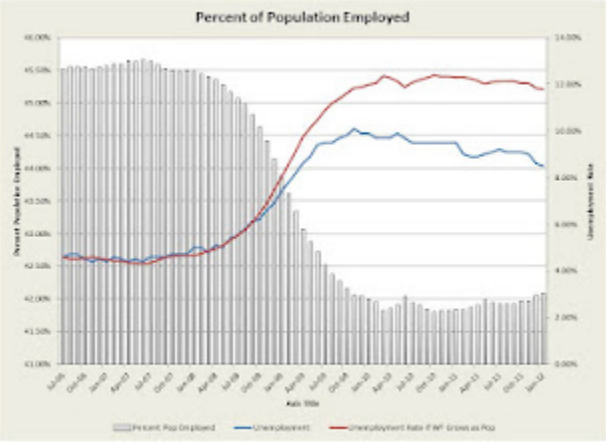
presents a planet on which we have no knowledge and we would never even want to understand it if we did. Thus unlike so many fans of the man, I felt he was the low point of my youth.
Labels: Books

SUNDAY, FEBRUARY 5, 2012

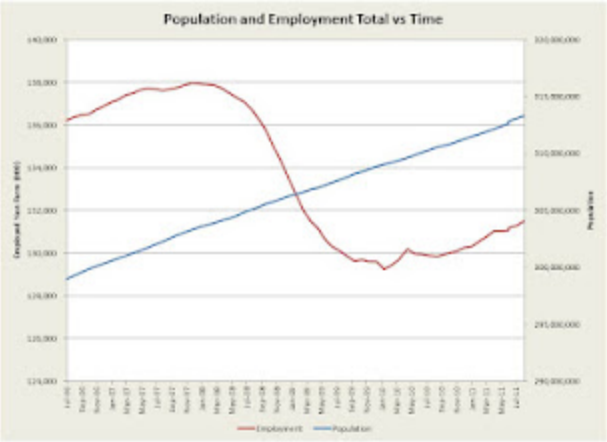
THE EMPLOYMENT NUMBERS



The above shows the employment numbers from a telling perspective. The curve showing percent in base has declined again, allowing the decrease in the reported numbers. And this is WITH the seasonally adjusted numbers. Thus the number is truly less optimistic than what has been presented.



The above shows that using the base of employables before the collapse that we are still at 12% or higher in unemployed. The rate may be declining but not when adjusted for the base.



The above shows population and employed. Note the dip but also note that we are now barely keeping pace in rate of growth. This does not bode well. The numbers are "good" only because they have been adjusted; adjusted by seasonal number and adjusted by reducing the employable base.
Labels: Economy

TUESDAY, JANUARY 31, 2012

ENGINEERS VERSUS ECONOMISTS

There is a piece today in the Harvard Crimson lauding the Economics course and in effect its instructor. However there is also a comment placed by someone, I really have no idea as to who this person is, but it is on point. The Harvard Economics Professor professes belief that if CO2 is harmful the solution is an economic one, the Pigou Tax. While we believe that such a tax has merit in certain areas we do not believe it functions here. The person commenting is spot on.

As the individual states:

By way of Example: ... is sold on the carbon tax. "The essential problem of climate change, scientists tell us, is that humans are emitting too much carbon into the atmosphere, which tends to raise world temperatures. Emitting carbon is what economists call a "negative externality"—an adverse side effect of certain market activities on bystanders." The ability to apply Pigouvian taxes is so addictive that he rather skimmed over the points that the earth hasn't warmed in the last decade, the AGW computer models predict nothing even approaching reality, and nobody really knows how much CO2 in the atmosphere is the best number.

The real issue is that if this is a real problem, and I remain a bit unconvinced having done a bit of work here a few decades ago, then one should seek for a real solution, and that is engineering and not economics. Try to find alternative energy sources, alternative power systems, and let economics play that hand not the hand of taxing which seems to be the standard practice of the left. The terrifying fact is that this Professor is allegedly the economics adviser to one of the dominant Republican Presidential candidates. One should remember that when that candidate was in Massachusetts there was another Professor, this time from MIT, who advised him on

health care. Perhaps candidates should be wary of academics, especially economists who have never created a single job, outside of Government work that is.
Labels: Economics

MONDAY, JANUARY 30, 2012

HOW DUMB IS GOOGLE

Now there has been a great flap about Google and its new "privacy" policy. Now privacy can be expected if one just takes oneself from society, the old right to be left alone. Well not anymore with the health care law but that was a tale for another day. No, I am talking about Google gathering info and pushing it on other web sites to continue the sales process. So for example I needed a new sump pump a few months ago. I did a search, and then on almost every web site or blog there were the ads for the same pump. Again and again.

But stupid Google, I bought the stupid thing already, so stop it. I am not buying a dozen sump pumps, there on my weather site, on blogs, etc. I also looked at a jacket, then whamo, it appears on the weather site again, and other sites I see for the first time. Ah, the joy of cookies. But poor Google, I did not like the jacket so I never bought it and in addition I got to hate it more each time they targeted an ad.

Now for searching, they must think I have a lapsing memory. If I ask for something the first ten references are mine! I know what I wrote, I want to see more. So off to Bing.

You see, Google wants to please me, or so they say, and the result is that they are like a nagging mother, eat your peas!

One must be careful, for a one trick pony they must not annoy the audience with the trick by spitting in the face of those paying. Remember if all else fails listen to the customer.
Labels: Google

SATURDAY, JANUARY 28, 2012

WHAT IS IN A WORD

It is interesting to see economists talk about taxes in the private equity world. Perhaps they will pose theories of astrophysics next.

The problem is that "it all depends". In the simplistic sense if a company pays a dividend and it is taxed at 15% and the company pays 35% tax then indeed the total was taxed at 50%. The problem is no private equity works quite that way. Especially for the general partner types who have really little at risk.

For example, consider a general partner who puts nothing at risk, and a company which has massive tax loss carry forwards which is sold for say $100 million. The funds get distributed to say the PE company. It is a capital gain at 15% depending on what is returned. No 35% was ever

paid, just a greater fool found to buy it. That by the way is the PE game. But without the PE player the company may most likely have collapsed.

So how should we view this? Well it is really very complicated and all these economists are apparently clueless finding one scenario after another to justify their conclusion, ad hoc propiter hoc.

How should we look at it? Well each case is separate. It is not simple and it cannot be simply explained by some smart Prof trying to make their point. Details count, welcome to the real world folks!
Labels: Politics

THURSDAY, JANUARY 26, 2012

WORDS MEAN SOMETHING, SOMETIMES

Level Playing Field, Fairness, Quality, Ethics, Integrity etc. What do they mean?

From Through the Looking Glass we have:

Humpty Dumpty took the book, and looked at it carefully. 'That seems to be done right--' he began.

'You're holding it upside down!' Alice interrupted.

'To be sure I was!' Humpty Dumpty said gaily, as she turned it round for him. 'I thought it looked a little queer. As I was saying, that SEEMS to be done right--though I haven't time to look it over thoroughly just now--and that shows that there are three hundred and sixty-four days when you might get un-birthday presents--'

'Certainly,' said Alice.

'And only ONE for birthday presents, you know. There's glory for you!'

'I don't know what you mean by "glory,"' Alice said.

Humpty Dumpty smiled contemptuously. 'Of course you don't-- till I tell you. I meant "there's a nice knock-down argument for you!"'

'But "glory" doesn't mean "a nice knock-down argument,"' Alice objected.

'When I use a word,' Humpty Dumpty said in rather a scornful tone, 'it means just what I choose it to mean--neither more nor less.'

'The question is,' said Alice, 'whether you CAN make words mean so many different things.'

'The question is,' said Humpty Dumpty, 'which is to be master-- that's all.'

Alice was too much puzzled to say anything, so after a minute Humpty Dumpty began again.

'They've a temper, some of them-- particularly verbs, they're the proudest--adjectives you can do anything with, but not verbs--however, I can manage the whole lot of them! Impenetrability!

That's what I say!'

'Would you tell me, please,' said Alice 'what that means?'

'Now you talk like a reasonable child,' said Humpty Dumpty, looking very much pleased. 'I meant by "impenetrability" that we've had enough of that subject, and it would be just as well if you'd mention what you mean to do next, as I suppose you don't mean to stop here all the rest of your life.'

'That's a great deal to make one word mean,' Alice said in a thoughtful tone.

'When I make a word do a lot of work like that,' said Humpty Dumpty, 'I always pay it extra.'

That is what they mean. Welcome to Washington!
Labels: Commentary, Politics

SATURDAY, JANUARY 21, 2012

TAXING THE WRONG THING

They are at it again, and they call themselves Republicans. They being in the NY Times, and they state:

Consider the tax on gasoline. Driving your car is associated with various adverse side effects, which economists call externalities. These include traffic congestion, accidents, local pollution and global climate change. If the tax on gasoline were higher, people would alter their behavior to drive less. They would be more likely to take public transportation, use car pools or live closer to work. The incentives they face when deciding how much to drive would more closely match the true social costs and benefits. Economists who have added up all the externalities associated with driving conclude that a tax exceeding $2 a gallon makes sense. That would provide substantial revenue that could be used to reduce other taxes. By taxing bad things more, we could tax good things less.

Let us again reconsider:

1. The middle and lower classes drive to work, not for pleasure. They often have no alternative. They may live in New Hampshire and drive to Cambridge. They drive say 100 miles a day at 20 mpg for 5 gallons. This Professor then will tax them an additional $10 per day or $3000 per year!

That is an additional tax. If we look at China we see the opposite. You see the poor guy in New Hampshire has no other realistic alternative, to get a home he must drive that distance and he must work long hours and he must have a car. In NYC you pay $25 in tolls, $50 for parking and then gas! However you can take public transport for a mere $30 plus a day. Only the self proclaimed elite would deny that person such access. It is a cost of production hidden in a reduction of compensation for the employee. Not everyone can own a mansion on Brattle Street.

2. Live closer to work, like say Newton, or perhaps Lincoln, and at what price? Perhaps South Boston. Somehow the upper reaches have lost touch with those who clean the streets.

3. Now as for bad things, one can truly argue as to these alleged costs. Congestion is due often to timing, accidents were pandemic in Boston because of the insurance system and yes drivers, and local pollution is dominated by other factors such as factories, and as for global warming, well I will not go there.

4. Real bad things are obesity. Just look at the recent JAMA articles. Currently 15% of annual health care costs growing at 15-18% pa, well outgrowing all others. That is a measurable and manageable problem, tax pounds or calories. Not gasoline.

However and whatever one should think through the details. Facts count, even in economics.
Labels: Economics

SATURDAY, JANUARY 21, 2012

SOMEHOW MISSING THE POINT

In the NY Times there is a long piece on Apple and manufacturing in the US. Also why China is getting so much of the work. Now this is hardly new. When I was at Warner in the early 80s we had Pioneer in Japan manufacture our cable converters. Quality, price and performance. That was not even new then. We saw disk drives being made in Asia, then in Mexico, business finds the lowest cost place to do this with possibly a quid pro quo. That gives the American consumer the best price and they then buy more which means ultimately higher profits. It is called business.

Now that is not the way the current administration sees it. The most absurd quote I have ever seen is:

"Companies once felt an obligation to support American workers, even when it wasn't the best financial choice," said Betsey Stevenson, the chief economist at the Labor Department until last September. "That's disappeared. Profits and efficiency have trumped generosity."

Nonsense. Total and complete and utter nonsense. One must look to the credentials of the source to see why.

Under our legal system, and under our economic system, at least as understood before the current administration, Companies have a fiduciary duty to make money, and the way they manufacture

is a reflection of this. In my opinion the very statement is a demonstration of a gross disconnect with reality, but a reason why we are in the mess we are in. If those in Government believe that a business has a first duty to support American workers over growth and profit then they are just wrong, business does not work that way.

I moved a company from New Jersey to Prague because of lower costs, reliable electrical supply, and good workers. The burdens of the US overhead, poor infrastructure and high taxes, plus regulation on everything, made moving the only alternative. Perhaps Washington should get some people with some real experience.
Labels: Economy

CAREER PLANNING

In 1959 when I was trying to determine what I wanted to do, I dismissed being a pure mathematician, most likely a great idea since I may be good on the applied side the pure stuff can become a bore and I was ultimately not good at it. But what I did was to sit down with the Sunday NY Times and look at the job section and determined that EE and Chem E was where the action was at. It was a rational decision process. There never was a question as to "what would I like to be when I grew up", it was "where are the jobs and how do I get there".

Now I read a report in C&EN, the American Chemical Society news organ and it appears that chemists are falling off a cliff. They state:

The U.S. chemical industry lost 15,000 jobs in 2008, down 1.7% from the end of 2007. That decline, to 847,000 jobs, was almost as bad as the 1.9% decline in jobs for the overall economy, which shed 2.6 million workers. Economists expect the situation to get worse in 2009.

They continue:

Chemical employment peaked at 1.1 million jobs in 1981, and has trended downward since, Swift notes. He attributes the decline to productivity gains, outsourcing, and jobs lost to overseas competitors. The one bright spot had been the pharmaceutical industry, a statistical subset of chemicals, which saw steady job increases over the decade through the end of 2007. However,

available data show that pharmaceutical makers cut about 4,700 jobs, down 1.6%, through the end of November 2008.

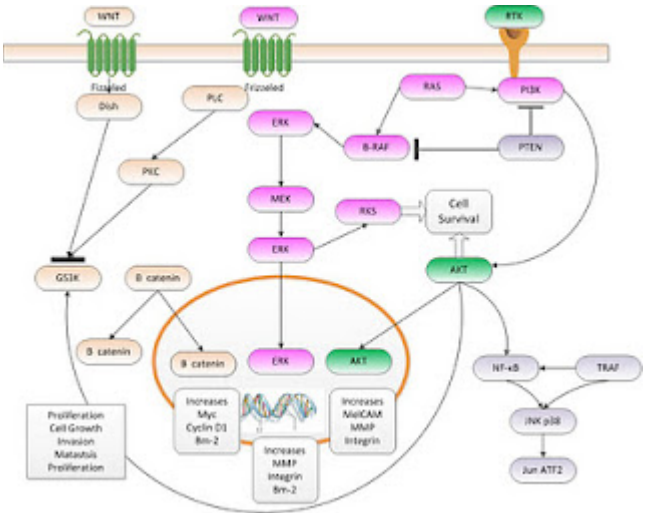
So from 1981 to now the jobs for chemists has dropped from 1.1 million to 840K, almost 300K jobs while the economy has been growing more than two fold despite the recent downturn. That means this is not a field one wants to enter.

Thus one wonders why anyone would go into chemistry. It is not that chemists are not valuable, they are indeed, but unlike EEs who have a strong entrepreneurial streak the chemists has gone to industry, academia or the government. What is amazing is the growing demand in biotech and especially now in informatics on biotech systems, and the lack of flow in that direction. It is not that the chemist training is out of touch, it may be more mindset rather than any competence deficiency.

The bottom line is now that students are determining what to major in, art history, social work, chemist, why not just look where the future jobs are, for today there is a wealth of information to help you, more than just the Sunday Times. I believe that this idea of doing what you want to do may be at the heart of many of our job problems. There are many in the younger generation who feel they are empowered to get a job they want, not what the economy needs or can provide. Carriage makers were put out by the auto, and auto factory workers by robots and off shore production. Nothing remains constant, one must assess the flow of the economy and then be prepared to change as it does. Creative Destruction is real, it is ongoing, and it is at the heart of a free economy. Trying to prevent it is akin to trying to hold back a broken dam with one's hands.
Labels: Academy, Economy

THURSDAY, JANUARY 19, 2012

PATHWAYS, CROSSTALK AND MELANOMA



NEJM has published an interesting article on what can be called cross talk amongst pathways. As is well known now the BRAF mutation found in certain melanomas can be somewhat controlled via the use of vemurafenib. However and possibly surprisingly there is an increase in other cancers.

The authors conclude:

Mutations in RAS, particularly HRAS, are frequent in cutaneous squamous-cell carcinomas and keratoacanthomas that develop in patients treated with vemurafenib. The molecular mechanism is consistent with the paradoxical activation of MAPK signaling and leads to accelerated growth of these lesions.

Pathways have cross talk, and when one pulls one string another may also be pulled. The authors further note:

The t→a transversion at position 1799 of BRAF (BRAF V600E) is present in approximately 50% of patients with metastatic melanoma.1,2 BRAF V600E induces constitutive signaling through the mitogen-activated protein kinase (MAPK) pathway, stimulating cancer-cell proliferation and survival.2 The clinical development of inhibitors of oncogenic BRAF, termed type I BRAF inhibitors, which block the active conformation of the BRAF kinase, has led to a high rate of objective tumor responses and improvement in overall survival, as compared with standard chemotherapy.3-5 However, nonmelanoma skin cancers — well-differentiated cutaneous squamous-cell carcinomas and keratoacanthomas — have developed in approximately 15 to 30% of patients treated with type I BRAF inhibitors such as vemurafenib and dabrafenib.

This may open a door to several new approaches. First understanding pathways better and deducing the effects on blocking one of the paths, and multi-drug analysis.

Labels: Cancer

SUNDAY, JANUARY 15, 2012

A DEAL IS NOT A DEAL UNTIL THE MONEY IS IN THE BANK

I should not be amazed but the commentary by self proclaimed "experts" is amazing. Some writer for the Washington Post under the headline "Bain's Dishonest Deals" and becomes "When Romney ran Bain Capital, his word was not his bond", states:

Here's how it worked. Private-equity firms are always eager to find companies to buy, allowing them to invest chunks of the billions of dollars entrusted to them and from which they earn hundreds of millions in fees. One ready source of these businesses is Wall Street bankers hired to sell companies through private auctions. The good news is that when a banker puts together a detailed selling memorandum about a company, chances are very high that company will be sold; the bad news is that these private auctions tend to be very competitive, and the winning bidder, by definition, is most often the one willing to pay the most. By paying the highest price, you win the company, but you also may reduce the returns you can generate for your investors.

But for anyone who has ever really done a deal we all know that "A deal is not a deal until the money is in the bank, for a week!" Deal get renegotiated all the time, the fail to reach

completion for hundreds of reasons, agreements are abandoned for frustration of purpose, material adverse changes occur and so forth.

One always finds problems, and often they are fatal. Thus the assumption that a deal is done on a hand shake is naive at best. Negotiations are just that, negotiations. In some places a contract is considered just the start of negotiations, I had found that out the hard way in Asia.

Thus as my daughter tells her fourth grade class, "A deal is not a deal ...", even they know, and these children may be better prepared to deal with reality than some opinion writers. But after all it is just the Post!
Labels: Politics

FRIDAY, JANUARY 13, 2012

GENES, GENES, TOO MANY GENES

The Scientist has written about a simple same day, $1,000, full genome sequencing system becoming available at about $750,000 per machine. The question is what will you do with all the data.

We know of say a few thousand germ line genes which may relate to their potential for disorders, BRCA and HOX B 13 being two we have discussed recently.

The challenge will be to develop sophisticated testing for prognostic profiles. But this may be a chicken and egg issue. It does however present a threat to the gene testing companies out there, because now the value added is analyzing the complex genetic structure and saying something about it.

The article gives costs as:

The Illumina HiSeq 2500 will allow researchers to generate 120 gigabases of data—40X coverage, or repeated sequencing, of a single 3 gigabase human genome—in 27 hours, the company announced. It is a significant increase in speed over the previous model, the popular HiSeq2000 machine, which sequences up to 5 human genomes (about 600 gigabases of data) simultaneously over 10 days. But the snappy new model comes with a hefty price tag of $740,000, Forbes reported.

The Life Technologies Ion Proton Sequencer, on the other hand, is priced significantly lower at $149,000 and will sequence an entire human genome with 20 to 30X coverage in a day for just $1,000, said company spokesperson Mauricio Minotta. Illumina declined to disclose a cost per genome for the HiSeq 2500.

Thus low costs may turn this into a PC type revolution allowing many people to develop APPS!
Labels: Health Care

WHAT IS WRONG WITH ACADEMIA

There is an article in Forbes by some Professor somewhere wherein he articulates his philosophy. Having taught at MIT, Columbia, George Washington, Polytechnic University and a few other places, and now taking Organic Chemistry, for the second time, at County College of Morris, a community college, I bring a somewhat different perspective. Also as one who has created a few jobs in 20 countries, I have a modicum of knowledge concerning people, some that work and some that don't.

Let me summarize this dictum from on high just a a bit:

First, I do not "take off" points. You earn them. The difference is not merely rhetorical, nor is it trivial. In other words, you start with zero points and earn your way to a grade.

Yes I would agree with that. But there are faculty who do "take off", for spelling for example, on a technical exam. I never did but I experience it now. Thus the issue is what is the content of the course and what is not. Some folks just cannot spell, I am one, perhaps it is the family dyslexia or not. But the function of a good faculty member is to also seek to understand why the student got something wrong. I did that frequently, from an undiscovered illness to severe family problems. Arrogant faculty are the bane of Academia.

Second, this means that the burden of proof is on you to demonstrate that you have mastered the material. It is not on me to demonstrate that you have not. My assumption at the beginning of each class is that you know somewhere between nothing and very little about basic economics unless you were lucky enough to have an exceptional high school economics course. Otherwise, why are you here? You might say that the course is a prerequisite for other things you want to do, but if that it is the case and you know the material, you're more than welcome to simply show up for the exams, ace them, and be on your way.

This is difficult sometimes. Perhaps my exams were too difficult, were wrong, etc. I remember that in December 1970 I gave out a take home exam that required that the students prove A > B. Well oops, I typed the inequality the wrong way, and the exam went out just before Christmas holiday and due Jan 3rd. Funny, all but one student "proved" the inequality the wrong way, one student just said I got the inequality wrong. He got an A the others I gave a pass. I apologized to all. Yet there were a few nooses prepared.

Now as to the assumption that the student comes to class ignorant, well I NEVER assumed that at MIT in EECS. One never knew. In my current Organic class the Instructor assumes we are all ignorant, well there are three MDs and a few other who have come back to refresh. As a Professor I never assumed anything other than we were peers in learning. The game was that the students would always try to find where I made an error, and my counter was to know it so well I never needed a note and I finished my 50 min lecture on the second.

Otherwise, why are you here?

Good question, but perhaps one should not be so presumptive, perhaps you should find out why the student is there. That one phrase is what prompted this response.

Finally, I'm here to be a mentor and instructor. This means that our relationship differs from the relationships that you have with your friends and family. Please don't infer from this that I don't care about you, because I do. A lot. I want to see you make good choices. I want to see you understand basic economics because I hope it will rock your world as it continues to rock mine and because the human consequences of lousy economic policy are enormous. That said, you should never take grades personally.

One of the things I learned early on at MIT once I started as an Instructor in 1969 was the care and attention to understanding each student. We were not necessarily friends, but one of my students became my best man, another an investor, and the list goes on, but that we understood why the student got what they did. We would list every grade for every student and then with the Teaching Assistants go through them one by one during the grading session. Each student grade was personally looked at in light of everything we knew. In a way we were more than a friend or family, we became forgiving of situations, and understanding of what they accomplished.
We "knew" each student as a person, not just a grade.

Did I still have them come and ask why, yes, but when I explained why, which I owed them, then they became true believers also.

Thus I have reason to differ with the good professor, hopefully for good reason.
Labels: Academy

HAPPY FRIDAY 13TH

It is Friday the 13th, and especially January and Friday. Watch for cracks in the sidewalk!
Labels: Commentary

THURSDAY, JANUARY 12, 2012

HOMEOBOX AND PROSTATE CANCER

The Homeobox and its related genes have played an interesting but challenging role in developmental biology and now in cancer pathways. The genes related to this 180 base pair section of DNA are the genes which control the development or organs and the time at which these development occur. Furthermore the structure of this gene collection is preserved across an dramatically large number of species, the human included. Thus it was interesting to see a paper in NEJM discussing the mutation of a specific Homeobox gene, HOX B 13, as relates to prostate cancer.

In the recent NEJM paper by Ewing et al the conclusion of the authors is stated as:

The novel HOXB13 G84E variant is associated with a significantly increased risk of hereditary prostate cancer. Although the variant accounts for a small fraction of all prostate cancers, this

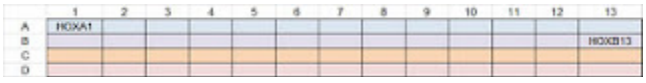
finding has implications for prostate-cancer risk assessment and may provide new mechanistic insights into this common cancer.

Now this appears as a significant new finding and we would like to examine this a bit. The HOX genes are quite unique in their functioning. They are built about a core Homeobox segment, which is preserved across chromosomes and species, and is hen connected with variable regions on differing chromosomes to generate some 4X13 possible genes (HOX (A,B,C,D) (1…13)). These genes are core to the morphological and embryological development of a broad range of species.

Now HOX B 13 is one of many Homeobox based genes. These genes are distributed across 4 chromosomes and have a fixed part called the homeobox part and a variable part. In a sense it is similar to the fixed and variable regions we see in the immune system. The gene is created as below:

HOX B 13 for example uses the Homeobox segment of 180 BP and is connected to variable region creating a unique gene but the binding site is based upon the common Homeobox segment. Homeobox is preserved across species.

Homeobox genes are clustered in the chromosomes and are expressed in the body in the same order in which they occur in the chromosomal DNA. The HOX genes, the concatenation of the respective Homeobox and its variable part are named by chromosome location as A, B, C, D, and then by number 1 through 13 at present. The number reflects what makes the Homeobox genes of interest, namely the genes control the development of the embryos, namely they control what cells do as a part of the development of an entity. The process goes from head to tail, and the numbering goes from the earliest or anterior to the latest or posterior elements in the development process. Thus HOX A 1 relates to an early development and HOX B 13 would refer to a later development of the embryo. The sequencing is shown below.



Retinoic acid activates the Homeobox genes sequentially in development.

Now the Ewing study examined patients with specific changes:

Given the consistent evidence of prostate-cancer linkage to 17q21-22 markers in our multiplex families with hereditary prostate cancer, we designed a targeted sequencing strategy to analyze 2009 exons of 202 genes contained in the most likely genomic interval defined by our fine-mapping studies. … Probands from four families were observed to have the same nonsynonymous mutation in HOXB13, a change of adenosine for guanine (transition,

c.251G→A) in the second position of codon 84 (GGA→GAA), resulting in a nonconservative substitution of glutamic acid for glycine (G84E)

The question is perhaps where does the term Homeobox come from. From Gehring and Hiromi we have the definition:

The term "homeosis" (originally spelled "homoeosis") was proposed by Bateson (8) to describe the transformation of one structure of the body into the homologous structure of another body segment. Homeotic transformation can result, for example, from abnormal regeneration of amputated structures (epigenetically) or from germ-line mutations

Thus the Homeobox genes are key to the development of embryos. They also lead to the discussions

Scott states:

Homeotic genes control cell fates during the development of all animals, as was first revealed by studies of the Drosophila homeotic gene complexes … Many of these genes contain a homeobox, a 180 bp sequence of DNA which encodes an evolutionarily conserved DNA binding domain, the homeodomain … A plethora of mammalian homeobox genes have been reported, among which 38 are located in four clusters. A new nomenclature for the mammalian Hox genes, approved … The new names take advantage of the elegant arrangement of the genes to provide a logical nomenclature system rather than the names given when the genes were discovered. The new system is initially designed only for vertebrate genes, although it is to be hoped that similar systems will be useful, and adopted, for other animals. In order to preserve as much clarity in the literature as possible, it has been agreed by a large number of workers in the field and by the nomenclature committees that homeobox genes not located within the Hox complexes should not be given names containing the word 'Hox'.

There are four clusters of Hox genes … now to be known as A, B, C, and D. Based on sequence similarity the genes can be sorted into 13 'paralog' groups, each group having, in most cases, a representative in each complex. The order of paralogs along the chromosome is preserved in the four complexes. The genes within a complex are transcribed in the same direction and are numbered according to their paralog group from 1 at the 3' end to 13 at the 5' end. In several cases a representative of a paralog group is absent from a complex, in which case the corresponding gene number is omitted …

HOX genes are key to the development of the embryo, it creates the head to tail and sets up the control of the development of the organs. As Lohmann and McGinnis report:

Hox genes play a major role in the morphological diversification of the anteroposterior body axis of animal embryos by switching the fates of segments between alternative developmental pathways . In their role of controlling segment diversity, Hox proteins are responsible for many different morphological structures and cell types within a given segment. But it is still largely a mystery how a single Hox gene can determine a morphological trait at a specific location within

a segment, and why that trait does not appear elsewhere in the same segment or in other segments.

… morphological and transcriptional responses to Hox genes can be highly local, sometimes only in a single cell, allowing one Hox gene to control a cavalcade of different traits within one segment and between different segments, depending on the information present. Another important lesson that we can learn from the papers of Rozowski and Akam and Brodu et al. is that, during development, Hox genes act at all levels in the developmental hierarchy.

If they act very far down in the hierarchy, as in these two cases, then the output is subtle, with Hox genes acting as cell-type switches rather than as major developmental pathway switches. If they are acting (apparently) far up in the hierarchy, then the fate switch is more dramatic, which is most beautifully demonstrated in the famous four-winged fly. But even at this general level, context is still crucial: loss of Ubx in the haltere does not generate a leg, but a wing.

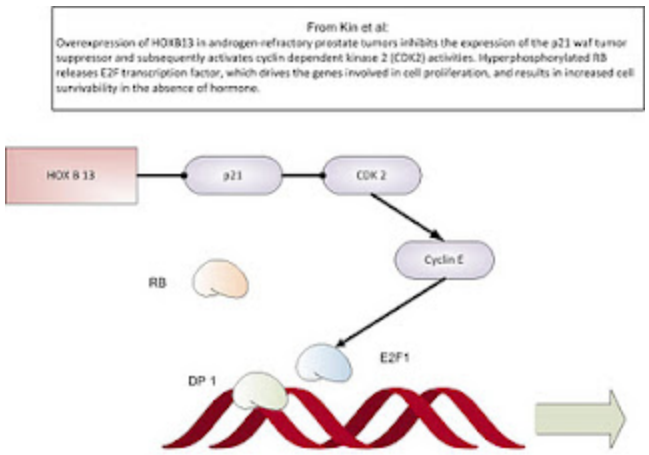
There are many debates still raging regarding Homeobox and Robert presents an interesting report summarizing some of them. His paper is worth the reading. It builds on the evo-devo issue, evolution and development, the ontogeny recapitulates ontogeny. Namely if the same HOX genes are present across many species, and preserved in structure, then is there really an underlying commonality across species.

We provide the details on the various HOX genes below. They all have the form as we had shown earlier and they are all numbered in a sequence consistent with what we have shown earlier.

Type	Location	Genes Produced
HOX A	chromosome 7	HOXA1, HOXA2, HOXA3, HOXA4, HOXA5, HOXA6, HOXA7, HOXA9, HOXA10, HOXA11, HOXA13
HOX B	chromosome 17	HOXB1, HOXB2, HOXB3, HOXB4, HOXB5, HOXB6, HOXB7, HOXB8, HOXB9, HOXB13
HOX C	chromosome 12	HOXC4, HOXC5, HOXC6, HOXC8, HOXC9, HOXC10, HOXC11, HOXC12, HOXC13
HOX D	chromosome 2	HOXD1, HOXD3, HOXD4, HOXD8, HOXD9, HOXD10, HOXD11, HOXD12, HOXD13

Note all HOX B are from Chromosome 17. In particular HOX B 13 is 17q21-22 region (see http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=retrieve&dopt=default&rn=1&list_uids=10481)

We now show from Kim et al the development of the pathway for the HOX B 13 that we have been discussing. It inhibits CDK and that in turn inhibits the activation via E2F of the cell cycle. It is the inhibition of the cell cycle that is of the most concern.



As Kim et al demonstrate the HOX B 13 blocks p21 and in turn CDK2 keeping the RB pathway from entering the cell into cell cycle reproduction. They state:

Taken together, the results of this study demonstrated the presence of a novel pathway that helps understand androgen-independent survival of prostate cancer cells. These findings suggest that upregulation of HOXB13 is associated with an additive growth advantage of prostate cancer cells in the absence of or low androgen concentrations, by the regulation of p21-mediated E2F signaling.

Now Ewing at al conclude as follows:

In summary, we have used linkage analysis in combination with targeted massively parallel sequencing to identify a recurrent mutation in HOXB13 that is associated with early-onset and hereditary prostate cancer. From a clinical perspective, testing for germline mutations in BRCA1/2 is recommended in some families, since mutations in these breast-cancer–susceptibility genes are associated with elevations in the risk of prostate cancer, particularly for BRCA2 However, neither of these genes has been shown to contribute to hereditary prostate cancer. HOXB13 G84E is associated with a significantly increased risk of hereditary prostate cancer.

This work suggests that future DNA sequencing studies using next-generation technology and study populations enriched for genetic influence (as evidenced by an early age at onset and positive family history) may identify additional rare variants that will contribute to familial clustering of prostate cancer. Although HOXB13 mutations will be identified in a minority of men with prostate cancer, rare genetic lesions can identify pathways that are found to be abnormal in more common, sporadic cases.

This leaves one to somewhat guess as to how prevalent this mutation is. The rough numbers given in the Weing paper is about 1.5%. It also begs the question of why as a mutation which is apparently inherited the progression of the cancer is so slow. Ewing at al show that the odds ration can be as high as 32.5:1 when the mutation is present. The age at diagnosis is lower with an odds ratio of 2:1 but with the problem one sees in pathway control one wonders why the cancer does not appear much earlier as seen in BRCA.

Thus this paper raises several questions:

1. The Homeobox mutation is a predisposing genetic risk factor. If tested and found positive for the factor what should be done next. Mastectomy is often what BRCA patients undergo, does this mean prophylactic prostatectomy?

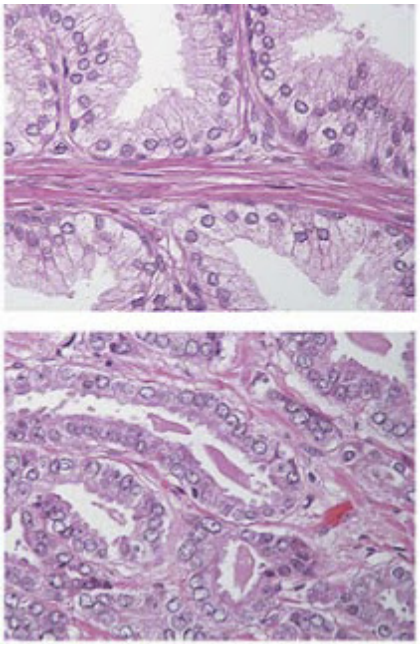
2. The pathway seems to be somewhat understood. The E2F family control the pathway and HOX B 13 controls that pathway. It blocks it to some degree. What can happen to HOX B 13 to cause this change in non-mutated individuals.

3. Can the disease propensity be regulated by genetic pathway control, is this possible as an alternative prophylactic measure.

4. What other pathway elements should be considered. Specifically, if we have a mutation on HOX B 13 then must we have other genes also altered to up surge cell replication. If so which ones. Is HOX B 13 merely a predisposing element. Also is there a HOX B 13 type change in other PCa?

5. Most importantly, why does it take so long for the cancer to develop, are there precursor hits somewhere and this this just eliminates other hits?

Ewing et al have an interesting slide showing normal versus HOX B 13 prostate cells and we replicate it below from the paper.



In the top slide we see well-structured prostate cells with basal and luminal layers not showing and aberrant growth, no PIN. In the slide below from a HOX B 13 patient with a mutation of the form: GGA to GAA Glycine Glutamic acid (See Ewing et al).

References:

1. Ewing, C., et al, Germline Mutations in HOX B 13 and Prostate Cancer Risk, NEJM, Jan 2012 V 366 N 2 pp 141-149.
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Labels: Cancer

HEALTH CARE COSTS

Yesterday the NY Times Editorial praised the low rate of health care costs this year.

They stated:

The data show that total health care spending by public and private sources, including households, rose by 3.8 percent in 2009 and 3.9 percent in 2010. Spending slowed for hospital care, physician services, nursing homes, home care and especially prescription drugs, as consumers increasingly chose cheaper generics. Growth in spending by both Medicare and Medicaid actually slowed in 2010 compared with 2009, even though the federal government ramped up its share of the nation's total health care spending while private businesses reduced their share.

Yet today HHS touts its use of the new act to dampen excessive Health Care costs. It states:

Health insurance premium increases in five states have been deemed "unreasonable" by the U.S. Department of Health and Human Services, ...After independent expert review, HHS determined that Trustmark Life Insurance Company has proposed unreasonable health insurance premium increases in five states—Alabama, Arizona, Pennsylvania, Virginia, and Wyoming. The excessive rate hikes would affect nearly 10,000 residents across these five states. In these five states, Trustmark has raised rates by 13 percent. For small businesses in Alabama and Arizona, when combined with other rate hikes made over the last 12 months, rates have increased by 27.2 percent and 18.1 percent, respectively. In addition to the review of rate increases, many states have the authority to reject unreasonable premium increases. Since the passage of the health care reform law, the number of states with this authority increased from 30

to 37, with several states extending existing "prior authority" to new markets. Examples of how states have used this authority include:

- *In New Mexico, the state insurance division denied a request from Presbyterian Healthcare for a 9.7 percent rate hike, lowering it to 4.7 percent;*
- *In Connecticut, the state stopped Anthem Blue Cross Blue Shield, the state's largest insurer, from hiking rates by a proposed 12.9 percent, instead limiting it to a 3.9 percent increase;*
- *In Oregon, the state denied a proposed 22.1 percent rate hike by Regence, limiting it to 12.8 percent.*
- *In New York, the state denied rate increases from Emblem, Oxford, and Aetna that averaged 12.7 percent, instead holding them to an 8.2 percent increase.*
- *In Rhode Island, the state denied rate hikes from United Healthcare of New England ranging from 18 to 20.1 percent, instead seeing them cut to 9.6 to 10.6 percent.*
- *In Pennsylvania, the state held Highmark to rate hikes ranging from 4.9 to 8.3 percent, down from 9.9 percent.*

So which of the two comments is true. And a better question is why the difference.
Labels: Health Care

WEDNESDAY, JANUARY 11, 2012

FREE WILL, PREDESTINATION, AUGUSTINE AND OBESITY

Augustine of Hippo in his attack on Pelagius, the British monk who alleged that man has free will and thus can do good acts and achieve salvation, restructured the concept of free will and introduced the concept of grace and perforce led the way to predestination. Simply man cannot achieve salvation unless God grants him individually grace and then his salvation is preordained since he cannot do anything which would then mitigate that end result.

What is the will and what do we mean by free will? Both have significant philosophical and theological facets and understandings.

Augustine fought Pelagius and to do so he had need of clarifying two elements; free will and grace. Now the will was well discussed in philosophical literature with Aristotle expanding upon it in Nicomachean Ethics. The concept of grace as a facilitator was a residual from Paul and his writings. The interaction of the two became a major factor in Augustine's thought.

Let me first begin with the concept of free will, or the will. In broad terms the will is the human element which allows the individual to make a choice, and in an sense as used by Augustine a moral choice. In contrast the ideas of Schopenhauer allows the will to be expansive and become an integral part of every human action. We will not look at the conjoined will of Schopenhauer but the more dualist will of Augustine. In our particular example the will to say no to a piece of cake or a serving of French fries.

Stump makes the following assessments regarding free will and Augustine (Stump, p 124, Augustine, Cambridge) which I shall paraphrase somewhat. She argues that there are at least two schools of thought regarding free will and they can be characterized as follows:

Compatibilism: The world can be causally determined yet a person can commit free acts with full moral responsibility.

Libertarianism: Consists of two claims:

(i) a person acts with free will only if the act is not causally determined by some exogenous agent, or:

(ii) a person acts with free will only if the person could have acted otherwise.

Stump adds a third form of a "Modified Libertarianism", it is defined as:

(iii) A person acts with free will only if their intellect and will are the sole determinants of the act.

In all of these cases the will is in many ways a dualistic forced, within the person, whereby the act they take is one amongst many yet this force allows the person to make a choice. The choice presented for selection one could argue have relatively equal compelling arguments, a possibly poor term but reasonable under the selection of having the intellect involved, for their selection.

Thus one may ask does a person who is "addicted" to say heroin have the free will to say no and eliminate that dependence? This would be problematic under many of the above definitions. However we know by experience that people can and do choose to stop drug use, tobacco use, even caffeine use. People stop consuming certain types of food, by choice. Thus is this not a clear example of free will. Yet we know that physiologically the drug addict finds the cessation a painful experience, the cessation of eating can also be physically painful and socially difficult.

Thus free will is part of the equation for Augustine. The other element is Grace, the "gift of God" to assist the will and the intellect in making the correct moral choice. Grace is needed according to Augustine because without it man is all too often prone to make the bad choice, read it evil or sinful. One must wonder whether this would apply to all things that the Augustinian will would be involved in, say eating a date versus a fig. But it is the need for this Grace that allows the will to act in a correct and moral manner. If God gives you grace then you can act accordingly, if God withholds grace then you cannot do the right thing, and for Augustine that would mean ever do the right thing.

Thus in the Augustine context one has a duality of body and will, a will which is fee, and a need for Grace to facilitate right choices. For Pelagius man could perforce of his fee will make those choices, and in a natural extension it would be via that free will per say that many passes or fails the acid test of living a moral life. To Augustine man needed Grace and thus God, by himself, with free will, he was still lost. Thus the Augustinian view of Grace is that being God given you need it to do truly good works, devoid of such good works one is lost, and God grants grace on

his own choices and thus one has the Augustinian basis for predestination, and the resultant Calvinistic views.

Now to obesity and genes. Instead of Grace we have genes, and instead of the free will to do right and wrong in a simply moral manner we have the will, assumed to be free, to eat or not eat. The current world view by many is in a sense an Augustinian extension of predestination, if you have the right genes you are fine and if not it is not your fault, the genes made you do it. Namely the strength of will alone is useless.

We need a Pelagius, we need the anti-Augustine to state that indeed man has free will, and that it is the will, in what may be a dualist manner, which can save us, genes notwithstanding. Pelagius may have had a point, albeit pushed to an extreme at the time. Pelagius recognized the power of the will for good and evil, the power of the will to select between what is good for one, albeit uncomfortable, and what is bad. Choosing is what makes humans somewhat unique. Understanding that was Pelagius' contribution. We should dismiss the Augustinian crutch of some exogenous factor which lets our free will take a back seat.
Labels: Health Care

TUESDAY, JANUARY 10, 2012

FRUSTRATION OF PURPOSE AND THE EPA

The NY Times has posted an article indicating that the EPA is fining oil companies for failure to include a bio fuel in gasoline when the bio fuel does not exist.

The article states:

When the companies that supply motor fuel close the books on 2011, they will pay about $6.8 million in penalties to the Treasury because they failed to mix a special type of biofuel into their gasoline and diesel as required by law. But there was none to be had. Outside a handful of laboratories and workshops, the ingredient, cellulosic biofuel, does not exist.

One wonders why the citizens have no faith or trust in their Government. Under standard contract law a contract is deemed null and void if there is a frustration of purpose, namely if for reasons beyond the control of the parties the agreement under the contract cannot be met. Classic English Law holds this principle to be a key element. One could see it evolving even from the Magna Carta and even Salic Law! But not in Washington.

Just wait until these characters get a hold of health care! Perhaps one should just die early and avoid the mess.
Labels: Government

PROTON THERAPY

A recent posting commented on the Emanuel piece which somewhat denounced the efficacy of the proton means of therapy for prostate cancer. Although proton therapy is less damaging than classic X ray therapy it has been problematic in prostate cancer, for a variety of reasons.

A recent study by Hoppe et al concludes:

Although the benefits to patients of reduced radiation-dose exposure with PT are quite obvious, concerns still exist regarding whether these dosimetric benefits are cost-effective. In a study by Konski et al,... the cost-effectiveness of PT was compared to that of IMRT with the assumption that PT could deliver a 10-Gy higher dose than IMRT, resulting in a 10% improvement in 5-year BFFS compared with IMRT. However, despite the improvement in BFFS, the resulting cost of PT for a 60-year-old man was $65,000, compared with $40,000 for IMRT, which would result in a cost-effectiveness of $56,000 per quality-adjusted life year (QALY). When compared to the commonly accepted standard of $50,000 per QALY, the value for PT indicated that it was not cost-effective. Although this study reaches some intriguing conclusions, the results are based on models and do not take into consideration a number of critical factors. First, Peeters et al... have predicted that PT may allow for hypofractionation, which would reduce the treatment costs of this therapy. Studies currently investigating hypofractionation with PT are ongoing at both Loma Linda University and the University of Florida Proton Therapy Institute. Second, a reduction in significant rectal and urinary toxicity afforded by PT will have a positive impact on overall costs of care in prostate cancer patients. Finally, the dose escalation and dose intensification via hypofractionation permitted by PT may result in increased cure rates, particularly in intermediate and high-risk prostate cancer patients,... which may also translate into reduced costs of care.

Namely it is a costly procedure. This has always been a concern. Proton machines are tens of millions, approaching in excess of 100 million, and thus are often prohibitive. They work well for certain childhood malignancies and in uveal melanomas of the eye. However there are still major clinical concerns.

The clinical conclusions of the paper state:

With a minimum follow-up of 2 years, the grade > 3 GU toxicity rate was 1.9% and the grade > 3 GI toxicity rate was <0.5%. Two studies out of Japan have also published early outcomes for PT for prostate cancer. Mayahara et al reported on 287 patients treated to 74 CGE with 190- to 230-MeV protons using opposed lateral fields; the rate of grade > 3 GU toxicity in this study was 1%, and the rate of grade > 3 GI toxicity was 0%. Nihei et al[30] reported on a multi-institutional phase II study from Japan in which 74 CGE was delivered in 37 fractions in 151 patients. With a median follow-up of 43 months, only 1% of patients developed grade > 3 GU toxicity, and 0% developed late grade > 3 GI toxicity. These studies, which are reported in the Table, confirm the safety of PT for prostate cancer over the first 4 years following treatment; however, longer follow-up is needed to confirm the low rate of late toxicity and long-term efficacy of the treatment (and the high rate of BFFS). Interestingly, Massachusetts General Hospital and Loma Linda University have reported a smaller series of patients treated with PT alone to 82 CGE, with a slightly higher rate of toxicity than observed in the University of Florida Proton Therapy Institute series with the same dose and dose per fraction.

It appears as if there is still an open issue here. More clinical trials are needed. Yet the clinical progress seems to be moving forward.
Labels: Cancer

COLLEGE, FOR WHOM?

There has been a great deal of discussion regarding the usefulness of college. Now from a personal perspective let me comment:

In June 1971 I got awarded a few doctoral degrees, in real stuff. However in the spring of 1971, for example, there were no job interviews at MIT and Harvard Med were sending grads still into the military. It was Vietnam. Furthermore there was no money for anything near research and Nixon just took us off the gold standard. So today is wonderful compared to June 1971.

But alas I had a plan B. I was thanks to my father an electrician. I could work with my hands, install circuits, switches, motors, etc. I had a skill and moreover my father now had a company that did electrical work on explosive sites, BU Gas and Exxon. Thus I had a job! Not in EE, medical research, just working with my hands, and yes head, and with a salary.

But upon telling the MIT faculty of my career movement I found myself back on campus teaching, I believe at $8,000 pa! I was making at the time, I believe, $50 per hour on my non-union electrician job. But back I went, remembering that if all else failed I could go back again, thanks to dad. The two rules he instilled in me were: (i) always have your own company and (ii) always have a skill which can be monetized, namely people are willing to pay you because you can do something of value. Plumbing, carpentry, electrician.

Thus this need for college for everyone is a total waste. There are more than 10 times the number of PhDs at MIT now than when I was there. Are there 10Xs the number of competent people, doubtful but there are clearly NOT 10X the number of jobs. And not one electrician in the bunch!
Labels: Academy

BUSINESS AND ECONOMICS

Krugman has written a piece asking why anyone would think a person who is successful in business has any skills as an economist.

He pontificates as usual:

For the fact is that running a business is nothing at all like making macro policy. The key point about macroeconomics is the pervasiveness of feedback loops due to the fact that workers are also consumers. No business sells a large fraction of its output to its own workers; even very small countries sell around two-thirds of their output to themselves, because that much is non-tradable services.

For years I had a sign:

"If all else fails listen to the customer!"

Talk of feedback! No matter how good you are customers must buy the stuff you make. As a business man you see the effects of your policy real time and you understand feedback better than any economist!

Ever hear of a Board dumping an economist! Just look at the overload at universities and the government. Just look at Romer, she stated that the Stimulus would do X and it did A. Fired, not really, writes on economic policy at the times.

I am a Darwinian and Spenserian at heart, survival of the fittest. Business does that, it tests the market and ones ability to respond to it. Now I do not include bankers here, in fact after the past few years I exclude them. The only thing that can get a banker fired it appears is saying the wrong thing about the administration, or really being away from the switch.

Krugman does not seem to understand business. It is not some Asmovian world, it is a market, a place where one can succeed or fail, depending on both your performance and the response to the market in toto.

Would I want some MIT Aero Prof who may understand the theory at the stick of a supersonic fighter in a dog fight, not likely, unless they flew for the Israeli Air Force perhaps, and I have met a few, but at least the Aero Prof knows how to design a plane. It appears that there is no such ability or consensus amongst economists. Thus the Krugman argument is without any merit. As usual it appears.
Labels: Economics

TUESDAY, JANUARY 10, 2012

THE COST OF THE ACADEMY

TNR has an article suggesting ways to reduce the burden of college costs.

In the midst of the article the author states:

This is essentially the story of public higher education over the last thirty years. Diplomas are, of course, not apples. But they are more like apples than colleges like to pretend. In particular, highly-profitable lower division courses in common subjects like Economics, Calculus, and Psychology have similar curricula at most colleges and rely on many of the same nationally-

marketed textbooks. ***They are often taught by people with no formal training in teaching. These courses are, in the education context, commodities.***

The last statement is typical of the union backing left wing of the Democrat Party. Namely that only by being trained to "teach", aka being in a union, can you teach. Nonsense! Universities often use their best faculty to teach the under graduates, at least the top universities. Yes they have TAs and Instructors who are PhD candidates but hospitals also have residents.

A hospital resident is a licensed physician, albeit one still in training, who is legally allowed by the state to practice, not by a union. A TA may very well be a PhD candidate, one who has a Master's Degree and has passed doctoral Board exams demonstrating exceptional competence.

Now a union high school teacher has allegedly learned teaching methods but may very well be clueless as to the subject matter. And worse is in a union. Imagine Harvard becoming GM! It may also go bankrupt. In more ways than one.
Labels: Academy

SUNDAY, JANUARY 8, 2012

THE REJECTION OF THE WILL AND THE CREATION OF THE VICTIM

The victim, the creation of our current society, is the person who through their own overt actions has found themselves in a bad situation and demands the rest of us bail them out. Drugs, bad school choices, homes they cannot afford, and of course obesity.

The NY Times epitomizes this today with an article on childhood surgery for obesity. They state:

There was no question, at 5-foot-1 and more than 250 pounds, she was overweight. But she resisted, saying she could diet. "I'll lose weight," (the patient) assured her doctor. (The doctor) said, prophetically, ***"It's not your fault, but you're not going to be able to do it."****Along with the obesity epidemic in America has come an explosion in weight-loss surgery, with about 220,000 operations a year — a sevenfold leap in a decade, according to industry figures — costing more than $6 billion a year.*

The article continues:

The operation took about 25 minutes. Child Health Plus, a state insurance plan for low-income families, covered the ***$21,369 cost. Medicaid in almost every state and many private health plans now cover bariatric surgery****, often more readily than diet or exercise plans. On many days, (the surgeon) performs three or four operations in a row.*

The cost is not Medicaid, it is the taxpayer, that 50% of the working force who pays for the rest of the workers and those not working.

The above two statements; (i) it is not your fault, (ii) Medicaid pays ... $21,369, reflect the

problem as it is posed. No responsibility and not understanding who really pays.

The irony is that in Mankiw's blog today he refers to his Pigou tax as as a way of saving lives with regard to drinking and driving. Yet a year ago he rejected the same out of hand regarding a carb type tax. Mankiw highlights:

A conservative estimate is that the federal tax reduced injury deaths by 4.7%, or almost 7,000, in 1991.

When the above highlights $6 B in costs due to an ever increasing tax burden. One could argue about the analysis referred by Mankiw as possibly flawed, it regresses on the amount of alcohol consumed but there clearly are multiple other factors as well, but with obesity the number are clear.

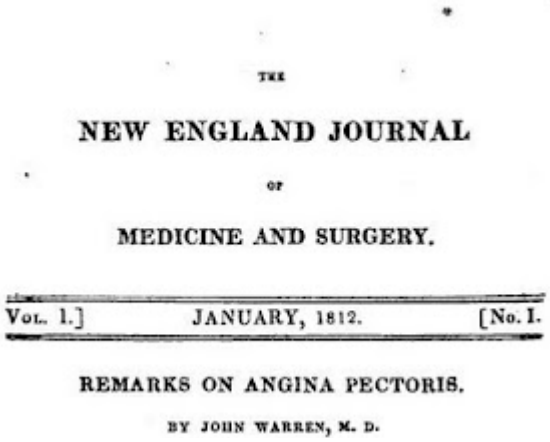
Obesity is the driving factor in health care costs. Stories as the above clearly demonstrate that we would rather pay exorbitant costs to solve it afterwards than prevent it. Here is a clear and direct case of a Pigou tax, one of the few I can believe in. Ironically the proponents of such taxes place them more freely on gasoline and alcohol, ones where it in my opinion are much more specious.

Finally the success of this surgery is highly erratic. Oftentimes the patient regresses back to the original state, after all they were told it was not their fault and there is no disincentive to reduce caloric consumption.
Labels: Health Care

FRIDAY, JANUARY 6, 2012

HAPPY BIRTHDAY NEJM

The New England Journal of Medicine celebrates its 200th anniversary this year. It is in many ways a main stay of American Medicine, and also from time to time a sounding board for health care policy, for better or worse.



THE

NEW ENGLAND JOURNAL

OF

MEDICINE AND SURGERY.

VOL. I.] JANUARY, 1812. [No. I.

REMARKS ON ANGINA PECTORIS.

BY JOHN WARREN, M. D.

The above is a copy of the first article in that first issue from NEJM. It is interesting to think that

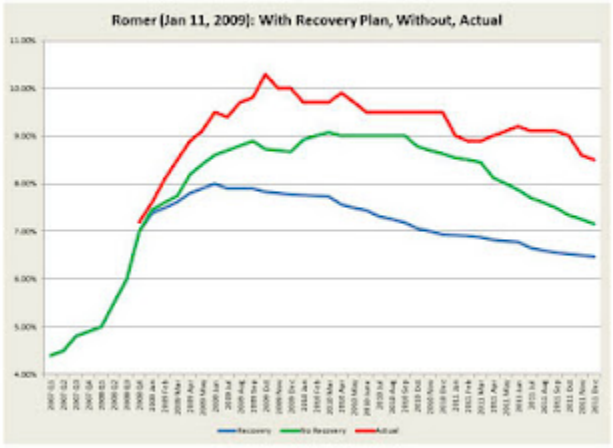
heart problems were the first to be discussed. Nabel and Braunwald have an interesting article detailing cardiology over this period. What is compelling about the article is Figure 1 which depicts an almost 80% reduction in heart death over this period. Yet the cost of achieving this has been substantial. In light of the current debates on health care costs one should look at this and consider progress versus costs.

As the authors state:

Until 1961, patients with acute myocardial infarction — if fortunate enough to survive until they reached a hospital — were placed in beds located throughout the hospital and far enough away from nurses' stations that their rest would not be disturbed. Patients were commonly found dead in their beds, presumably from a fatal tachyarrhythmia. Indeed, the risk of death occurring in the hospital was approximately 30%. The development of the coronary care unit, which provided continuous monitoring of the electrocardiogram, closed-chest cardiac resuscitation, and external defibrillation, reduced in-hospital mortality by half among patients admitted with acute myocardial infarction.

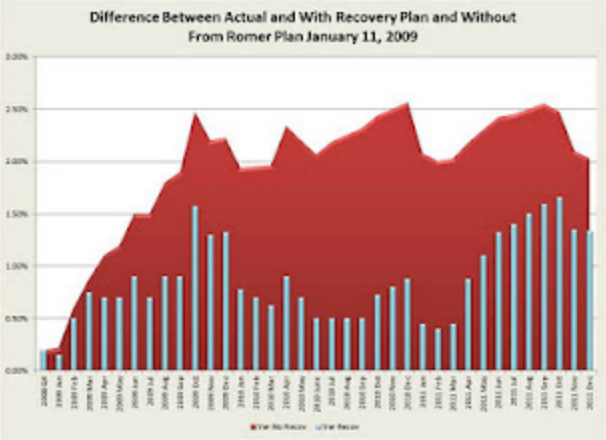
Was it better in 1961, for the costs were lower, or are we better off today. I would argue the latter, but there are some who believe the costs are excessive, until perhaps they become that 30%.
Labels: Health Care

EMPLOYMENT DATA END 2011

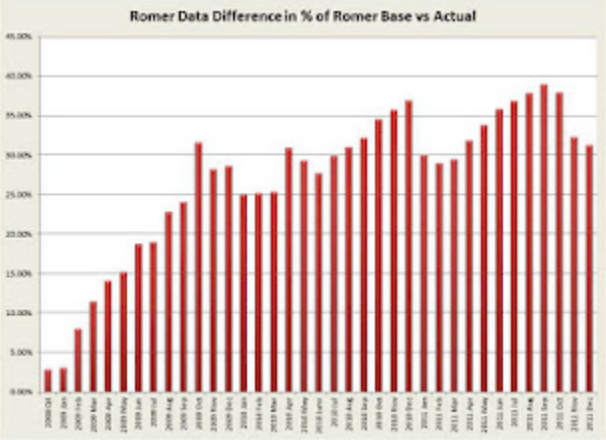


The BLS released its December 2011 employment data and their bottom line is 8.5%. However as always it is worth looking a bit deeper.

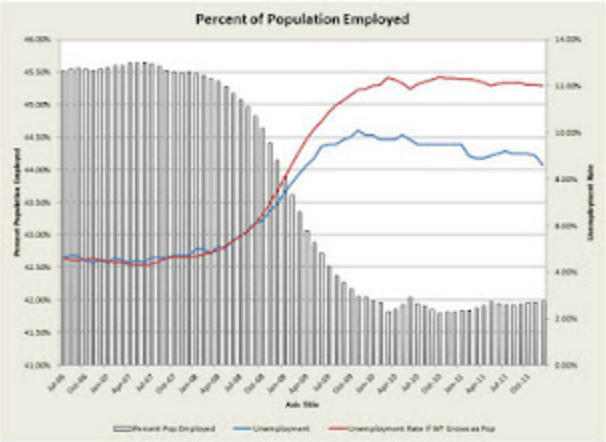
The curve above is the Romer curve. Now three years after she published her now infamous projections we can still see how far they are from reality. That is the problem of showing how little one knows as compared to reality.



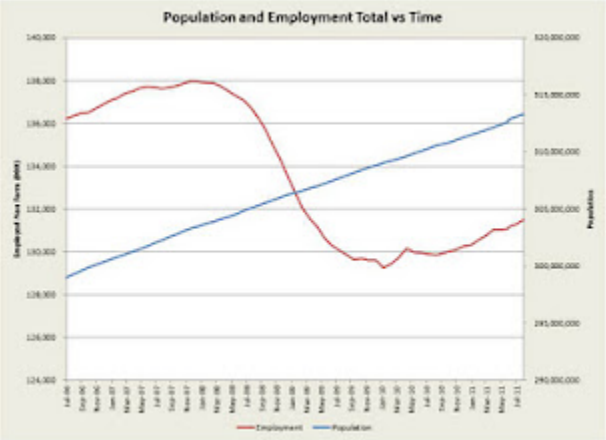
The above shows the variances from what she predicted with and without the Stimulus. Clearly the data shows that the Stimulus failed to do what she and the current Administration predicted. We show this again in detail below:



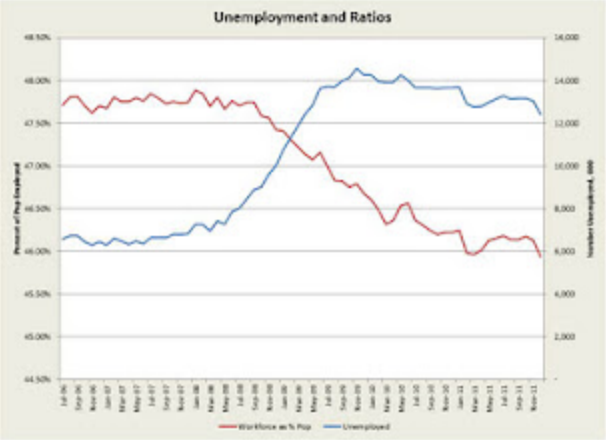
We now show below the unemployment as stated by BLS versus the unemployment as based upon July 2006 employment base.



The above shows we are still at 12% plus unemployment because we have lost so many from the base. In fact if one looks at the base line it has been flat for a year at 12% plus. The problem is that BLS seems to assume that all new people based on population entering the employment pool are never counted. In reality the population does grow.



The above shows the population growth and the pool employed. The pool employed is growing but not at the same as the population!



The above demonstrates what we have been saying in some detail.
Labels: Economy

THURSDAY, JANUARY 5, 2012

WATER IS WET! EATING TOO MUCH MAKES YOU FAT!

In a new paper in JAMA the authors conclude:

*Among persons living in a controlled setting, **calories alone account for the increase in fat**; protein affected energy expenditure and storage of lean body mass, but not body fat storage.*

Holy Flying Cows, Batman! Calories have always been the determinant. This was funded as follows:

This study was supported in part by the US Department of Agriculture grant... and by funding from Louisiana State University.

We have observed that for generations. I am amazed that someone would fund this again and again, but it is the Federal Government and Agriculture at that. We all knew the conclusion. Is it any wonder that people are frustrated over Government and Health Care.
Labels: Health Care

WEDNESDAY, JANUARY 4, 2012

PATHWAY CLASSIFICATION OF MELANOMA

There is an almost daily set of markers for a variety of cancers which are announced often with great fanfare. However the markers may or may not have any true meaning. We have discussed this in a prior posting and there we discussed the work by Venet et al as summarized by DeTours:

The signatures' prognostic potential can then be tested instantly in genome-wide compendia of expression profiles for hundreds of human tumors, all available for free in the public domain. Besides stem cells markers, signatures linked to all sorts of biological mechanisms or states have been shown to be associated with human cancer outcome. Indeed, several new signatures are published every month in prominent journals.

But such correlations are not all that they seem. The accumulation of signatures with all sorts of biological meaning, but nearly identical prognostic values, already looked suspicious to us and others back in 2007. It seemed that every newly discovered signature was prognostic. We collected from the literature some signatures with as little connection to cancer as possible. We found, for example, a signature of the blood cells of Japanese patients who were told jokes after lunch, and a signature derived from the microarray analysis of the brains from mice that suffered social defeat. Both of these signatures were associated with breast cancer outcome by any statistical standards.

Namely DeTours and his co-authors seem to say that it is all too easy to get markers for almost anything. In the context of Dougherty and his work, one must have an underlying verifiable model for the process and then from that verifiable model one can attempt to ascertain what elements may have failed. Then and only then can one obtain truly prognostic determinants which in turn may lead to means and methods to reduce the disease state.

For example in just the recent past we have papers which have identified the following for melanoma:

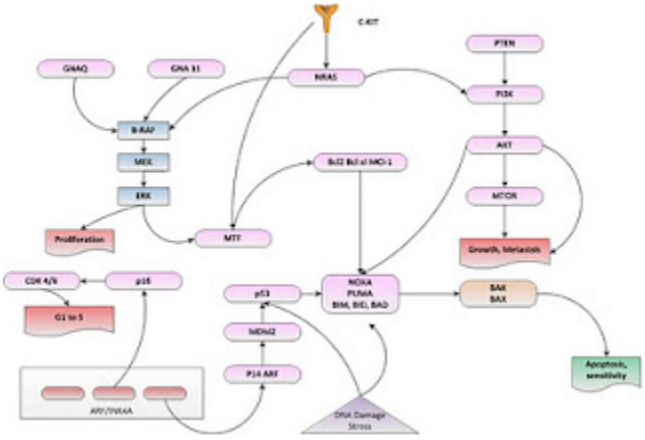
1. MAP2K1 and MAP2K2 mutations (Nature Genetics, 2011)
2. MAP3K5 and MAP3K9 mutations (Nature Genetics 2011)
3. ACP5 (Cancer Cell 2011)
4. The following complex (Cell Oct 2011):
a. A Sleeping Beauty screen followed by MuTaME analysis discovered putative PTEN ceRNAs
b. The PTEN ceRNA ZEB2 regulates PTEN in a miRNA-dependent manner
c. ZEB2 loss activates PI3K/AKT signaling and promotes cell transformation
d. Attenuated ZEB2 expression is found in melanoma and other human cancers
5. SNPs as reported at (Nature Genetics, 2011):
a. an SNP in ATM
b. an SNP in MX2 and
c. an SNP adjacent to CASP8 .
d. A fourth locus near CCND1 remains of potential interest,

And the list goes on. As DeTours states, it may be all too easy to find aberrant genes, and even more so SNPs, independent of specific pathway models. And as I have argued, just within a pathway one may have a concern because it is also the intercellular signalling that is a concern as well. Even more so is the understanding of the process. Specifically:

1. A melanocyte may be normal until something happens. What is it that happens, does a SNP occur, why, when, and then what happens after that?

2. If a SNP occurs is that during the development of a DNA reading for protein generation or during cell replication. The opening of DNA for transcription may be the event which places the melanocyte at risk. If so then what is the risk process. Could it be radiation as suspected, or is it the next step in a Vogelstein like progression. Namely there may have already been SNP damages and this one could be the final straw. Is it a micro RNA problem? The dynamics of this are essential.
3. Knowing pathways, is it possible to work backward and determine what the aberrant change or changes were? Pathway changes are reflected by their products.
4. What of the stem cell theory, must we look for the melanoma stem cell alone, and if so how can we identify it. The stem cell communicates, and that is a powerful mechanism to spread the cancer. How does it communicate and how is that related to the pathway.

Thus we look to understanding cancers in the context of pathways and then in the context of their intercellular pathways as well.



Understanding the pathway dynamics of melanoma has been progressing fairly well over the past few years. In a recent paper by Vidwans et al, the authors develop an interesting classification of melanoma based upon the specific pathway elements which may go awry. This is one of the first such classifications which goes beyond the classic morphological approach and even those using cell surface markers, This methods now looks at the cell dynamics and examines the malignancy based upon what specific pathway elements have failed. We show the pathway model used in the Vidwans paper above.

The now somewhat well understood B-RAF mutation, namely the V600E and discussed in the paper by Chapman et al:

Approximately 40 to 60% of cutaneous melanomas carry mutations in BRAF that lead to constitutive activation of downstream signaling through the MAPK pathway.10,11 Approximately 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (BRAF V600E), although other activating mutations are known (e.g., BRAF V600K and BRAF V600R).

As Chapman et al state they have an inhibitor of the mutated B-RAF as follows:

Vemurafenib (PLX4032) is a potent inhibitor of mutated BRAF. It has marked antitumor effects against melanoma cell lines with the BRAF V600E mutation but not against cells with wild-type BRAF. A phase 1 trial established the maximum tolerated dose to be 960 mg twice daily and showed frequent tumor responses. A phase 2 trial involving patients who had received previous treatment for melanoma with the BRAF V600E mutation showed a confirmed response rate of 53%, with a median duration of response of 6.7 months.16 We conducted a randomized phase 3 trial to determine whether vemurafenib would prolong the rate of overall or progression-free survival, as compared with dacarbazine.

As Bankhead states:

Patients with metastatic melanoma had an "astounding" 63% reduction in the risk of death when treated with an investigational agent that targets a mutation found in about half of the tumors, data from a large international trial showed.

Treatment with the BRAF inhibitor vemurafenib improved progression-free survival (PFS) by 74%. Analysis of six-month overall survival (OS) showed a 20% absolute difference between patients treated with vemurafenib versus dacarbazine.

Though follow-up is brief, the results already make a case for vemurafenib as the comparator for future trials of new agents for advanced melanoma, Paul. B. Chapman, MD, of Memorial Sloan-Kettering Cancer Center in New York City, said at the American Society of Clinical Oncology meeting.

"The median follow-up was only three months, yet the hazard ratio for death was 0.37 in favor of vemurafenib," Chapman said in an interview with MedPage Today. "That's an astounding difference that is almost never seen in oncology trials."

From 40% to 60% of cutaneous melanomas have BRAF mutations that activate downstream signaling through the MAP kinase pathway. About 90% of the mutations involve a specific substitution at codon 600 (BRAF V600E), Chapman and co-authors wrote…

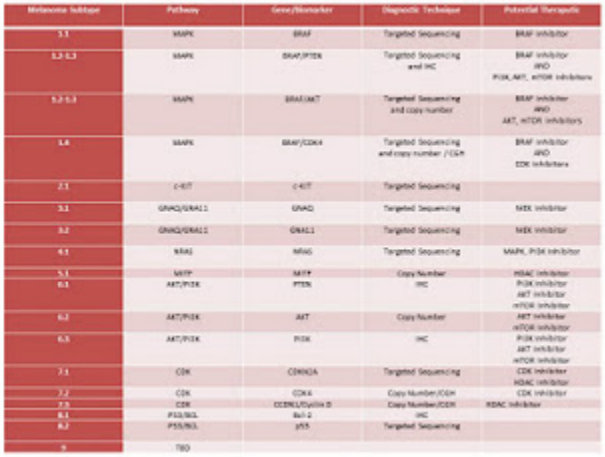
The above demonstrates how understanding pathways we can target pathway drugs to mitigate the progression of the disease. However progression free survival is of limited duration. The cancer cell finds alternative paths to mutate. Thus the question is does one target one path after another as they progress or try a multi mix cocktail in hopes of preventing the development of any new paths. Is it possible, for example, to stop the transcription of melanocytes all together, and thus stop any and all expression so as to silence say all pathways.

In another piece Bankhead states the cost issues:

Vemurafenib has an estimated cost of $56,000 for a six-month course of therapy, and ipilimumab costs about $120,000 for four weeks of treatment. Both drugs also have potentially serious adverse effects. In approving ipilimumab, the FDA cautioned that the drug has been associated with severe adverse effects that have included "severe to fatal autoimmune reactions."

The problem is that although the results are highly favorable for the short term, approximately six months, the long term is still questionable. It may be like imatinib and CML, namely there is a change in the cancer stem cells allowing a work-around of the blockage. Thus the costs would be considerable. Also the use of multiple drugs may as in leukemias result in "cures". However the above costs, which may be at $20,000 per month of life extended, are excessive. The quality of life extended may not be the best and the drug while providing a "benefit" has not truly changed the end state, namely death of the patient. It has merely delayed the inevitable.

The issue of drugs, pathways, and targeting a sustainable remission is more than likely the target. As one has seen in many childhood cancers the goal of a sustainable remission is achieveable with cocktails of drugs and perhaps such may be the case here as well. Vidwans et al refer to their web site (see http://mmdm.cancercommons.org/ml/index.php/A_Melanoma_Molecular_Disease_Model) which provides a superb interactive asset for linking pathway elements, disease stage, trials and specific modalities for possible mitigation and control. The Table below is a modified version of the Vidwans table taken from their paper.



Now in contrast we have seen, as previously indicated, many papers where we have been presented with prognostic markers for melanoma and its development. Yet none seem to develop and verify them in the context of an underlying system model. The above mentioned work of Vidwans et al seems to be one of the first to commence that effort.

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2. Bankhead, C, Melanoma Survival Benefit Called 'Astounding' MedPage; http://www.medpagetoday.com/Oncology/SkinCancer/30413
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Labels: Cancer

TUESDAY, JANUARY 3, 2012

NEW THERAPIES: AND THEIR COSTS

Again the brother of the former White House Chief of Staff writes on health care and how it should be rationed, in his opinion. The discussion this time is on proton beam treatment of prostate cancer. He has a point worth considering but presents a conundrum as well.

In the NY Times he states:

The most promising option is a new approach called dynamic pricing. Medicare would pay more for proton beam therapy, but only for diseases that are proven to be treated more effectively by the therapy than by other forms of radiation. For cancers like prostate, it would pay only what it pays for the cheaper alternatives. But if studies were done showing that proton beam therapy was better than other treatments, the payment would go up. If no studies were done, or the new evidence demonstrated no advantages, then coverage would continue, but at the lower reimbursement.

Now this is a somewhat rational approach. Namely a new therapy comes along and it is expensive yet unproven clinically. However clinical tests to "prove" its effectiveness would require many years and many patients, depending on the desired end point. For example if death is the end point then one may have to test for say 10 years or more and then look at survival, especially when looking at prostate cancer.

This proposal may hit a brick wall when we start to look at many of the new genetically developed pharmaceuticals treating cancers. These have passed clinical three phase trials where efficacy has been proven but their costs are often monumental and the effectiveness may prolong life but a small amount. Thus will he then deal with these as the Brits, namely the QALY approach, and pay on some similar pari passu basis?

As they say, paraphrasing, the cost we will always have with us.
Labels: Health Care

TUESDAY, JANUARY 3, 2012

OBESITY, FAT, TASTE AND MISSING THE POINT

The Scientist had an article on fat, taste, an why we are seeing more obesity. Now one must always remember two things:

Input-Output = Net Accumulation

and

3500 cal = 1 pound

These are constants of nature. Eat too much and you get fat. Will power exists, especially in humans, delayed gratification has been around for years, forgoing the candy bar has been a cornerstone of good health, at least until now. Finding some exogenous factor other than ourselves to blame for the problem has become the status quo. It is the environment, genes, a disease, whatever. It never is our own weakness.

The Scientist states:

People the world over are getting fatter. Today more than one-third of adults in the United States are obese, and the rates in other industrialized countries are catching up. Obesity is no longer considered a condition particular to affluent societies—it has now spread to developing nations such as China and India, resulting in a global health crisis. According to the World Health Organization, 500 million adults worldwide are now obese, and this number is expected to climb well into the foreseeable future. Obesity is so problematic because it poses serious threats to personal health and well-being. Obese people are at an increased risk of chronic and potentially debilitating diseases such as cardiovascular disease and stroke, certain forms of cancer, type 2 diabetes, osteoarthritis, and asthma, among others. And the impact of obesity on an individual's work and family life can be far-reaching, affecting a person's employability, work productivity, and ability to pursue interests and activities of daily life.

All true, but, they continue:

A great deal of progress has been made in identifying the genes that may contribute to obesity. According to recent estimates, 135 different candidate genes have been linked with obesity and the eating patterns associated with it. Except for a handful of single-gene mutations that produce extreme obesity, the common, everyday form that we typically encounter on a city street probably reflects very modest contributions from each of a large number of individual genes.

It is NOT the genes fault. It is lack of will power period. Blame not the gene, blame the person. The gene approach is another excuse generating solution which results in more medication for a problem which really does not exist. They are just fat, so stop eating. A human can survive 90

days with water and no food, just burning their stores. So as a New Year's resolution, shut the mouth now.
Labels: Health Care

HEALTH CARE AND COMICS

Perhaps this tells more than was intended. Gruber from MIT has published a comic book explaining the new health care law of which he was allegedly a part of as advisor to the current administration. It may very well be the first hardcover $30.00 comic book ever.

The praise comes from the as expected corners of progressives and left wing elements from Massachusetts.

For a Bill exceeding several thousand pages being reduced to a comic book one wonders what has happened. After all we were told that one had to pass it to see what was in it, and alas it is a comic book after all.

I wonder if the rest of the MIT campus is doing the same, I retire and we get this, pity.
Labels: Health Care

ETHICS AND THE PRACTICE OF MEDICINE

In an editorial by Ezekiel Emanuel, the, in my opinion, erstwhile proponent of medical care limiting and rationing, in the Annals of Internal Medicine the author states regarding the recently released Ethics Manual for the members of American College of Physicians (ACP):

But then the ACP Committee elaborates a very significant obligation:

Physicians have a responsibility to practice effective and efficient health care and to use health care resources responsibly. Parsimonious care that utilizes the most efficient means to effectively diagnose a condition and treat a patient respects the need to use resources wisely. . . .

Most physicians were inculcated that ideal physicians are thorough, comprehensive, and exhaustive in their workups and treatments—and ignore costs in the process. Here is an authoritative medical body using such words as "efficient" and "parsimonious"—and without "qualifications"—to describe the ideal physician's practices. And to be sure it is not missed, this statement is placed in a "call-out" box. This is truly remarkable.

The issue here is the use of parsimony. Now one can interpret that in many ways. For example for lower back pain an MRI may not be the first step in determining the problem. Fifty years ago there was no MRI and the physician used their knowledge of anatomy to isolate the problem and recommend a course of treatment. And of course all too often an MRI finds what may require additional investigation which in turn is oftentimes costly and of no benefit. Parsimony in treatment may mean focus, focus, focus, but it could in the author's words mean cheap, cheap, cheap.

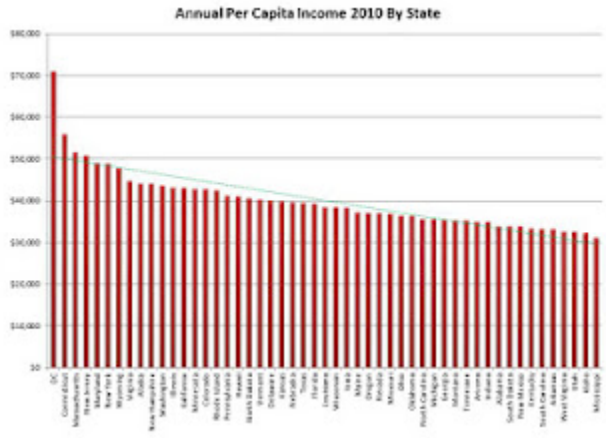
This may be the next step in the current health care debate.
Labels: Health Care

MONDAY, JANUARY 2, 2012

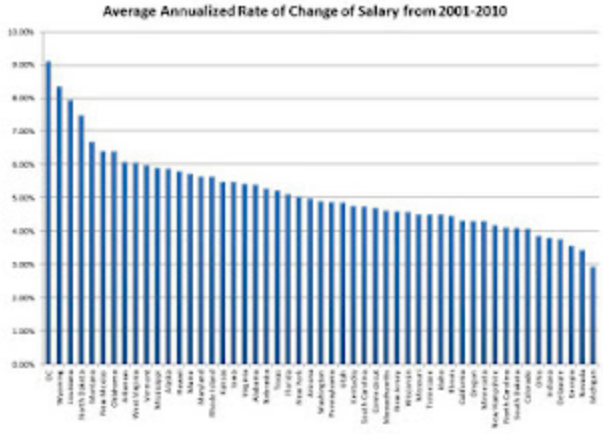
GUEST BLOGGER

Braeden Bottner has been a guest blogger today.
Labels: Commentary

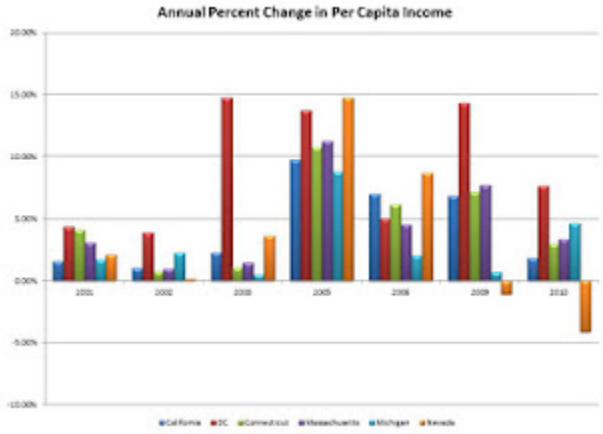
OBSERVATIONS ON INCOME



The above is a plot of per capita income by state, including DC. Talk of income disparity, look at DC, it is well above $70,000 per capita making it over $200,000 per HH! The now infamous 1%. Now one wonders why DC is worth this when at the bottom is Mississippi at $30,000 and near the bottom the next door state of West Virginia.



The above is the annualized rate of change averaged over ten years. Note again DC is well above 9% pa! Michigan is below 3%. The rate of income gap change with those growth rates is fantastic. Again the creation of the 1%.



Finally a year by year snapshot of the change, and again DC comes out ahead. Is there something wrong with this picture.
Labels: Economy