Obesity and Type 2 Diabetes: Cause and Effect

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Obesity and Type 2 Diabetes: Cause and Effect

By

Terrence P McGarty

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Preface

This work was written as a result of having read an editorial piece by Prof Mankiw of Harvard who was protesting the imposition of a carbohydrate tax on soda. I have been following Mankiw trying to understand him amongst the plethora of other macro economists with little luck because their theories seem to be top down, whereas science is often and essentially built from the bottom up, namely from facts. That approach all too often may put the two at odds.

What had become clear to me over the past decade was that for the most part, not always, and it is the not always that really provides scientific insight, was that Type 2 Diabetes was caused by obesity, obesity was caused by overeating, and specifically the overeating of carbohydrates. One could create a bottoms up synthesis from primary experimental work a model demonstrating that. To me it had become obvious. But as I replied to Mankiw it was clear that it was not obvious. Thus the need for this work.

This is not a medical book, not a scientific treatise, but it is a reasoned dissertation based upon primary research which explains what obesity, self imposed for the most part, is the single cause of Type 2 Diabetes, and that the cost of this is now in excess of 12% of our total health care budget and growing. If we hope to control health care costs we must address the issue of obesity. The total cost exceeds out energy costs! The CO2 produced starts to compete with auto emissions. This euphemistically is the 800 pound gorilla in the room. This book attempts to tie together the facts that are available in the literature today and effective demonstrate the problem and propose solutions.

To some degree one must abstract parts of what is available and look at the conclusions in the context of what the intent of the researcher was. For example we all too often see genetic causes for obesity. In reality humans have free will and society exists such that it can exert group influence in a Wilsonian sociobiological manner on the group. Namely we can tell obese individuals that their behavior has costs, that they are free to choose their behavior but that concomitant with their costs they must pay for them. This in many ways is the Pigou approach discussed by Mankiw.

This document started out as a White Paper, which it is as a draft issue. However we have seen that it can be expanded into a book form. The intended audience is the reasonably well educated but not necessarily technically proficient reader who can deal with abstracted reviews of somewhat complex ideas. This is not a medical text or a scientific dissertation on Obesity or Diabetes. It does rely upon primary research in parts to emphasize key points. It is our belief that using the primary sources allows the intelligent reader to return to them directly and read them in detail if so desired. It also establishes a basis for the development of our argument from the primitive facts available. Thus we have used secondary sources only in those areas where we believe that the knowledge is generally available and accepted. Where we drift from that is in establishing our reasoning that obesity is self inflicted, it is the primary cause of Type 2 Diabetes, and that the costs to our health care system is 12% of the total and growing as obesity itself expands.

This document is also an extension to the other works we have written on health care matters. Our book from last year, Health Care Policy, was written to allow readers to see what was good and not so good in the proposed health care law. Generally we are opposed to what was passed, not in principle but in the details of how it was implemented.

Our approach herein is to start with the assertion. as I understand it. by Mankiw that personal choice should be protected in what one eats, and that taxes on carbs, like to proposed soda tax is an invasion on personal liberty. Whereas Mankiw sees a Pigou tax on fuels, and other CO2 emitters as acceptable, albeit unlike carbs, there may very well be no alternative and the tax just take money from the economy which could be better put to use starting new businesses.

Our approach herein is that of a systems analyst, trying to establish questions and linkages and then validating the linkages with experimentally proven facts. Thus we are bottom up, fact based, in our assertions, relying on the proven results of others.

This is still a working paper and is subject to modification, expansion, and possible substantial change. However we believe that our logic and conclusions will stand.

Terrence P McGarty
Florham Park, NJ 07932
June 2010

1 INTRODUCTION

This document is in response to comments made by certain economists who contend that having some form of negative incentive on carbohydrates would have no effect on Type 2 Diabetes and it sequelae. We contend quite the opposite and in early 2009 we had prepared a report on the costs of Type 2 Diabetes and used the general consensus that the primary cause was obesity. The logical jump in that report required some filling in. This document attempts to accomplish that task.

This document attempts to establish a framework of logical steps which take the reader from understanding what obesity is and what its causes are to Type 2 Diabetes and what it is and how it relates to obesity as a prime driver. We then look at the sequelae of Type 2 Diabetes and then using data from the literature develop a cost model for the health care system as it deals with this sequelae.

Thus we address the following issues:

1. Obesity: What is it and what are its causes. We argue that the evidence is quite overwhelming that the simple cause in almost all cases is merely excess calories consumption. Is there a genetic correlation between obesity and the genes, apparently so, but the driver is increased calories consumption.

2. Type 2 Diabetes: What is it. We show that T2 Diabetes is simply a decaying ability to produce insulin.

3. Is Obesity a Cause for T2 Diabetes?: We show that the data is overwhelmingly there that there is a causal relationship.

4. What are the sequelae of T2 Diabetes: T2 Diabetes in and of itself is not the problem, it is what T2 Diabetes sets up as sequelae in the others specific systems in the body, from heart, to kidney, to eyes and almost everywhere. We details these and show the4 causal relationships, inflammation being one of them.

5. What is the incidence and prevalence?: There is significant data on the past and projections into the future for both the US and the rest of the world. It is clear that this is an epidemic.

6. What are the Costs? There are some studies which we have used before. We will rely upon them ad utilize them again in this analysis.

7. What Remedies can Reduce this Problem? The remedies are generally straightforward, lower caloric consumption. However how this end is accomplished is more problematic. Can the remedies also be economic remedies? We address this issue as well. If we look towards the Pigou approach we would tax the carbs as the primary cause of obesity which in turn is the primary cause of Type 2 Diabetes and its sequelae. However we also note

that taxes are negative drivers to the economy taking money from investments and having it spent by the Government in its redistribution agenda. Thus another alternative is a separate fund to pay for the sequelae. We believe that such a fund is possible and discuss it at length.

These are the issues we detail herein. There is o new results presented, this is a review of the existing literature with the intent to show reasonable causality.

1.1 THE BASIC ARGUMENT

Our overall argument is as thus:

1. Obesity is the primary cause of Type II Diabetes. True fact, you see Diabetes is a carbohydrate metabolism disorder. Type I is a result of an immune system attack and unavoidable, Type II is a personal choice issue, you eat too much.

2. Type II Diabetes causes a plethora of diseases, all chronic, and costs over $300 billion a year in 2010.

3. Obesity is a disease of choice, you choose the carbs, and like many other such diseases, it has costs, well defined costs, and these costs can be quantified on a per carb basis. Recall 3500 kcal per pound, and we can see that 30 gm carb yields 200 kcal. Thus 600 gm carbs is 1 pound.

4. We can now propose a carb tax which says that if your BMI is 2000 kcal per day, this means 300 gm of carbs, and anything is excess should be prorated to the $300 billion costs. Then the money raised should pay for the costs. Simple.

This is a real and simple example of an externality. It is akin to the Coase example of the railroad and the farmer. A fat person is fat because they eat too much. The major cause of that is carbs, not fats or proteins. The fat person chooses to do this act, like the alcoholic, cigarette smoker, drug addict, person afflicted with a sexually transmitted disease, these are all diseases of choice. They have well determined costs. In the current system the costs are distributed to those who choose not to behave as such.

In a fair system these people should be burdened with the costs of their behavior. There is a one to one quantitative nexus and thus there is a basis for a remedy. In a Coasian sense perhaps we should just create a class action suit and seek the remedy out of court[1]. Yet the transaction costs are too high and thus it is a Governmental issue.

Now some economists have compared such management of externalities with the Pigou Tax, and have applied it to CO2 emissions. First, people do not always choose to emit. There is no alternative. People choose to eat, there is a safe and health alternative, stop.

[1] We are strong believers in the Coase model in dealing with negative externalities. In the case of Type 2 Diabetes we can actually put a price on each carb and the resulting cost of care. This in many ways is unlike many other examples of such externalities especially the CO2 based ones.

Shut your mouth! You cannot say that to the poor person driving to work. What would you say, walk, stop working, find a new job in walking distance? How ignorant are you who proposes such a solution. Would such a person walk from Wellesley to Cambridge, doubtful!

In a recent opinion piece in the NY Times, Harvard based Professor Mankiw, a strong proponent of the Pigou Tax, which we believe is a negative and confiscatory tax, one which I have never understood, takes shots at the carb tax[2]!

Mankiw states:

There is, however, an altogether different argument for these taxes: that when someone consumes such goods, he does impose a negative externality — on the future version of himself. In other words, the person today enjoys the consumption, but the person tomorrow and every day after pays the price of increased risk of illness.

This raises an intriguing question: To what extent should we view the future versions of ourselves as different people from ourselves today?

To be sure, most parents have no trouble restricting a child's decisions on the grounds that doing so is in the young person's best interest. Few teenagers are farsighted enough to fully incorporate the interests of their future selves when making decisions. As parents, we hope that someday our grown up children will be grateful for our current restrictions on their behavior.

But people do not suddenly mature at the age of 18, when society deems us "adults." There is always an adolescent lurking inside us, feeling the pull of instant gratification and too easily ignoring the long run effects of our decisions. Taxes on items with short run benefits and long run costs tell our current selves to take into account the welfare of our future selves.

If this is indeed the best argument for "sin" taxes, as I believe it is, we are led to vexing questions of political philosophy: To what extent should we use the power of the state to protect us from ourselves? If we go down that route, where do we stop?

Taxing soda may encourage better nutrition and benefit our future selves. But so could taxing candy, ice cream and fried foods. Subsidizing broccoli, gym memberships and dental floss comes next. Taxing mindless television shows and subsidizing serious literature cannot be far behind.

No, I would disagree, this is not protecting us from ourselves. his is charging for the costs that a person will incur for their choice of behavior. Plain and simple. Who cares about mindless shows. This is almost 12% of the total health care costs. You are the one

[2] http://www.nytimes.com/2010/06/06/business/06view.html

wanting to tax gasoline for the poor guy trying to get from Milford, NH to his job in Norwood, MA.

He cannot afford a home in Norwood so he drives each day five hours. Or the guy in Allentown, PA who drives to Secaucus NJ to get the train. The good Professor does not give a tinkers dam for the guy creating value but screams for the porker getting a well definable free ride.

This is a simple back of the envelope calculation, real simple. It is what we engineers do each and every day. You macro economists cannot do it once in your lives, it appears. What amazed me is that Mankiw, if I interpret him correctly seems to reason as follows:

1. The Pigou tax is a valuable tool to regulate human behavior.

2. The use of gasoline for driving generates CO2 and that is bad behavior.

3. Tax gasoline and that should reduce bad behavior.

Thus far so good, except, the consumer has no replacement for gasoline and the tax is used to pay the Government and as such takes money from the economy which could be best put to use generating new jobs. We all know the Government is a poor allocator of resources.

1.2 SOME PREFATORY DETAILS

Now we look at what I believe Mankiw is saying about carbs. He seems to state that eating them and the consequences, obesity, Type II Diabetes and the sequelae are personal choices.

Yet again my logic:

1. Carbs cause Type II Diabetes

2. Type II Diabetes has a cost which is not paid for gets allocated to everyone and there is no incentive to reduce the created load on health care. The fatty gets a free ride, almost.

3. If one taxed carbs by a formula which collected the costs and then redistributed them to pay for the costs incurred, then there is no free ride. choice remains in the system, and health care for those complying is reduced accordingly.

My logic says vote against Pigou because it removes investment from the system and allocate costs to those who incur them. Simple, no?

Leonhardt of the Times responded to Mankiw and his rant about the unfairness of the soda tax[3]. I covered this gross misunderstanding of the principle of equity yesterday but in reading the comments to Leonhardt I truly believe in two things:

1. The public is becoming aware of this as an issue.

2. The public has no clue

and a side observation:

3. Leonhardt tried to do some numbers but he is way off. But I compliment him of doing what the economist fellow from Harvard should have done in the first place. Numbers do have some merit, especially if they are obvious and even more so if done on the back of an envelope.

You see if you are out trying to raise money as I have done many times for my own businesses in foreign lands, then when you make your pitch, you need eye contact, to assure the person on the other side that you know what you are doing, and even though you have all those power point slides they want to know that you know the numbers in your heart...they look at your eyes. The numbers have to be on the napkin, the envelope, whatever, but the numbers must be there. Mankiw did not do his homework...but alas even in his favorite book, he infrequently deals with the inconvenience of numbers, macro types so seldom do.

Leonhardt states:

A soda tax obviously would not solve the obesity epidemic. But it appears to be one of the most promising responses, given the central role that sugary drinks play in the epidemic and the fact that they have no nutritional benefit. A tax would also help reverse the big decline in the price of soda over the last few decades, at the same that the price of fruit and vegetables has been rising. Finally, as with a gasoline tax, a soda tax would help cover the broader costs that the product imposes on taxpayers.

But I use a simple metaphor. Let us assume you are an auto, a pickup, an 18 wheeler. You pay a tax on gasoline. But, as an 18 wheeler you also pay a road use tax. Your heavy loads wear out the pavement the rest of us drive on in excess of the gas tax you may pay.

Thus the heavy load 18 wheelers should pay a tax for their costs. Should we weigh people when they file a tax return each year, we already check their health care payment status, why not the weight, we already have invaded parts of the body, why not go for the gold!

I will detail the data on the soda tax issue somewhat more for those who may be unfamiliar. Just for those of you who have been following us, we did put a book up on the

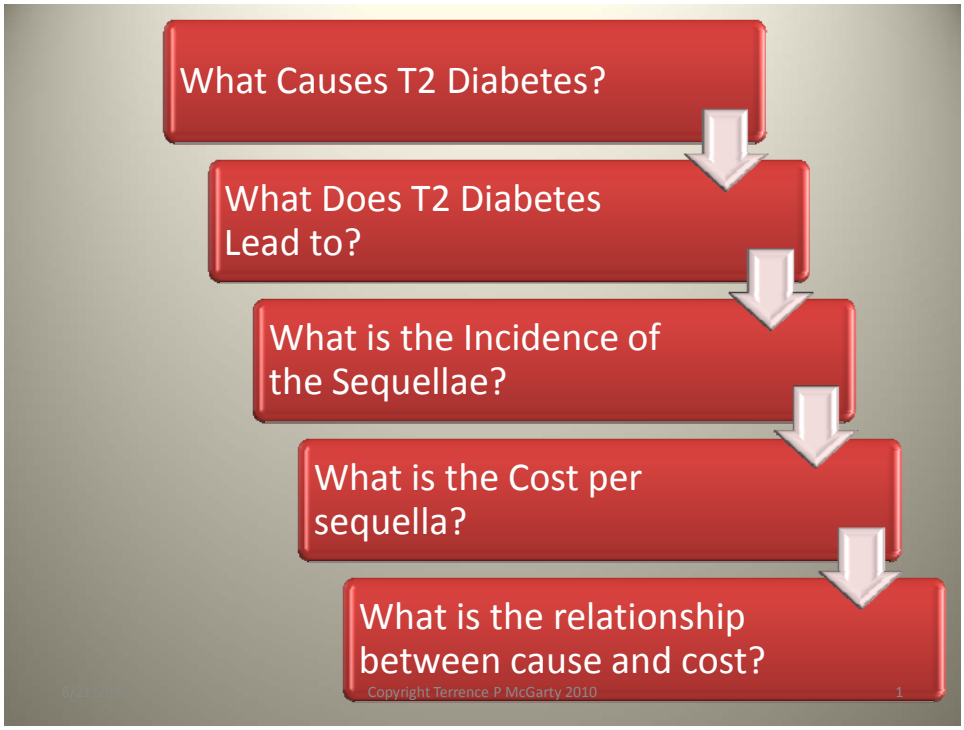
[3] http://economix.blogs.nytimes.com/2010/06/07/greg-mankiw-on-the-soda-tax/

web a year ago on Health Care Policy plus White Papers detailing the economics of Type 2 Diabetes and Obesity. But here we go again. Hopefully it strikes home. Also the slides on this discussion are available on our web site under Type 2 Diabetes and Obesity.

1.3 A PREFATORY STATEMENT OF COVERAGE

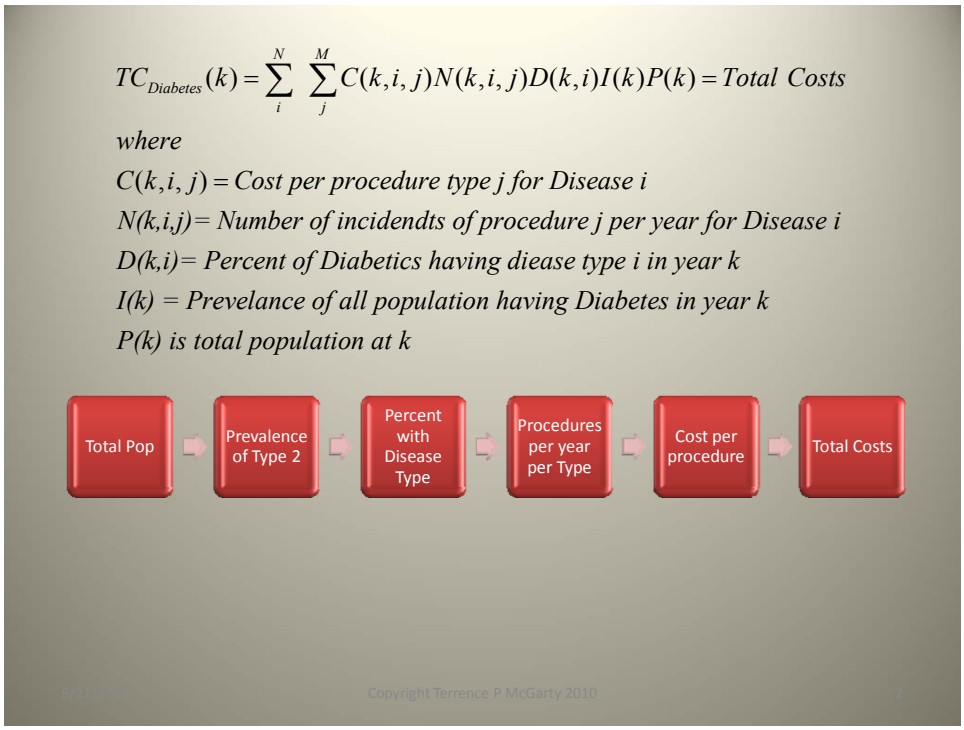
Let us begin the discussion by posing and answering several key questions and/or issues.

1. First we pose the major questions which we need to answer. This we show below. This list is what we are seeking to obtain answers to and we shall accomplish this via the primary clinical research literature.



The issue of what causes Type 2 Diabetes has been looked at by many and generally we all know it is a carbohydrate disorder, along with some lipid and protein issues as well, by as Banting and Best knew from the then clinical practice on Type 1 Diabetes, controlling carbs, near starvation, kept Type 1 patients alive, barely, but Type 2 patients could actually revert to normal if the BMI was brought below 22.5 early on in the disease.

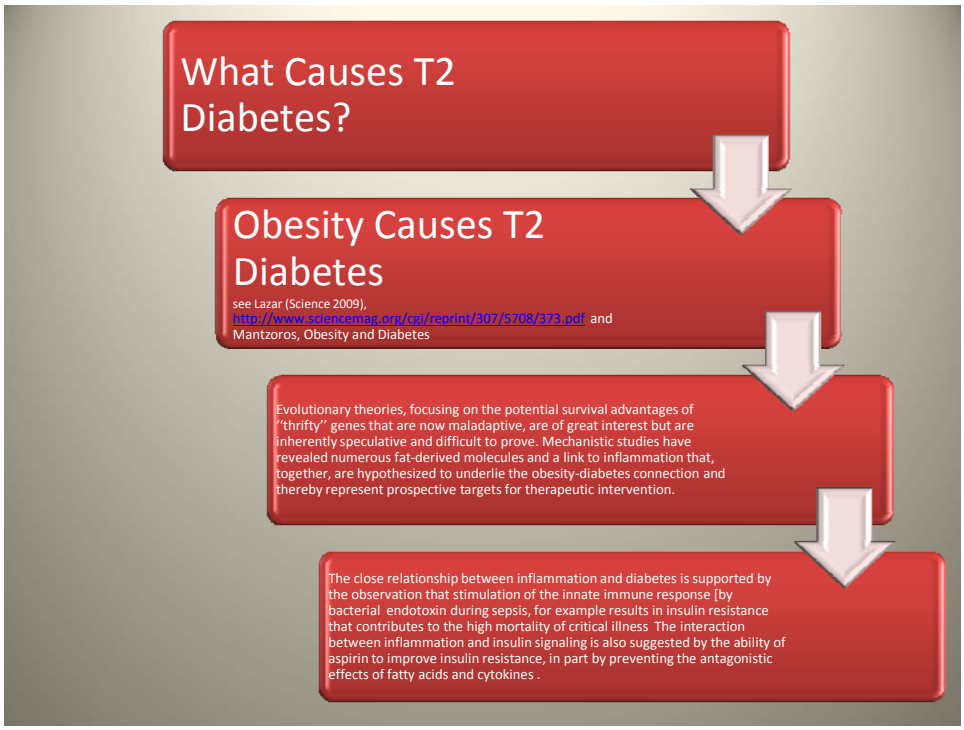
2. If we can answer the above questions then we can put them in a simple economic model for costing out the overall societal costs for Type 2 Diabetes. We summarize that below.



In the above model, which we shall come back to later in this document, is a simple and straightforward description of the sequelae and their costs. We know or can kow all the elements, they are readily available and the approach is a bottoms up approach.

So we can see what the incidence, and in turn prevalence is for T2 Diabetes and then add it to the model. Remember incidence is new cases and prevalence is total so we must add all the above up. Also one must remember that T2 sequelae are long lasting. Unlike lung cancer, where the patient frequently dies quickly, T2 sequelae patients may linger for years, well into the Medicare period as well.

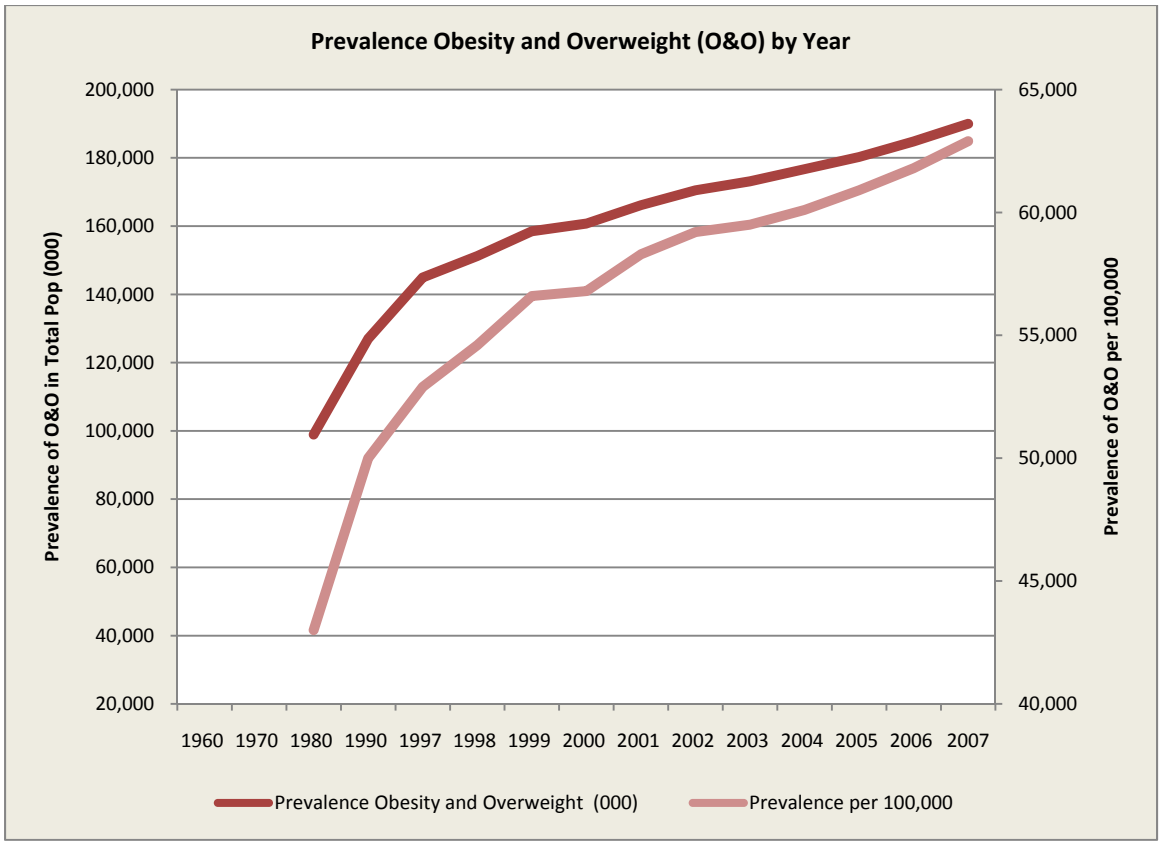
3. Obesity causes T2 Diabetes.



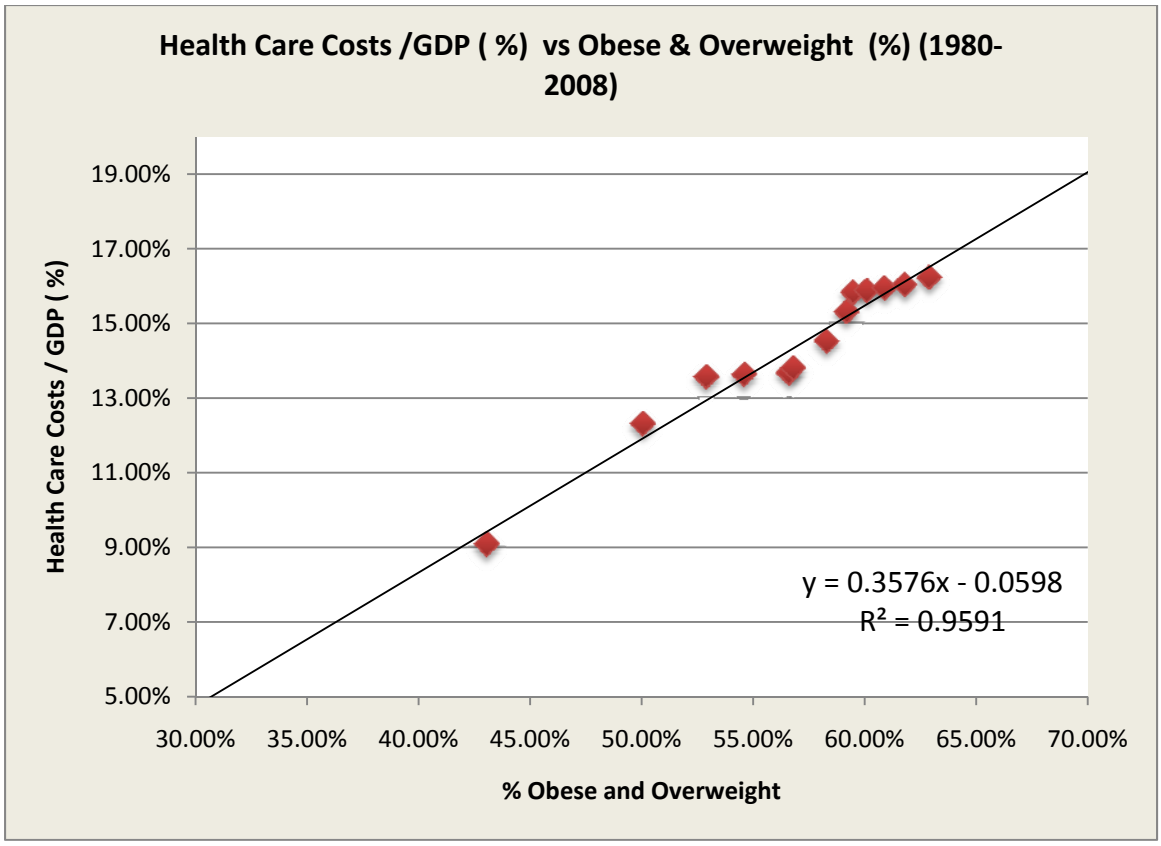
There are multiple papers and books with the latest summary being in Science in 2009 by Lazar. There may still be some rough edges to the analysis, but it is compelling, more so than almost all other studies. There is also the book by Mantzoros on Obesity and Diabetes which provides substantial data through 2005.

One may then ask what causes obesity, for the most part it is simply excess calories, but we will return to that. The answer of the nexus between obesity and T2 Diabetes is unquestionable, the details are a work in progress, and the literature is extensive. Clinically any physician in day to day practice dealing with T2 Diabetes is also confronting obesity. It has been that way for years.

4. The prevalence of T2 Diabetes is increasing significantly. We show the data below. Clearly the growth from 1070 shows the main driver between T2 Diabetes and obesity.



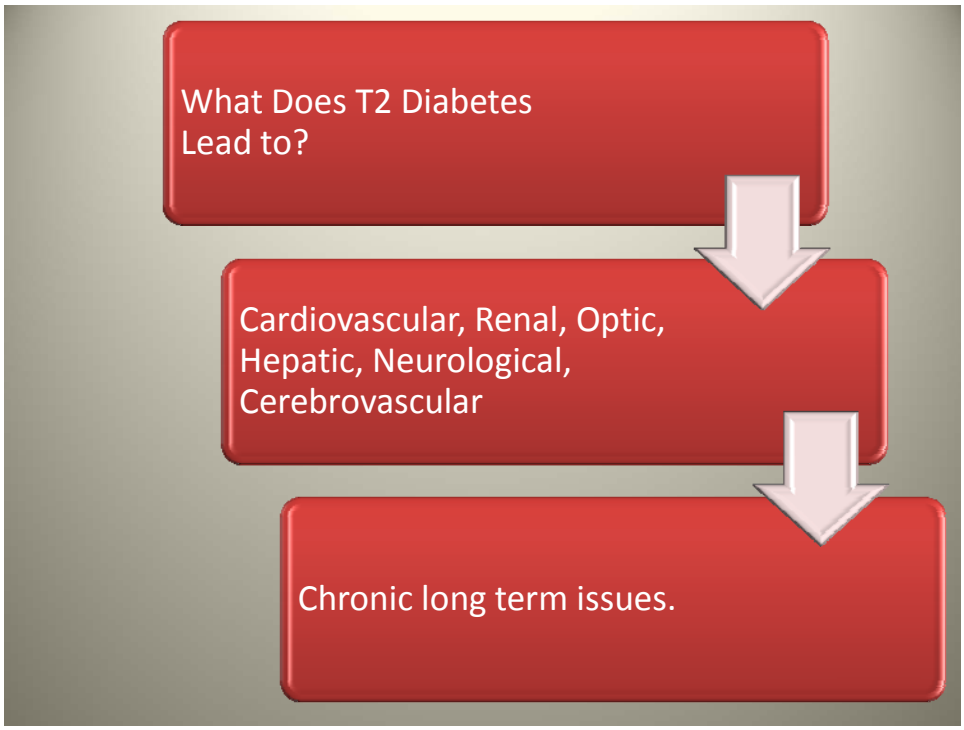
5. If one were to plot the cost of health care as a % of GDP versus the % prevalence of obesity in the US one obtains the curve below.



This curve, albeit statistical, and separate from the studies under 3 above, shows a strong correlation. It shows costs due to obesity taking over the health care expenditures. It shows that there is a strong statistical correlation between obesity and the explosion in health care costs. We will detail that shortly.

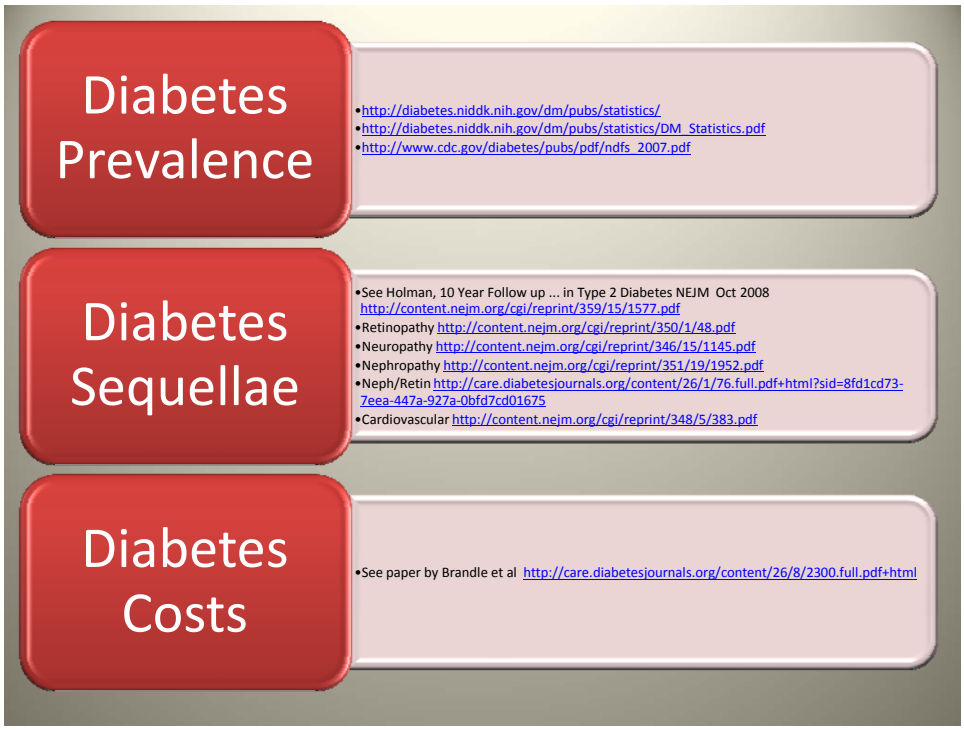
Yet is critical not to underestimate the importance of this curve. It portrays the trend which we seek to find way to eliminate.

6. So what does T2 Diabetes lead to. The next set of questions we posed under 1 above. Well we all know the answer, cardiovascular, nephropathy, neuropathy, retinopathy, and the list goes on!



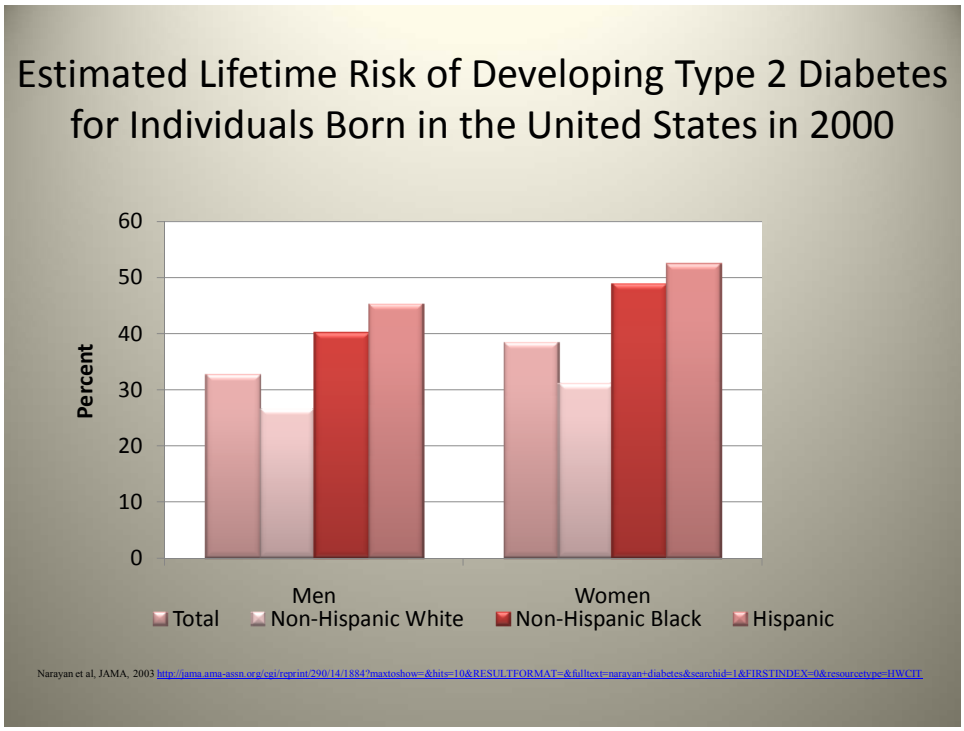
The problem with these is that they last a long time and cost a great deal of money. Take a stroke, that can have costs which last decades! Again dramatically unlike smoking and many cancers. Cancers are either cured or they kill you. For the most part we have limited success turning cancer into a chronic disease. CML may become one of the first.

7. Here is some of the most recent data on the sequelae, their incidence, prevalence, and treatment options.



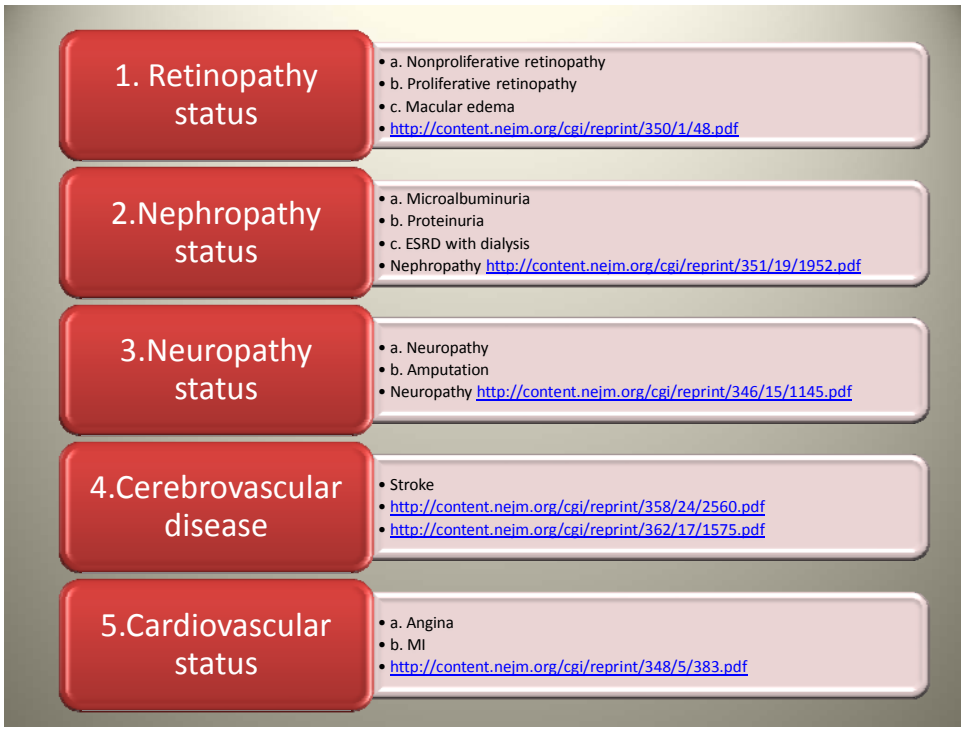
This is quite costly.

8. Looking forward we now have to worry about the lifetime risks of T2 Diabetes. This is shown below.



This means that one third of the people born in 2000 will develop T2 Diabetes! Does anyone really know what that means. It is not the cancer problem, we may have actually solved that by the time this tsunami hits.

9. These are some of the sequelae that this growth will cause.



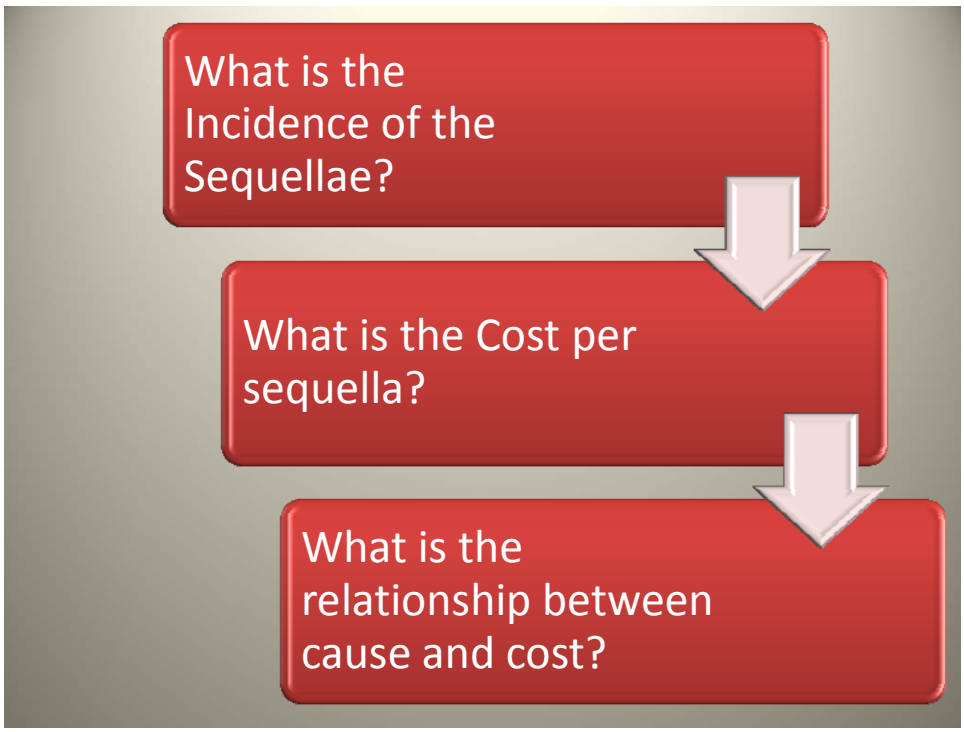
10. And these are some of the current stats on the disease as we see them today.

DISTRIBUTION OF FIRST-LISTED DIAGNOSES AMONG HOSPITAL DISCHARGES WITH DIABETES AS ANY LISTED DIAGNOSIS, ADULTS AGE 18 YEARS OR OLDER, UNITED STATES, 2006

First-Listed Diagnosis (ICD-9-CM Codes)	Number (in Thousands)	Percent
Circulatory Diseases (390–459)	1488	28.5
Respiratory Diseases (460–519)	553	10.6
Diabetes (250)	553	10.6
Digestive Diseases (520–579)	476	9.1
Injury and Poisoning (800–999)	356	6.8
Genitourinary Diseases (580–629)	318	6.1
Musculoskeletal System and Connective Tissue (710–739)	309	5.9
Other Endocrine, Nutritional, and Metabolic Disease and Immunity Disorders (249–279, not 250)	192	3.7
Neoplasms (140–239)	177	3.4
Mental Disorders (290–319)	173	3.3
Diseases of the Skin and Subcutaneous Tissue (680–709)	158	3.0
Infectious and Parasitic Disease (001–139)	136	2.6
Diseases of the Nervous System and Sense Organs (320–389)	84	1.6
Pregnancy/Childbirth/Puerperium (630–676)	15	0.3
Other	227	4.3
Total	5214	100.0

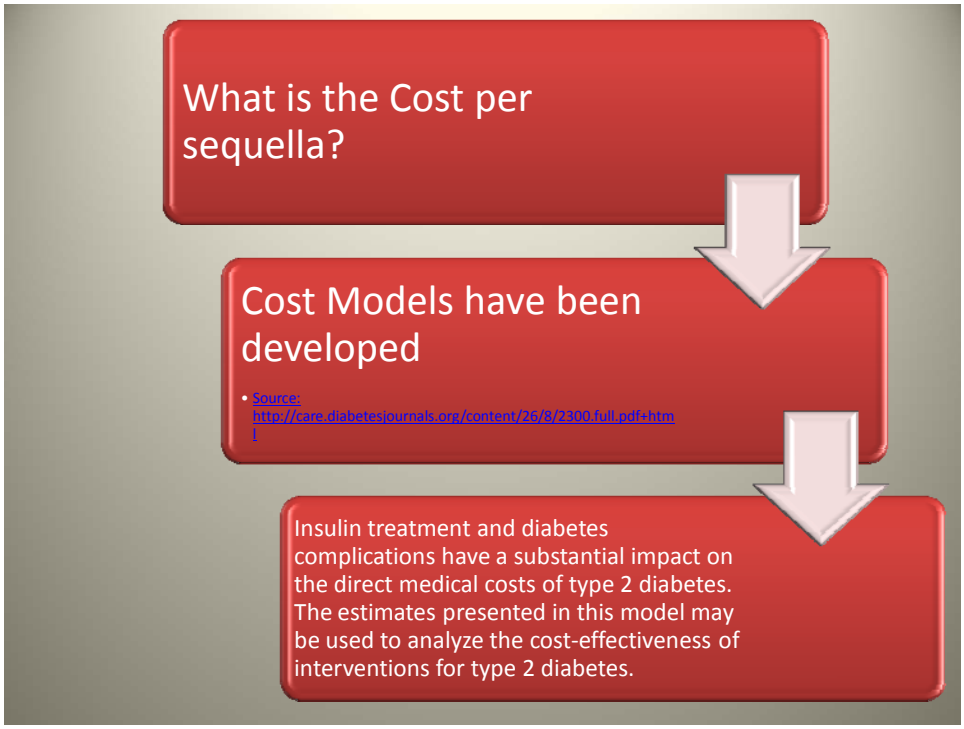
http://www.cdc.gov/diabetes/statistics/hosp/adulttable1.htm

11. We now want to goes back to item 2 above to continue to fill in our cost model. This can be followed as below:



We now need to get data for the costs of the sequelae and better stats on their occurrence. We do that as follows.

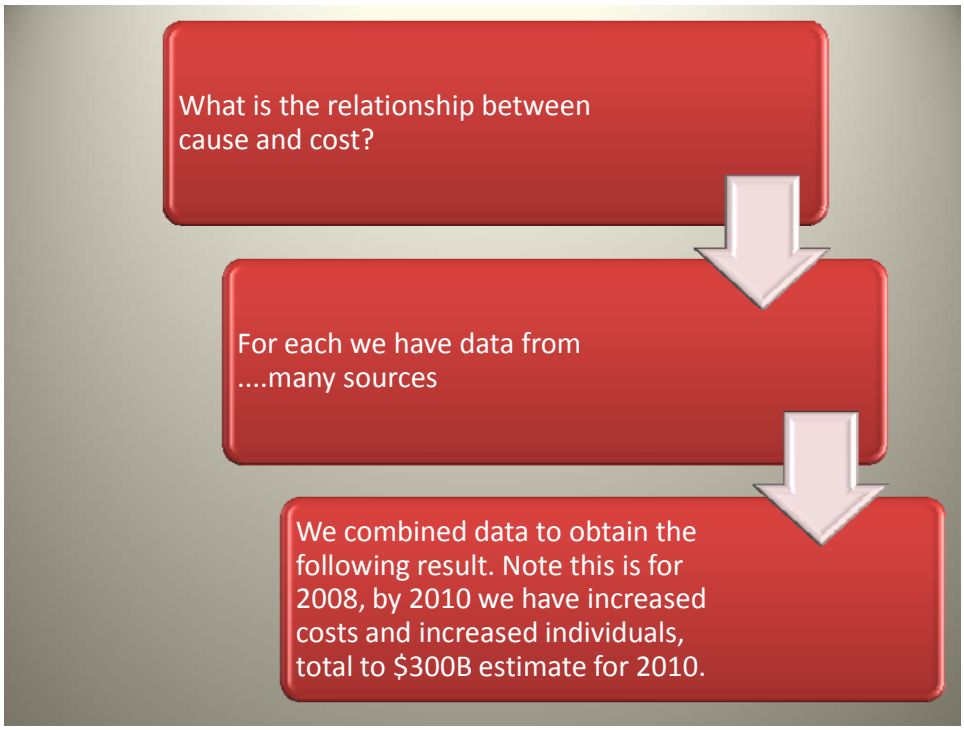
12. The following is a great study which benchmarked all of these costs. It is one of dozens but it is the one which I have come to rely upon.



The study we well done and should be studied.

13. The study performs the steps as we show below. We reached the answer that in 2010 it costs $300 B. That can be demonstrated in the next point.

We detail the numbers through 2008 and we obtain approximately $250 B and then we expand the prevalence and inflate the unit costs and we estimate the 2010 number to actually exceed $300 B. That is about 20% than the annual costs of all imported oil for the same period!

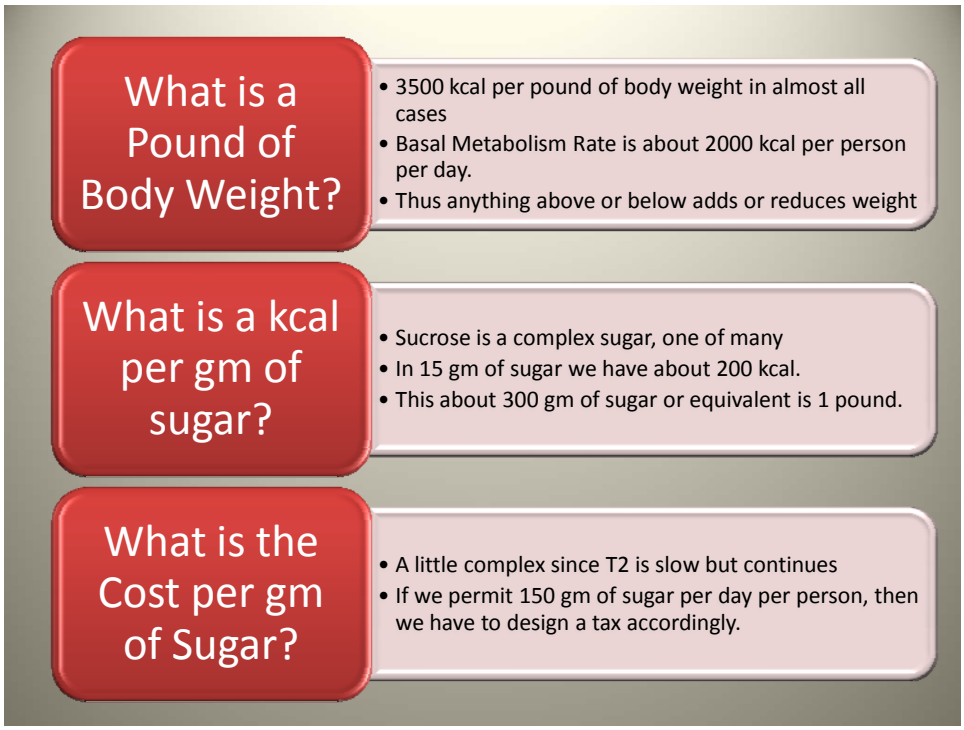


14. The details of the cost model using the 2007 study yield the following data:

Disease Element	*Prevalence %*	*Total Prevalence*	*Unit Cost per Year*	*Total Cost ($000,000, in 2008)*
Diabetes intervention			$0	
Oral antidiabetic medication	3.32%	584,622	$3,275	$1,915
Insulin	1.45%	254,687	$4,734	$1,206
High blood pressure				
Treated blood pressure	35.26%	6,206,452	$3,692	$22,915
Retinopathy				
Nonproliferative retinopathy	12.46%	2,193,548	$0	$0
Proliferative retinopathy	3.01%	529,032	$0	$0
Macular edema	2.13%	374,194	$0	$0
Nephropathy				
Microalbuminuria	7.26%	1,277,419	$3,484	$4,450
Proteinuria	15.18%	2,670,968	$3,871	$10,339
ESRD with dialysis	0.44%	77,419	$31,353	$2,427
Neuropathy				
Clinical neuropathy	39.88%	7,019,355	$0	$0
History of amputation	1.83%	322,581	$0	$0
Cerebrovascular disease	14.59%	2,567,742	$3,871	$9,939
Cardiovascular disease				
Angina	4.25%	748,387	$5,151	$3,855
History of MI	26.61%	4,683,871	$5,657	$26,498
Peripheral vascular disease	39.44%	6,941,935	$3,900	$27,077
Acute Illnesses				
Stroke	6.45%	1,135,484	$47,031	$53,403
Acute MI	6.16%	1,083,871	$43,318	$46,951
Amputation	3.45%	606,452	$66,480	$40,317
Total		39,278,018		$251,291

Here we took data for 2008, demographics and prevalence, and then used the study data from Brandle et al to modify the data in the above table. Then we used the cost increase data from 2008 to 2010 and the increased prevalence from 2008 t0 2010 and the increased population from 2008 to 2010 and voila we get $300 B! That is 2X the CDC numbers from 2007. But we argue that the numbers must (i) reflect the uptick as we just described it, and that (ii) the CDC numbers should be adjusted to reflect the Brandle methodology.

15. The following is a summary of my argument from yesterday and the day before regarding costs on a per carb basis.



Here we have laid out the logic and the referring source materials. Is this the definitive study, not yet, it will continue to evolve.

Mankiw responded in his blog as follows:

When writing my article, I contacted several prominent health economists to ask whether a complete accounting of both budgetary costs and benefits has been done for obesity, as has been done for smoking.

Yes the definitive study has not been completed, most likely will never be done. Yet this analysis and the ones we refer to provide a reasonable basis for policy formulation. The approach herein is to seek the specifics from primary research results, coordinate them in a consistent manner and from this construct a logical model demonstrating causality and costs. I have provided adequate detail at a level that a rational business person would use to make an informed decision.

2 OBESITY

Obesity has become pandemic throughout the world. In this section we review the current literature as well as present a simple model for understanding diabetes. There is a tendency to find a genetic cause for everything that ails humans but we argue here that the genetic effects, if truly there, are at best secondary, except in those specific genetic disease syndromes, rare as they may be.

Obesity is a process wherein the body accumulates more body fat than it needs. The issue of body fat measurement is a bit complex and the term "it needs" is even more so. These two factors will be the major issue when one tries to deal with obesity. Is obesity delimited to measurements of body fat, say percent body fat as a percent of total body weight, and is the issue of weight needed a clearly definable term, even if described as a range. Or is obesity seen only via its effects. Namely is one obese only if there is some sequelae of a more classic disease process, such a nephropathy that results and then one says that the weight issue or body fat accumulation is the co morbidity problem as well.

One of the issues here is that weight and body fat per se are not the problems, but what results from the accumulation of body fat over some period. The fat frequently results in secondary changes which result in forms of disease.

In this section we present an overview based upon the current literature of obesity, its definition, its "cause", the uses of the energy consumed, and the net process in the ultimate accumulation of weight. As we shall demonstrate, the primary driver in the accumulation of weight, and in turn obesity, is the growth of the fat cells or adipocytes. This cell is somewhat unique in the human body because it has the capacity to expand as it fills itself with fat. The source of the fat for the most part is glucose, and the source of glucose is a carbohydrate input. We detail from primary sources the current understanding of these processes.

2.1 DEFINITION

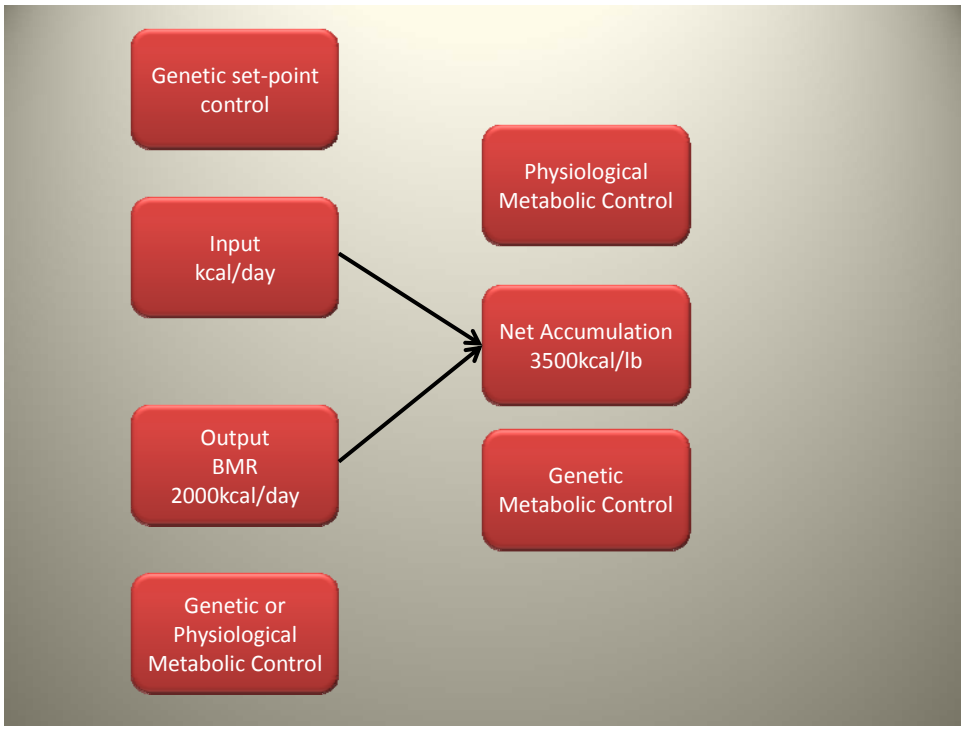
Obesity simply is having more body fat than one should have. The current standard measure to determine this is the Body Mass Index, BMI, which is the ratio of kg of body weight to sq m of body area. Thus normal BMI is between 18 and 25. Anything between 25 and 30 is overweight and over 30 is obese. To some degree this may be totally arbitrary, since it does not define a specific physiological state, such as a white blood count number or the like. However is has become the standardized measure and has been augmented by other metrics which we shall discuss. A recent summary of obesity and its clinical implications is in Yanovski and Yanovski.

The first question we have addressed is how does obesity occur. The simplest explanation is simple mass balance. Namely

Input Output = Net Accumulation

Input is measured in kcal of energy input from food. Output is the expenditure of energy in some period as the input, say a day. Net accumulation is the excess input or net lack of input over expenditure. We demonstrate this fundamental relationship below.

Before continuing however it is essential to note that the definition of obesity is somewhat arbitrary and is often determined as a result of the sequelae that result from being at some percent of body fat or similar measure. As we shall show increases in body fat do give rise to physiological effects which in the long term may be harmful. However the effects are not always present, just frequently. Thus we have the genetic possibilities which control sequelae. Unlike Type 2 Diabetes where we can measure insulin and blood glucose, in obesity the measure to determine it is still elusive to some degree.



The next issue is what causes the input and what causes the output. Alternatively is there some genetic control mechanism which influences the input and output. Generally we see that 3500 kcal of excess net accumulation results in 1 lb of additional weight. However some people may have a different number, due to the way they convert kcal to body mass.

Thus the three questions regarding obesity are:

1. What is the conversion rate of kcal net accumulation to body mass, and how is that accomplished? For example certain gastrointestinal diseases can cause poor absorption so that higher kcal inputs would be required.

2. What drives the input elements, namely food consumption, and is there some genetic set point mechanism which drives the physiological system, or is it just a "desire" to over consume?

3. What controls the output, the daily consumption by the body of kcal. Are there genetic factors, physiological factors or others? For example certain thyroid disorders can cause faster or slower use of kcal in a person.

In the paper by Kopelman he defines obesity as follows:

"In clinical practice, body fat is most commonly and simply estimated by using a formula that combines weight and height. The underlying assumption is that most variation in weight for persons of the same height is due to fat mass, and the formula most frequently used in epidemiological studies is body mass index (BMI). … It allows meaningful comparisons of weight status within and between populations and the identification of individuals and groups at risk of morbidity and mortality. It also permits identification of priorities for intervention at an individual or community level and for evaluating the effectiveness of such interventions.

The authors then state what we have been saying all along, BMI is not necessarily the correct metric. They state:

" It is important to appreciate that, owing to differences in body proportions, BMI may not correspond to the same degree of fatness across different populations. Nor does it account for the wide variation in the nature of obesity between different individuals and populations. A World Health Organization (WHO) expert committee has proposed the classification of overweight and obesity that applies to both men and women and to all adult age groups ... "

Finally the authors address the issue we have belabored, namely what is the "health weight" and for that I would call it optimal body fat number. They continue"

"Defining a 'healthy weight' for a particular society presents problems. First, the definition is based on total mortality rates, which can be misleading. People frequently lose weight as a consequence of illness, which may go unrecognized at the time of survey, but results in death. This implies a higher mortality among those with lower weights and is referred to as reverse causation. A second major concern is the confounding factors, such as smoking, that may distort the association between body weight and mortality.

The Nurses' Health Study, which prospectively studied 116,000 women in the United States during a 17 year period, shows a U shaped relationship between mortality and BMI in an overall age adjusted analysis. However, the relationship becomes a simple positive association when reverse causation is accounted for and the analysis limited to those who had never smoked."

Despite these shortcomings in the calculation, there is a close relationship between BMI and the incidence of several chronic conditions caused by excess fat…, including type 2 diabetes, hypertension, CHD and cholelithiasis. This relationship is approximately linear for a range of BMI indexes less than 30 (kg m^{-2}), but all risks are greatly increased for those subjects with a BMI above 29, independent of gender[8,9]. Waist circumference correlates with measures of risk for CHD such as hypertension or blood lipid levels. The choice of cut off points on the waist circumference continuum involves a tradeoff between sensitivity and specificity similar to that for BMI.

Gender specific cut off points for waist circumference may be of guidance in interpreting values for adults: proposed cut off levels are shown in Table 2, with level 1 being intended to alert clinicians to potential risk, whereas level 2 should initiate therapeutic action."

In the Doctoral Thesis by Moffett (2002) the author states:

"Obesity occurs when energy intake exceeds energy expenditure and the surplus energy is stored as fat in adipose tissue.

In addition to environmental influences such as dietary content and physical activity, there are many physiological pathways that regulate energy balance.

Insulin and leptin, two adiposity hormones, circulate at levels corresponding to an individual's body fat and stimulate the central nervous system (CNS) to reduce energy intake thereby helping to regulate weight gain when adipose stores are at sufficient levels …. However, many obese individuals are both insulin and leptin resistant and require higher levels of the hormones, and therefore adipose tissue, to produce a response by the CNS…"

Increased adipose tissue lipolysis and subsequent elevation of free fatty acids is also associated with insulin resistance …. In addition, energy expenditure in the form of heat is under close physiological control and disruptions in these thermogenic pathways are thought to contribute to the development of obesity … Mutations in genes such as leptin, the leptin receptor and the melanocortin 4 receptor can lead to monogenic forms of obesity, but these simple genetic forms of obesity are very rare in the general population…

Many potential susceptibility loci for obesity have been identified through various forms of linkage studies. Human chromosome regions such as 2p (pro opiomelanocortin), 7q15 (neuropeptide Y), 7q31 (leptin), 10p, and 20q13 have been linked to obesity traits … When potential human homologs for mouse qualitative traits are included in the list of potential obesity susceptibility loci, every human chromosome except the Y chromosome shows at least one region of … Another approach to finding genes contributing to obesity is to identify polymorphisms in candidate genes known to regulate energy balance then look for associations with obese phenotypes.

The candidate gene approach has identified a ***long list of possible obesity related genes, but the results of these candidate gene association studies have been inconsistent among various populations and in some cases the functional significance of the identified polymorphism is questionable****..."*

The Thesis is an attempt to support the gene hypothesis for obesity. That is the theory that the "genes made me do it". The observations have been made that in certain animal models, rats for example, if the leptin pathways are disturbed than the rats will tend to eat more and even to the extent of overeating. Yet the rats are in captivity and the stress and other factors may exacerbate the problem. Despite that experimental observation with rats nothing explains the massive increase in obesity in the past fifty years. Genes just do not change in a population that quickly. The argument for individual choice and lack of control is more compelling.

2.2 PHYSIOLOGY

This section presents an overview of the various mechanism which control the Input, the Output, and the Net Accumulation elements as relates to obesity. We will focus on:

1. Input: What drives the physiological system to continue to demand input in excess of what would be required for stasis? There is a moral question here as well, since the general presupposition is that obesity is a disease and it has an organic cause and if the cause is corrected then obesity will also be corrected. However, unlike mice, humans can be "trained" and "managed" to consume less. There are multiple possible incentives. Thus is this a disease or a lack of will power. We examine some of the pathways driving the input side but one must always remember that there is will power at play as well.

2. Output: This is the ability of the body to consume the input and do things with it other than storage. It depends on the cell usage of input. The classic extreme example is the cachexia in patients with cancer. There, the cells just fail to process the energy input and the cells just wither and die off. The drivers here are the basal metabolism rates, exercise, and the overall ability to burn energy as a matter of course for the person.

3. Net Accumulation: This is the ability of the body to store the results of the net consumed energy. The question is where is it stored ant at what levels of efficiency.

We now address each of these three areas. The initial one will be the most difficult because much research has been done looking at animal models in confined conditions. The conclusions there are twofold. First there are pathways to the hypothalamus which can control the desire to eat in animals and that the same pathways exist in humans. Second that the tests were done under laboratory conditions with animals and the extension to humans in non lab environments and with putative will power may change the assumptions dramatically. The output area is generally just the consumption of energy by cell processes. To some degree there are controls in the body which may make consumption rates change, such as thyroid gland control and set points, but generally the

general understanding here is well grounded. Finally the accumulation as we have already stated is done by the expansion of the adipocyte.

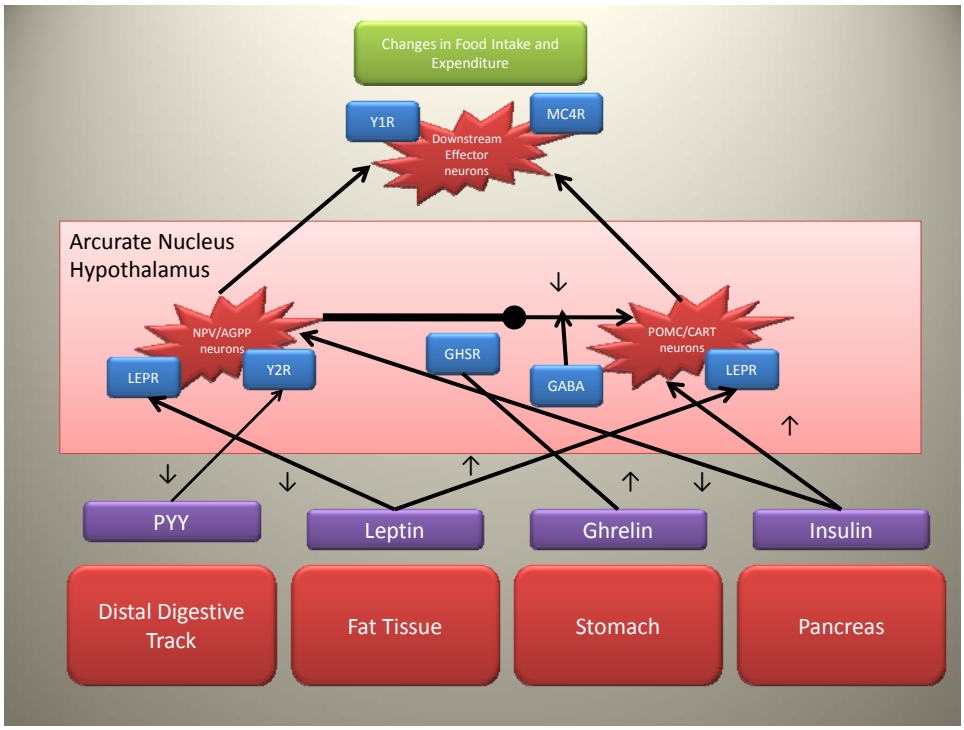
2.2.1 Input Mechanism

The input mechanism is simply the consumption of energy via the consumption of food. The food can generally be divided into carbohydrates, fats and proteins. We defer discussions on these until later. However our concern here is the question of what drives a human to eat. This has been found to be a complex question and many of the suppositions have been driven by studies in mouse or other animal models. Such studies take a significant factor from the equation, namely the question of will power, an element which may at times find little social acceptance but one which we will maintain throughout our discussions.

Let us begin with some rats. The issue of course is that humans are not rats and as we think of rats we think of non sentient creatures which respond to primal urges. The class experiment was performed in 1940 by Hetherington and Ranson (see Elmquist et al). The experimenters examined the hypothalamus and observed:

"A condition of marked adiposity characterized by as much as a doubling of body weight and a tremendous increase of extractable body lipids has been produced in rats by the placing of electrolytic lesions in the hypothalamus. Examination of these lesions has shown them to be very large, but they all have in common extensive bilateral damage to the region occupied by the dorsomedial and ventromedial hypothalamic nuclei, the arcuate nucleus, the fornix, and that portion of the lateral hypothalamic area ventral to it, and probably also the ventral premammillary nuclei."

The following Figure depicts a summary of the current understanding of how this drive to eat functions. This model looks towards the hypothalamus as the controlling region of the brain which if activated in a certain manner compels the animal to seek and consume food. The hypothalamus is activated by certain chemicals such as leptin which if released and are above or below certain set points will activate the hypothalamus. The animal will eat and eat. We will come back to this diagram again.



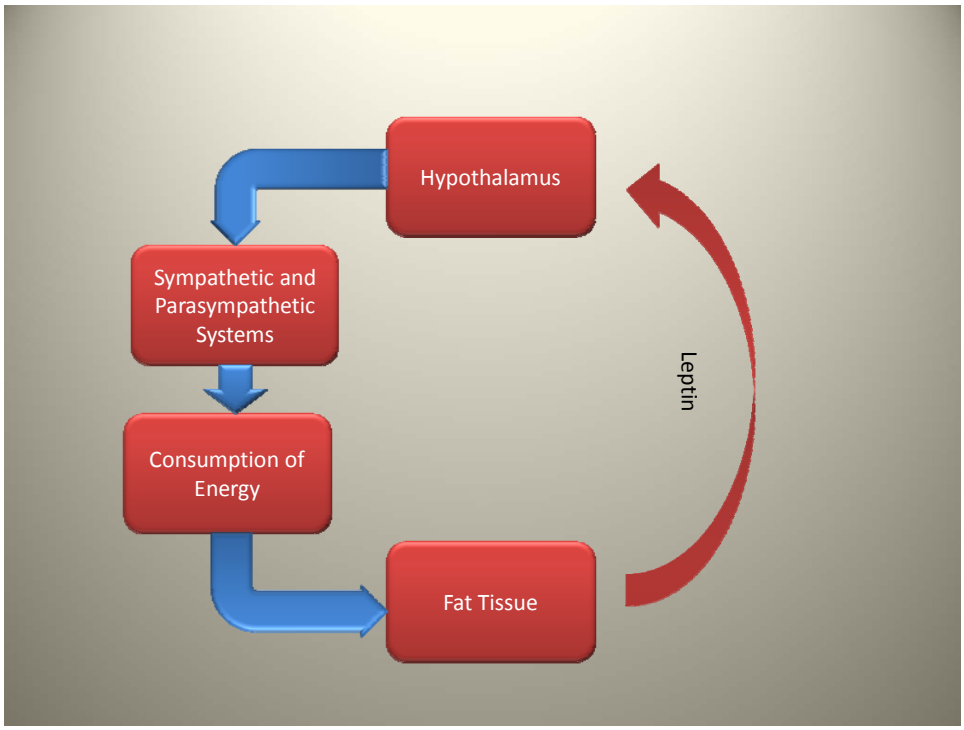
The authors Elmquist et al state:

"Conversely, Hetherington and Ranson noted that lesions in the adjacent lateral hypothalamus could lead to decreased food intake (Hetherington and Ranson, 1940; Stevenson, 1970). Anand and Brobeck (1951) pursued this observation in greater detail, demonstrating that lesions of the lateral hypothalamus at the level adjacent to the ventromedial nucleus caused loss of feeding, inanition, and even death by starvation. Thus, the concept arose of the lateral hypothalamic area serving as a "feeding center" and the ventromedial nucleus as a "satiety center"..".

Thus it has been demonstrated that the hypothalamus is the organ, or part of the brain that controls the reflex to eat. I eschew to use the term desire because desire connotes a human response as compared to a chemically induced reflex that was observed by Hetherington and Ranson. The question than is what drives the hypothalamus and what in turn does the hypothalamus do to instigate the reflex to consume food? Simply, what are the input and output mechanism which drive the hypothalamus? From the possible answer to this we can thus obtain answers to the question of what genes give rise to the signaling substances that cause this process in the first place, and are these genes unique or changed in obese individuals?

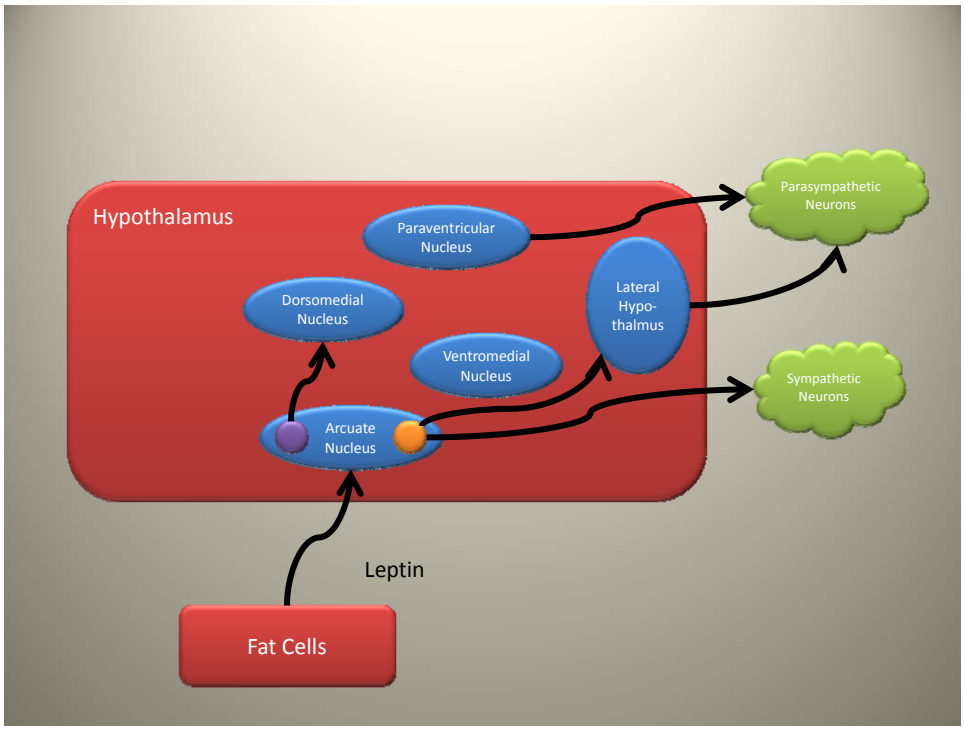
The answer was found in the discovery of Leptin in 1994. Leptin is a protein produced in fat tissue and it activates the hypothalamus as shown below and in accord with what we presented above.

Thus we have a feedback system of the type shown below:



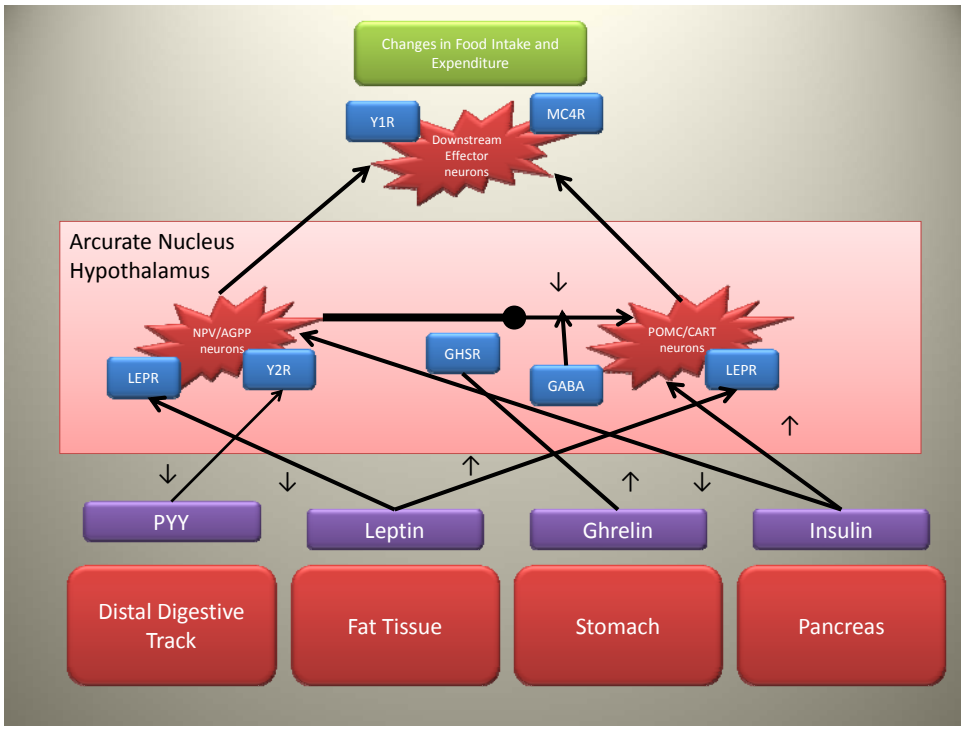
The diagram above is a simplified diagram of how a protein, Leptin, activates the hypothalamus, which in turn activates the sympathetic and parasympathetic systems, which in turn activates the consumption of food or energy, and in turn builds more fat and the cycle continues.

The details on the fat cell and hypothalamus connection is shown below (this is a modified version of Fig 7 from Elmquist):



The above demonstrates the various nuclei in the hypothalamus, nuclei being collections of nerve endings, and their signaling back and forth.

Other similar proteins, products of genes have been elucidated, and a better picture is shown below:

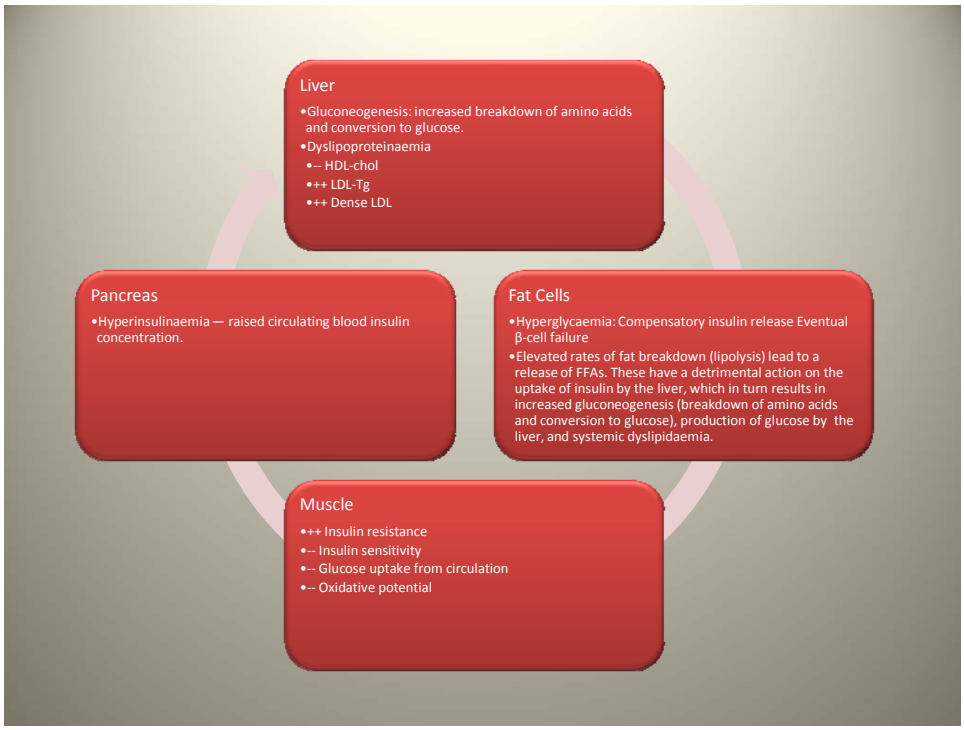


In the above we show the effects of several organs, the digestive track, the fat tissue, the stomach, and the pancreas. Each organ puts forth a signaling protein which then activated the pathways in the hypothalamus.

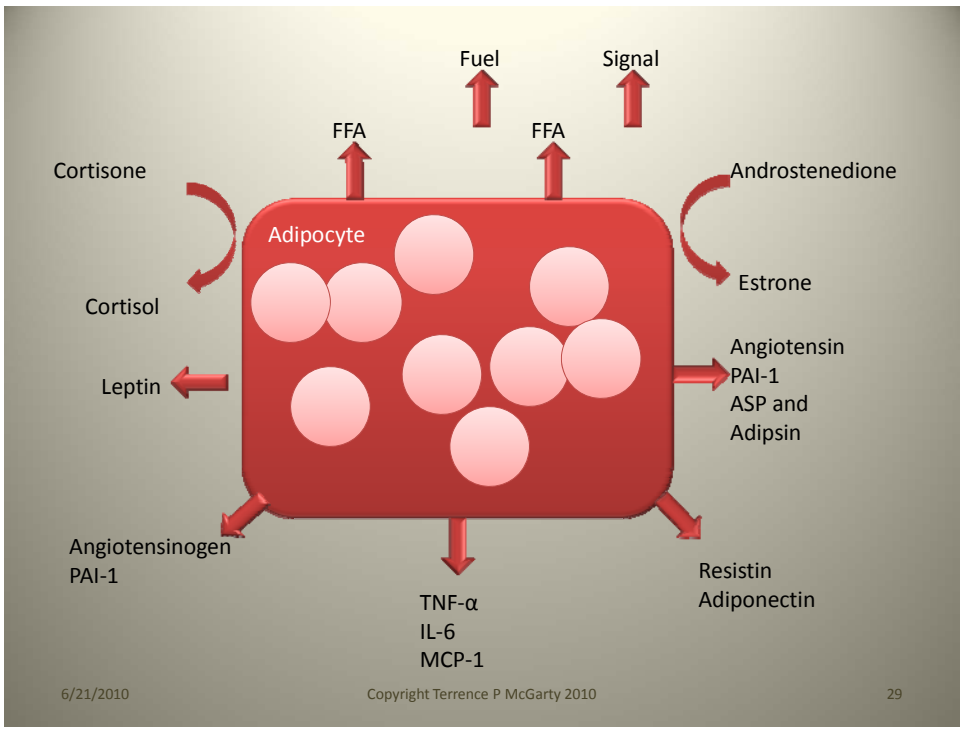
As Bell et al state:

> *"Obesity is caused by perturbations of the balance between food intake and energy expenditure, which is regulated by a complex physiological system that requires the integration of several peripheral signals and central coordination in the brain.*
>
> *The hypothalamus functions as a central regulator in this system. It receives information about energy balance through neuronal and hormonal signals to several tissue nuclei within it — particularly the ventro medial, paraventricular and arcuate nuclei — and to the lateral hypothalamic area.*
>
> *The arcuate nucleus in the hypothalamus has an essential role in this system; it contains two sets of neurons,*
>
> 1. *one produces agouti related protein (AGRP) and neuropeptide Y (NPY) and*
> 2. *the other produces pro opiomelanocortin(POMC) and cocaine and amphetamine related transcript (CART).*
> 3. *the first type are orexigenic, promoting food intake and reducing energy expenditure, and*
> 4. *the second type produce the opposite anorexigenic effect.*
>
> *The central arcuate nucleus processes these different inputs and exerts its effects by signalling to various downstream effector neurons.*
>
> *These include the*
> 1. *orexigenic melanin concentrating hormone (MCH) neurons and*
> 2. *orexin or hypocretin neurons in the lateral hypothalamus16, the*
> 3. *thyrotrophin releasing hormone (TRH) neurons that are involved in regulating the hypothalamic– pituitary–thyroid axis17 and the*
> 4. *γ aminobutyric acid (GABA) releasing interneurons in the paraventricular nucleus (PVN),which modulate orexigenic or anorexigenic effector neurons.*
>
> *Further inputs to this system include the dopamine, serotonin and endocannabinoid signalling systems."*

The Figure below shows the interactions of the organs themselves independent of the hypothalamus.



The fat cell, the adipocyte, also acts as an endocrine cell as well, releasing a set of chemical signals and regulators. We depict this below:



The cell can release a multiple of such signalling proteins which in turn can result in multiple secondary effect. The schematic above (modified from Mantzoros et al) depicts

many of the endocrine type functions. We will discuss a few below and we will return to those related to the immune and inflammatory side later. For example the TNF, tumor necrosis factor release, is one which in excess can cause significant inflammatory damage.

Thus there are several signaling proteins activated by their genes which are now known to activate the channels exciting the hypothalamus and brain stem inciting the individual to consumer energy. These are:

1. Leptin: Leptin is a 167 amino acid protein and as we have discussed can act as a driving factor in the hypothalamus drive to eat. It can become a compulsive driver which in turn leads to obesity if no managed by the person. Leptin levels increase as the fat sores increase and leptin levels decrease as the fat stores are depleted. Leptin levels decrease during dieting and increase when overeating., It has been found that the administration of leptin to leptin deficient mice results in significant weight loss. As with many other such proteins they find themselves in pathways and leptin is in the PI3K pathway that we find in many cancer pathways. As we have also indicated most but not all leptin cell receptors are located in the arcuate nucleus of the hypothalamus.

2. IL 6 and TNF α: These two cytokines, elements of the body's immune system, are produced mainly by the immune cells but surprisingly can be produced by the adipocytes. TNF causes lipolysis and inhibits adipogenesis, as if excess fat is considered by the body as an external assault requiring immune response. The same is true of the IL 6.

3. Adiponectin: This is a 247 amino acid protein generated exclusively in adipocytes. Adiponectin decreases with increasing central and overall adiposity and increases with long term weight reduction (Mantzoros) and it appears to regulate insulin sensitivity. It also is a regulator on multiple signaling pathways including the PI 3K pathway. Adiponectin seems to stimulate vasodilation and stimulates angiogenesis. Adiponectin is an activator of immune responses.

4. Ghrelin: This is a 28 amino acid protein and is expressed mainly in the stomach. It is a hormoine which stimulates food intake. Ghrelin levels rise before meals and in response to diet induced weight loss. It falls after feeding. The fall is blunted in those who are obese.

5. Resistin: This is a 114 amino acid protein and is expressed primarily in white adipose tissue. Recent studies seem to indicate that resistin negates leptin and adiponectin influence. From the work of Shuldiner et al, they state:

"Resistin may be an important link between increased fat mass and insulin resistance. In mice, resistin is expressed predominantly in white adipose tissue and is detectable in serum, suggesting that it is secreted by adipocytes and acts at distant sites. The findings in obese mice that serum levels of resistin are markedly increased and are decreased by rosiglitazone and other thiazolidinediones that increase sensitivity to insulin point to resistin as a mediator of insulin resistance. Moreover, neutralization of resistin activity

by the injection of antibodies against resistin decreases blood glucose levels and improves insulin sensitivity in obese, insulin resistant mice, and the injection of resistin into mice worsens glucose tolerance and induces insulin resistance. In an adipocyte cell line, resistin inhibits insulin stimulated glucose uptake and antibodies against resistin enhance glucose transport in these cells, suggesting that endogenous resistin has autocrine effects….

Whether triglycerides are stored in adipocytes or broken down and released from adipocytes depends on whether there is a positive or negative energy balance, respectively. The adipocyte actively modulates energy balance through the secretion of hormones and other signaling molecules. For example, leptin is secreted by triglyceride laden adipocytes, travels through the circulation, crosses the blood–brain barrier, and reaches the hypothalamus, where it modulates a host of neuroendocrine and autonomic nervous system activities, resulting in decreased food intake and increased energy expenditure. Resistin, as well as tumor necrosis factor a, adiponectin, free fatty acids, and possibly other factors released by adipocytes, act in peripheral tissues to influence sensitivity to insulin and other cellular and metabolic processes involved in the use and partitioning of substrates"

Others include; Acylation Stimulating Protein, Cholecystokinin, Peptide YY and many others. These and others are discussed in some detail in Mantzoros.

Yet despite these pathways, they are at best ex post facto in humans and they function in other animal models where the animal is in captivity or genetically modified. It still begs the question as to how the human with a "free will" can have their individual behavior modified so as to resist the inherent pathway activations resulting in excessive energy consumption.

2.2.2 Output Mechanism

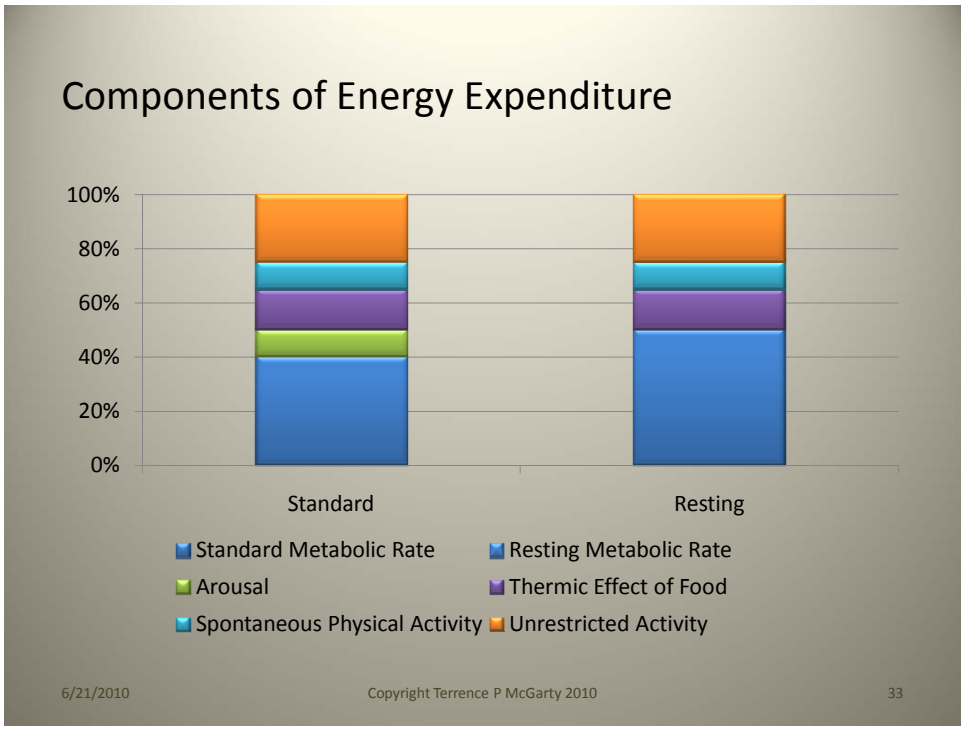
Now we address the internal uses of the consumed energy. Namely what does the body do with what it consumes, and further how much does it use of what it consumes if not more than that.

The following chart depicts two views of output usage of energy from the human, one in an active state and one in a resting state. The charts is relative to a 100% and does not depict specific kcal usage. We defer that until later. However what is evident is the assumption in all cases that there is some utilization above that of pure resting.

The term energy expenditure, EE, is used to depict the total energy used by a person in the course of a day. EE is divided into two gener4al types; obligatory or basal and adaptive or facultative. Basal EE includes all expenditures which account for the maintenance of the basic metabolic and physiological processes. This expenditure included all energy required for the sets of chemical and biological processes required for living in a resting state. The amount of energy used for these processes is called the Standard Metabolic Rate, SMR.

Adaptive rates would include cold induced and diet induced consumptions, called Diet Induced Tehromgenesis, DIT. Bachman states that there is often an overlap and describes the thyroid hormone control which is required for up to 30% of the SMR and that adaptive increases in the thyroid hormones are required for normal cold induced responses.

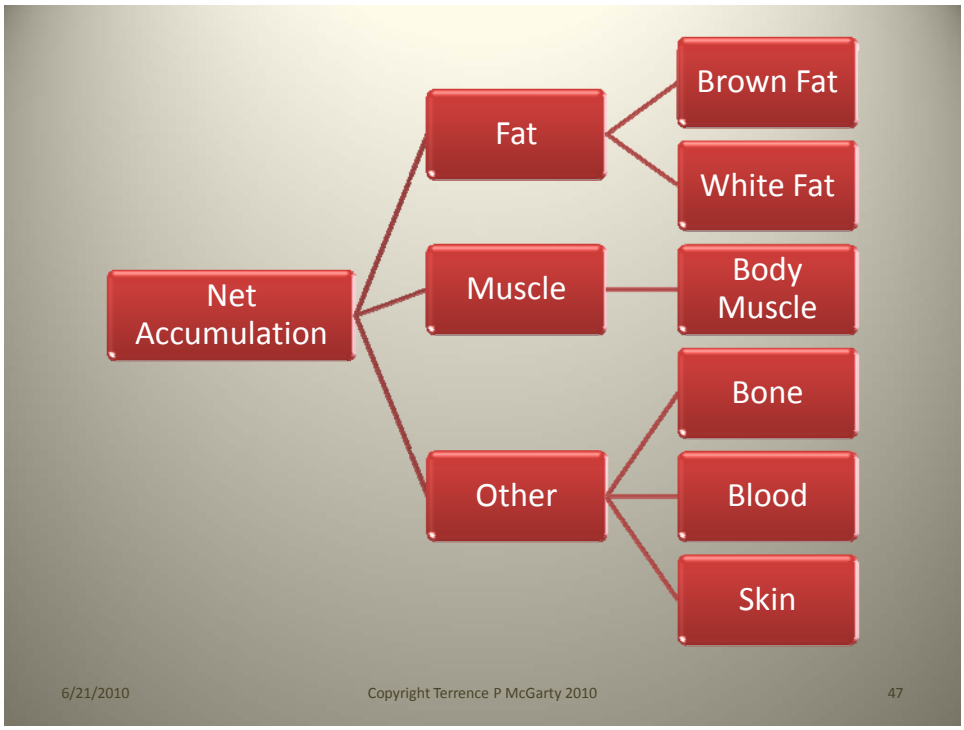
Physical activity can affect the Resting Metabolic Rate, RER, and such physical activity is considered a separate category. At the cellular level, according to Bachman, up to 90% of the EE in mammals derives from oxidative phosphorlyation of substrates in the mitochondria. This is the classic ATP/ADP reaction for the most part which is the primary energy transmission engine in mammals.



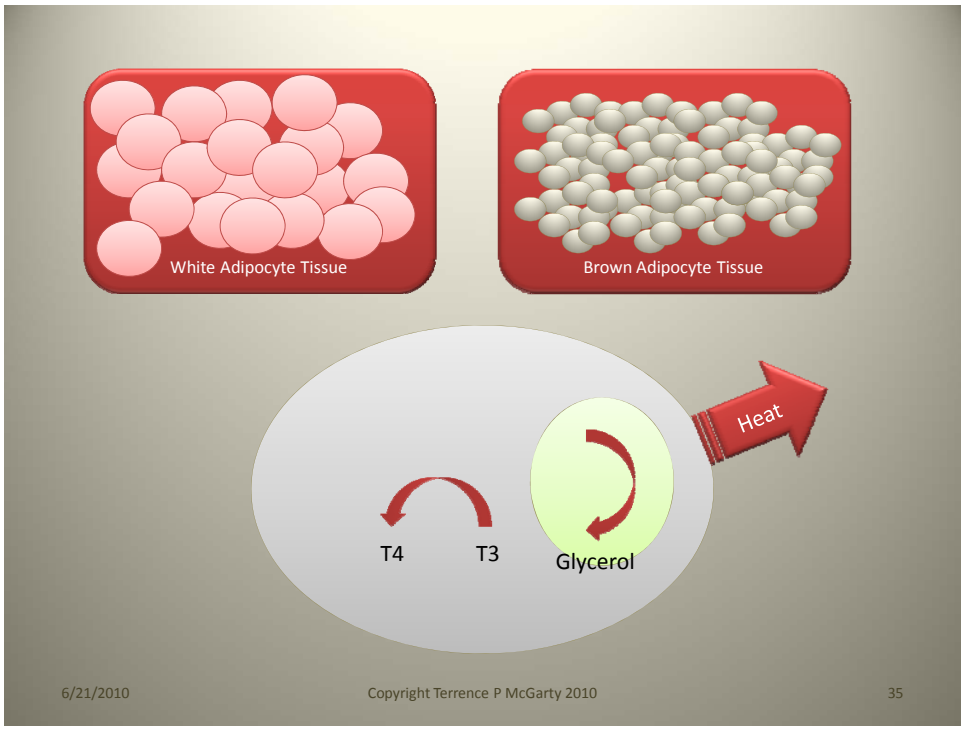
One of the key parts of cell use of calories will be found in the fat cells, the adipocytes, and there are basically two distinct type, Brown Adipose Tissues and White Adipose Tissues and we depict them below with the cell energy cycle.

2.2.3 Net Accumulation Mechanism

The Net accumulation model is a complex issue since the excess of input less output is in kcal of energy and it then is transformed into fat, muscle and other body parts and the rate of conversion may be significantly different from person to person. This in turn may lead to the fat content difference.



The above graphic gives a template for the use of energy. The red cells are replenished on about a 90 day cycle so there is an amount of energy used in that process, albeit a modest amount, The skin is always growing and again a modest amount of energy is used there. Yet like the blood cells there is not additional accumulation. Thus bone, blood, skin, muscle for the most part is using energy but in a stasis manner. The excess energy consumed is relegated to storage, and storage in the fat cells. The dominant net accumulation as we shall see is in the fat cells.



The fat cells therefore have the unique capability of expanding in an almost limitless manner. They become the storage areas for the excess energy consumed, and in most ways the dominant area of accumulation. As Rajala and Scherer state:

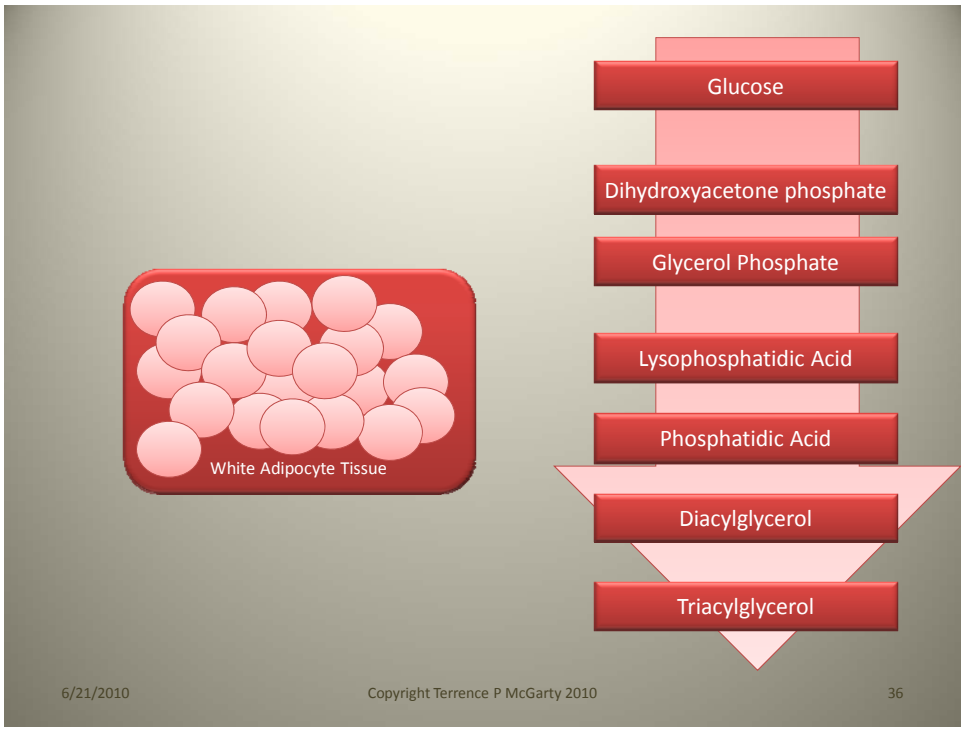
"The adipocyte is a remarkable cell type in several respects. It stores excess energy in the form of lipids and is thus able to dramatically change its size in accordance with changing metabolic needs. This ability gives adipose tissue an almost unlimited capacity for growth, making it perhaps the only tissue in the body with the ability to so drastically increase its size without an underlying transformed cellular phenotype. Adipose tissue is responsive to both central and peripheral metabolic signals and is itself capable of secreting a number of proteins ….

These adipocyte specific or enriched proteins, termed adipokines, have been shown to have a variety of local, peripheral, and central effects that will be discussed below. Adipose tissue is therefore able to integrate signals from other organs and respond by regulating secretion of multiple proteins. As an active participant in whole body energy homeostasis, adipose tissue can negatively influence other systems when dysregulated. Although adipocytes are capable of increasing in size, the cellular homeostasis and the secretory profile of larger adipocytes becomes altered and increasingly dysregulated compared with adipocytes of smaller size….

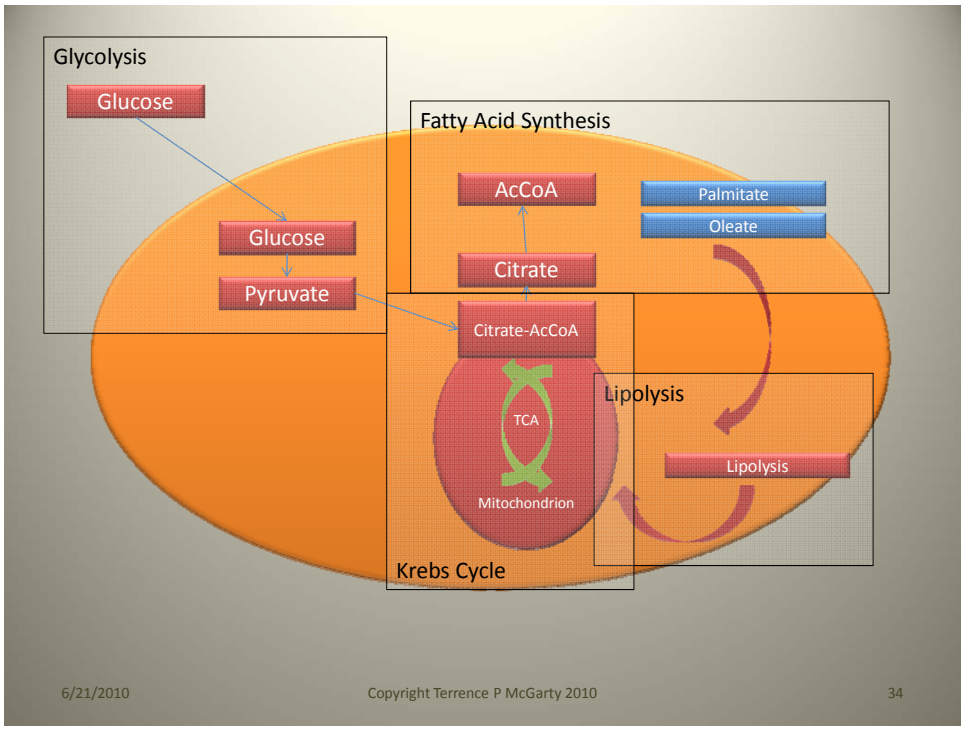
Although the total number of adipocytes is increased with increasing fat mass, the increased number and percentage of these large adipocytes may partially account for the inability of adipose tissue to function properly and contribute to some of the problems associated with obesity."

Thus to understand the "Accumulation" portion of the energy balance one must have an understanding of the adipocytes. They fall into two categories, brown adipose tissues and white adipose tissues. We detail their characteristic below along with the underlying biochemical factors. The key fact from the above statement is that the adipocytes are capable of significant expansion as well as proliferation. With increased energy one does not see growth in blood, bone, liver, or other types of cells, what one sees is the growth in the fat cells.

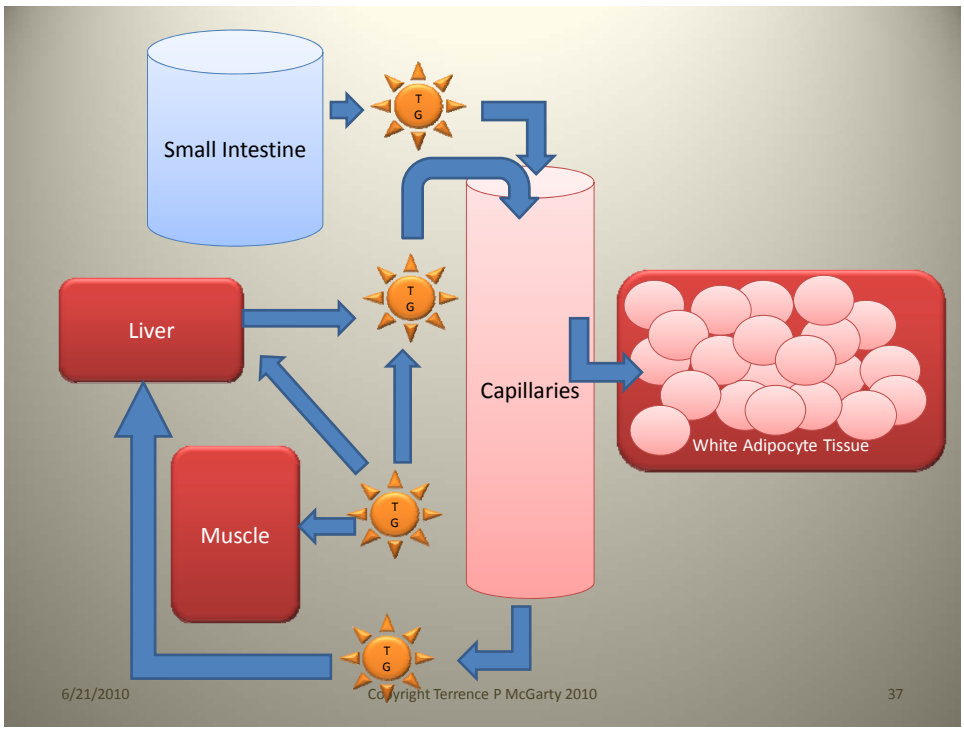
The flow from glucose to triacylglycerides, or TG, is depicted below (see Champe and Harvey).



The process in a fat cell is one where the glucose enters and as a result of multiple chemical transitions in the glucose pathway the output is triacylglycerol, or the building blocks of triglycerides. This is a well established pathway and process. We depict this below:

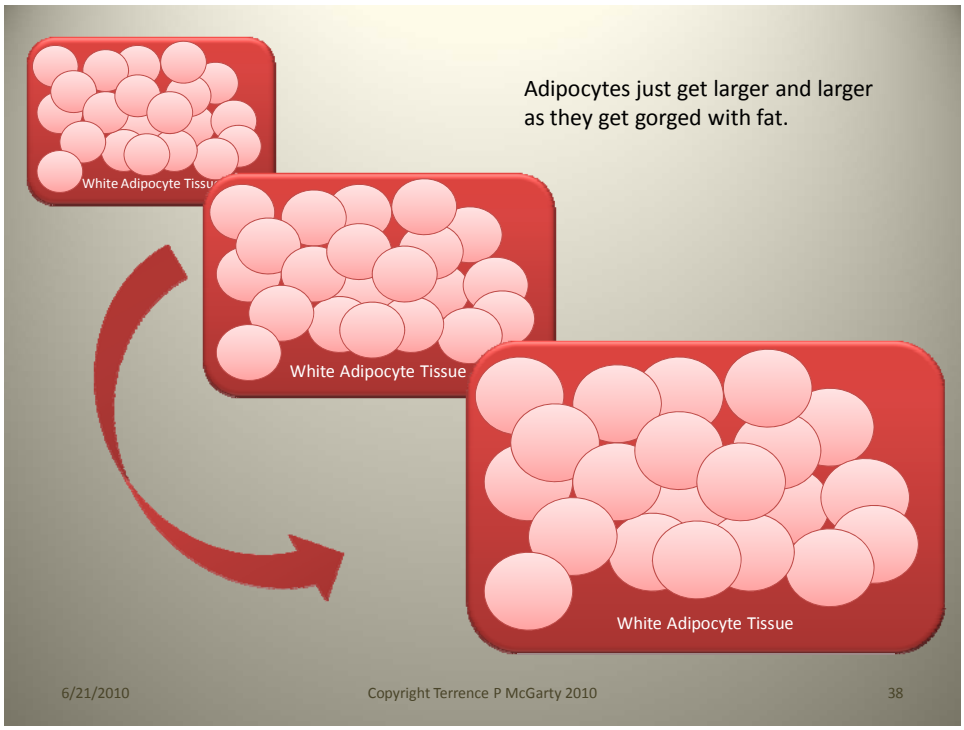


The overall feedback mechanism from gut to the cells is shown below.



The storage is in the adipocyte or fat cell and as glucose is taken in, directly or through some form of carbohydrate breakdown it is converted to TG and then sent and stored as fat in the adipocyte. The adipocyte continues to expand as it manages to carry more and

more fat. In a sense the adipocyte is quite unlike many other cells whose size and function is defined and circumscribed. For example a malanocyte in the skin is bound to the basal layer as in the liver a hepatocyte is bound to the interior cells of the liver. Adipocytes are ever enlarging storehouse of fat. We depict that below:



We now look briefly at the two types of fat cells in the human body.

2.2.3.1 Brown Adipose Tissue

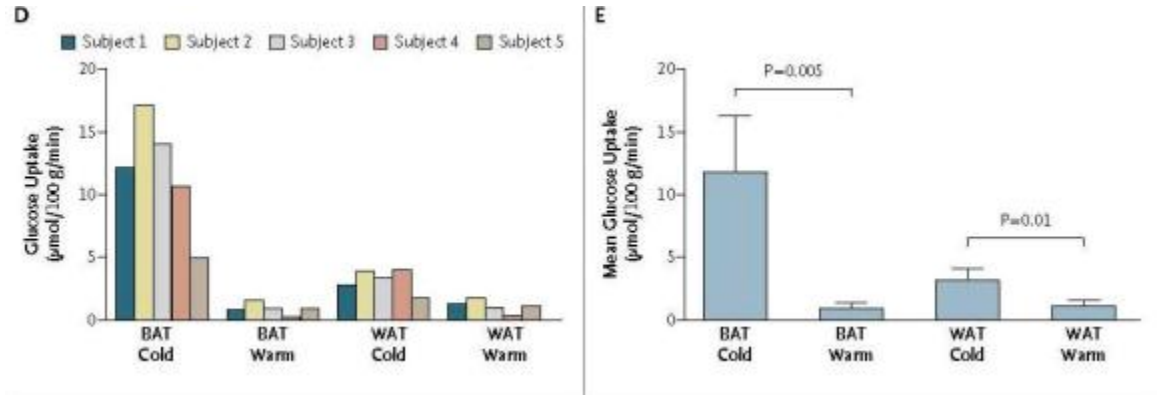
Brown Adipose Tissue, BAT, is the key cellular element in tissue thermogenesis, the production of thermal output. It has been thought to be only in infants and some other mammals and that it disappears in adults. As Hahn and Novak have stated, BAT was found to have a key role in nonshivering thermogenesis. The production of non shivering heat is stimulated by norepinepherine.

However, as Virtanen et al state:

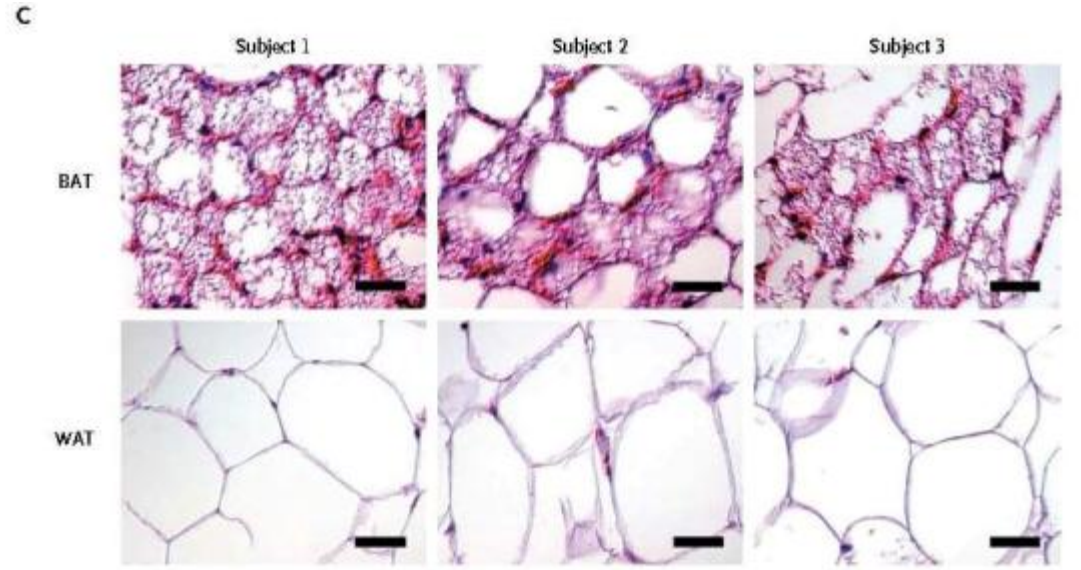
"Active brown adipose tissue helps maintain normal body temperature in newborn infants. It is believed that this tissue regresses with increasing age and is completely lost by the time a person reaches adulthood. However, the capacity to produce brown adipose tissue in adulthood has been shown in patients with catecholamine secreting tumors such as pheochromocytomas and paragangliomas, in whom distinct brown adipose tissue depots develop…"

From the Virtanen paper above the authors present a comparison between brown and white fat and the energy consumed or generated and it is depicted below:

87



Clearly the brown fat burns energy at a much more rapid rate than white fat. That is most likely why it is so prevalent in infants and seems to regress, albeit not totally, in adults. The comparison between white and brown cells upon which this data was obtained is shown below:



In summary from the seminal work of Hahn and Novak we have the observation of BAT as follows:

In summary, BAT in neonatal mammals plays an important role in nonshivering heat production. Fatty acid oxidation is of prime importance. Nevertheless, glycolysis and Krebs cycle intermediates are necessary for normal BAT function. Partial uncoupling of mitochondria seems to be induced by released fatty acid. An interesting point is the very high activity of phosphoenolpyruvate carboxykinase. This suggests the possibility of a cycle between this enzyme and pyruvate kinase and might account for the dissipation of

energy resulting from a decrease in the P/O ratio induced by increased cellular fatty acid content, while substrate level phosphorylation, which apparently is functional in BAT mitochondria, remains unaffected.

2.2.3.2 White Adipose Tissue

White Adipose Tissue takes in glucose and creates and store fats which may be used from time to time through lipolysis to run the TCA or Krebs cycle. We show below the cycle of glucose entering the cell, the TCA cycle processing it to produce the fats via fatty acid production and then when necessary the fats being broken down for energy in the TCA cycle.

In summary from the work of Hahn and Novak:

"In summary, the development of white adipose tissue in both man and rat must be considered in relation to the increase in fat content, and thus cell size, with age. This change can explain the decreases in many enzyme activities expressed per unit of wet weight observed during postnatal development. In addition, however, some enzyme activities per unit of cytoplasmic or mitochondrial protein are also found to be changed with age and also appear to be affected by the diet (e.g., fatty acid synthesis during the suckling period when a high fat diet is fed). Such developmental changes seem much more pronounced in man than in the rat."

2.2.3.3 The Adipocyte as a Source and Target for Inflammation

As Rajala and Scherer state:

"Obesity is associated with an increase in TNF production in adipose tissue …. The locally elevated TNF directly interferes with proper insulin signal transduction through specific phosphorylation of critical serine residues in the insulin receptor and insulin receptor substrate 1, thereby leading to a local desensitization to insulin signaling …). In addition to local increases in TNF, a systemic increase in inflammatory markers has been shown to be associated with obesity. C reactive protein (CRP) is an unspecific acute phase reactant that serves as an excellent indicator of systemic inflammation... Insulin resistance is not only associated with a significant increase in CRP, but a whole host of additional acute phase reactants that are elevated as well. Many of these additional factors including IL 6, 1 acid glycoprotein, and serum amyloid A (SAA) are expressed in adipose tissue... All of these proteins (with the exception of CRP) are up regulated in adipose tissue in the insulin resistant state. Increased serum IL 6 is predictive of future cardiovascular problems…. SAA can effectively compete for binding of apolipoprotein A I on high density lipoprotein particles, thereby altering trafficking of these particles ..."

Thus the fat cells are generators of inflammatory products that place added stress upon the body.

Further work as discussed by McGillis also focuses on the immune system response to excess adipocytes. McGillis states:

"Over the last decade, the immune system and inflammatory processes have been implicated in many diseases where their involvement had not previously been appreciated. Diabetes, a serious metabolic disease, and Alzheimer's disease, a neurodegenerative disorder, are but two examples ... We also have recognized that the immune system, once considered by many to function independently of outside influence, is subject to regulatory actions of both neural and endocrine systems…. Now a study by Sennello et al. … in this issue adds an important piece of evidence to the growing list suggesting that WAT and its soluble products adiponectin and leptin influence immune and inflammatory functions…"

We shall discuss this later when we look at Type 2 Diabetes.

2.3 CAUSES OF OBESITY

The next question that must be asked is what are the causes of obesity. If we understand the processes that lead to it then can we better understand what precipitates and drives these processes. We looked briefly at this when we examined leptin and the hypothalamus link but the question behind that is are there drivers which we can then attack and thus change the propensity towards obesity, namely is there treatment or a cure, other than simply watching what you eat. Bell et al state:

"Obesity is caused by perturbations of the balance between food intake and energy expenditure, which is regulated by a complex physiological system that requires the integration of several peripheral signals and central coordination in the brain.

The hypothalamus functions as a central regulator in this system. It receives information about energy balance through neuronal and hormonal signals to several tissue nuclei within it — particularly the ventro medial, paraventricular and arcuate nuclei — and to the lateral hypothalamic area.

The arcuate nucleus has an essential role in this system; it contains two sets of neurons, one produces agouti related protein (AGRP) and neuropeptide Y (NPY) and the other produces pro opiomelanocortin(POMC) and cocaine and amphetamine related transcript (CART). The first type are orexigenic, promoting food intake and reducing energy expenditure, and the second type produce the opposite anorexigenic effect."

This somewhat summarizes the general position of many researchers today. It is a process driven via the hypothalamus and this process creates an overwhelming urge that forces people to over eat and thus towards obesity.

Yet we still argue that the explosion of obesity cannot be logically explained by the above hypothalamus argument, otherwise it would always have been with us to some degree. It must be explained for the most part by the availability of certain types of high energy food, its ease of access and the inability of humans to control their consumption.

2.4 GENETIC INFLUENCES

There has been a great deal of work trying to understand if there is a genetic basis for obesity. For the most part the studies have focused on the Input portion of the obesity problem and there is little if any work performed in the Output or Net Accumulation elements.

Bell et al have presented a good summary of the genetics of obesity focusing on the hypothalamus link and we have found this an excellent summary source for the current status of the work in this area. Loos and Bouchard look more closely at obesity as a genetic disorder and their focus ultimately appears to be seeking a pharmacological means to control the desire to over eat. Feigelson et al provide a summary of the specific genes and they extend this to demonstrate the correlation between obesity and breast cancer. The work by Comuzzie and Allison is an older effort which summarized the status over twelve years ago. It is worth reviewing the development from this point onwards. Farooqi and O'Rahilly provide a more recent update on the genetic targets.

Before continuing it is worth a brief mention of the primary genetic target, leptin. The work by Elmquist et al is an excellent summary of the leptin research at the end of 1999. Wang et al discuss the synergistic capabilities of leptin with Cholecystokinin in the control of obesity which opened up alternative genetic control patterns. Levine and Billington discuss the measurement of leptin as reflective of true body adiposity because there is still confusion of the true measurement of body fat. Lonnqvist details the current state of the obese gene ob and leptin. The focus there is again at a pharmacological control. Halaas and Friedman look closer at the leptin receptor as an alternative and somewhat specific target for such a pharmacological approach. Bray and York also look broadly at leptin as the control. Finally the paper by Enriori et al is a recent contribution looking at leptin and obesity, specifically the generation of leptin resistance.

As Enriori et al state:

"We can speculate that "physiological" leptin signaling attempts to limit body weight, even in obese states, but that other factors are opposing this. In modern society, ***we might suggest that hedonic cues to over consume are one such factor****. The effects of leptin are more obvious in a controlled dietary paradigm, because the background influence of variable diet is absent. This interpretation suggests the question: "Is obesity caused by increased hedonic and cortical cues to over eat, which overwhelm the normal counter regulatory responses to increased obesity?" As an additional complication, we might hypothesize that in some situations leptin signaling can cause desensitization, perhaps when levels are elevated for a significant period of time, and that only after leptin signaling is reduced for a period (such as after a long hypocaloric diet) can the system resensitize."*

This quote alludes ever so slightly to the "hedonistic cues" to "over consume" which all too often is the way the genetic approach has been focused. As we shall see, one observes correlation between siblings, yet that may very well be imprinted behavior rather than

genetics. Cultural imprints where social life is focused on food may be more important than genes.

We continue with a quote from Loos and Bouchard where they state:

"Obesity is one of the most pressing problems in the industrialized world. Twin, adoption and family studies have shown that genetic factors play a significant role in the pathogenesis of obesity. Rare mutations in humans and model organisms have provided insights into the pathways involved in body weight regulation.

Studies of candidate genes indicate that some of the genes involved in pathways regulating energy expenditure and food intake may play a role in the predisposition to obesity. Amongst these genes, sequence variations in the adrenergic receptors, uncoupling proteins, peroxisome proliferator activated receptor, and the leptin receptor genes are of particular relevance. Results that have been replicated in at least three genome wide scans suggest that key genes are located on chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 11q, 17p and 20q.

We conclude that the currently available evidence suggests four levels of genetic determination of obesity: genetic obesity, strong genetic predisposition, slight genetic predisposition, and genetically resistant. This growing body of research may help in the development of anti obesity agents and perhaps genetic tests to predict the risk for obesity….

Obesity results from a chronic disruption of the energy balance. The long term relations amongst energy intake, energy expenditure, nutrient partitioning and adipogenesis determine the amount of energy stored in the body. When energy intake chronically exceeds energy expenditure and when fuel partitioning favours lipid storage and carbohydrate oxidation, the resulting imbalance causes expansion of fat cells and increased number of fat cells…..

With few exceptions, obesity is a complex multifactorial disease. As for other complex human diseases, the identification of genes and mutations causing obesity in a small number of cases does not directly address genetic causes in the population as a whole, but can illuminate candidate pathways involved in the pathophysiology of obesity.....

Individuals affected with Mendelian obesity syndromes or single gene disorders represent only a small fraction of the obese population and cannot explain the magnitude of the obesity problem that industrialized societies are facing today. Obesity is a complex multifactorial phenotype; interindividual variation in such phenotypes is thought to result from the action of multiple genes and environmental factors….

Candidate genes involved in the regulation of energy expenditure. Although all single gene disorders causing obesity identified thus far result from defective genes altering primarily food intake, most association studies have focused on genes that are involved in pathways of energy expenditure and lipid and adipose tissue metabolism. The

mitochondrial uncoupling proteins (UCPs) have been examined extensively for association with energy expenditure phenotypes. UCP1 dissipates the proton electrochemical gradient across the mitochondrial membrane, thereby uncoupling substrate oxidation from conversion of adenosine diphosphate to adenosine triphosphate, leading to generation of heat. UCP1 plays an important thermogenic role in brown adipose tissue.

There are a few genetically inherited or mutated genetic diseases which include obesity. Some of them are:

1. Prander Willi syndrome; an autosomal dominant disease characterized by obesity, muscular hyotonia, short stature, hypogonadism, mental retardation, small hands and feet. This is a result of a deletion or disruption on 15q11 q13.

2. Albright Hereditary Osteodystrophy: autosomal dominant with obesity, round facies, short stature, brachydactyly, mental retardation. It is related to the GNAS1 gene.

3. Bardet Biedl syndrome: characterized by obesity, mental retardation, Pigmentary retinopathy, polydactyly and hypogentialism. There is a genetic alteration on 15q22.3 q23.

Loos and Bouchard state:

"Although causative mutations underlying the above obesity syndromes have been identified, no clear mechanistic link between the product of mutant gene and disordered energy balance has been defined ..."

What this clearly states is that although genetic markets can be found in those with these syndromes and not in those without, the process which leads from that market to the disease process is unknown. That is the crux of all of the studies regarding obesity and genetics.

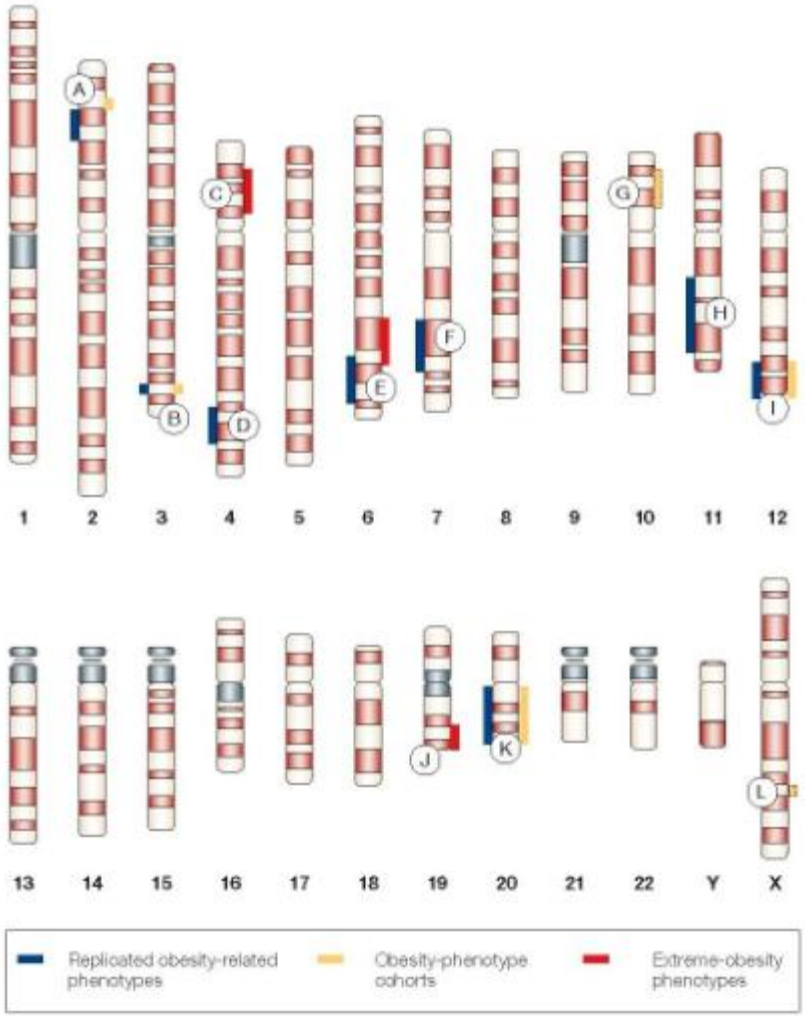
In the paper by Bell et al , the authors state:

"The most important message after nearly a decade of searching for genes that are involved in human obesity is that such genes, perhaps surprisingly, really do exist despite the key role of modern lifestyles in the current obesity epidemic. These genes seem to be important in the development of most severe early onset forms of obesity that have strong effects on morbidity and mortality. Their characterization has still to be completed, but should unravel the molecular mechanisms of an affliction that affects hundreds of millions of people, opening up new avenues in the management of a disease for which no efficient treatment, apart from major surgery, currently exists. By the discovery of novel genes that are involved in this condition, new aetiological pathways will be revealed that should lead to innovative therapies, preventive measures and insights into the pharmacogenetics of such strategies."

Ball et al present the following Table of putative genes as causative for obesity.

*Gene**	*Gene name**	*Location‡*	*Phenotypes measured||*
ACDC	Adipocyte, C1Q and collagen domain containing, adiponectin	3q27	BMI, waist circumference BMI
ADRA2A	Adrenergic receptor α 2A	10q24–q26	Skinfold ratio, abdominal fat Skinfold ratio
ADRA2B	Adrenergic receptor α 2B	2p13–q13	Basal metabolic rate, weight gain
ADRB1	Adrenergic receptor β 1	10q24–q26	Weight, fat mass, BMI
ADRB2	Adrenergic receptor β 2 surface	5q31–q32	WHR, obesity, BMI, subcutaneous fat accumulation, obesity Adipocyte lipolysis
ADRB3	Adrenergic receptor β 3	8p12–p11.2	WHR, BMI, weight gain capacity, earlier onset
LEP	Leptin (obesity homologue, mouse)	7q31.3	Obesity, BMI
LEPR	Leptin receptor	1p31	BMI, fat mass, overweight Fat mass, overweight Fat mass
NR3C1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	5q31	Obesity, overweight
PPARG	Peroxisome proliferative activated receptor, γ	3p25	BMI, weight, fat mass BMI, overweight, fat mass
UCP1	Uncoupling protein 1 (mitochondrial, proton carrier)	4q28–q31	Weight, BMI WHR
UCP2	Uncoupling protein 2 (mitochondrial, proton carrier)	11q13	Obesity BMI, obesity, skinfold thickness
UCP3	Uncoupling protein 3 (mitochondrial, proton carrier)	11q13	Caloric intake, fat intake, fat mass, WHR, BMI Skinfold thickness

The following is also taken from the same paper and is a graphic of the Human Chromosome and the locations of many of these putative obesity genes.



To summarize from Loos and Bouchard:

"The obesity epidemic we are facing today occurred only over the past three decades and can clearly not be explained by changes in our genome. The rapid weight gain in the population is more likely due to a changing environment that encourages consumption and discourages expenditure of energy, behaviours that are poorly compatible with our pre agricultural hunter–gatherer genes. Therefore, most obesity cases come about not as a result of a markedly defective biology but are rather caused by maladaptive behaviours nurtured by an obesogenic environment. "

This statement is quite telling in that it tells the basic fact of Mendellian genetics. Namely changes in genetic makeup take long periods of time. Obesity is a recent phenomenon and is growing globally, especially in places where it was once unheard of, with no discernable genetic flow. One need look no further than China in the past thirty years. Thus as Loos and Bouchard state, in the middle of their paper, ***can clearly not be explained by changes in our genome***, then it is most likely NOT genetic and is most likely individual choice.

3 TYPE 2 DIABETES

In this section we look at Type 2 Diabetes and we look at this disease as a reaction to obesity and as well as a genetically influenced disorder.

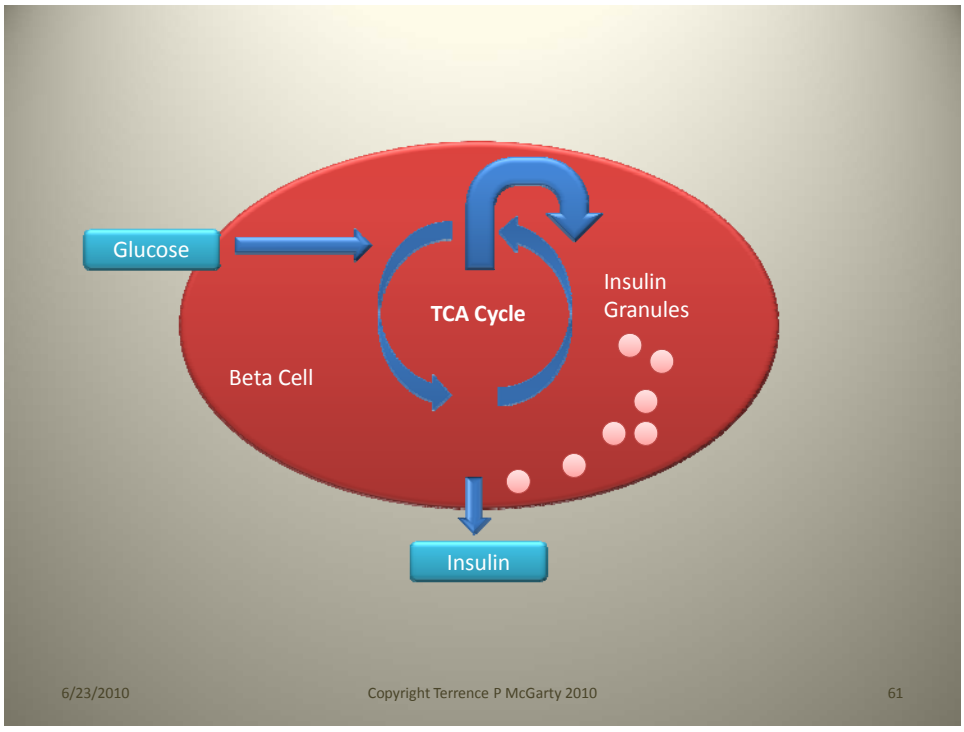
We first look at the underlying metabolism and then return to develop a clear definition of what we mean clinically by Type 2 Diabetes. Simply stated, Type 2 Diabetes is a degenerative disease of insulin control and secretion. Unlike Type 1 Diabetes, where the pancreas beta cells have been made totally non functional, in Type 2 there is a deadly cycle of degradation, where secretion of insulin increases in an attempt to keep up with the glucose and as glucose increases the insulin increases until a burn out occurs.

As is often the case, if caught early ad if the glucose load is decreased by diet, the process may be halted and in some cases reversed. We shall address that later.

First we want to summarize the basic elements of Type 2 Diabetes physiology and its consequences.

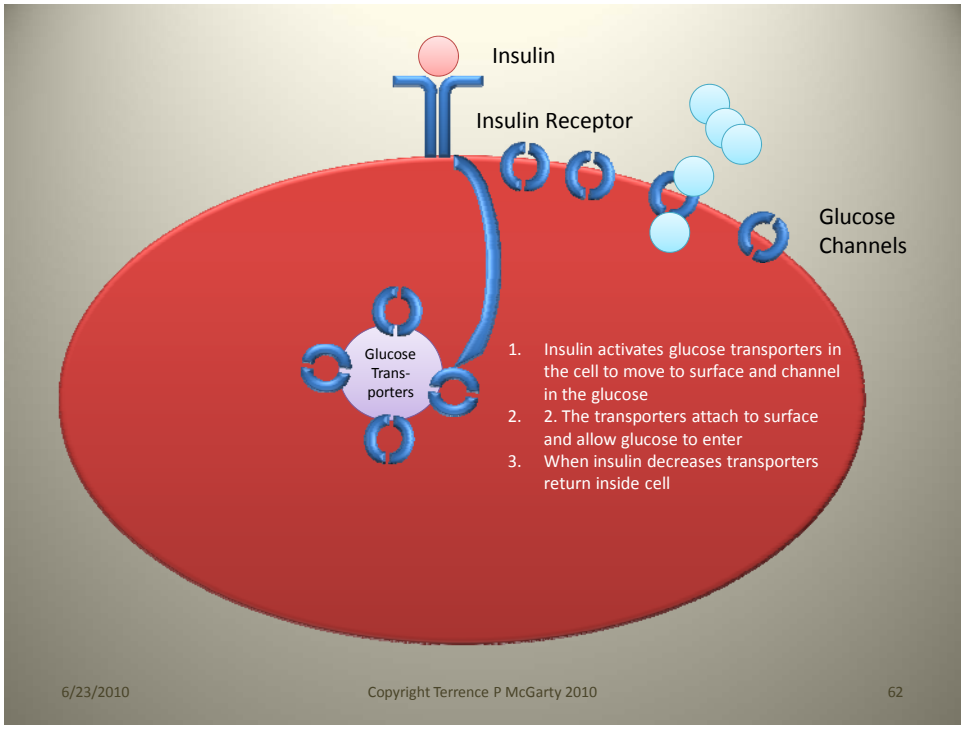
3.1 BASIC METABOLISM

The basics of glucose control is the operation of the Beta cell in the pancreas. It sense glucose and outputs insulin. We depict this below:



In the simplest of worlds this is the beta cell. Now the glucose comes from the breakdown of the carbohydrates as we discussed earlier. The glucose is in the blood

stream and the cell has access to it. In simplest terms the insulin when released to the blood activates channels which permit glucose to flow into a cell and be used for energy purposes. We show this below:



This is the plain and simple function of insulin and glucose. In Diabetes this process gets

In the paper by Fernandez Mejia, the author presents a good summary of the molecular element of Type 2 Diabetes. She starts:

Insulin secretion in response to glucose is a complex, multistep process that requires transport and oxidation of glucose, electrophysiological changes and fusion of insulin containing secretory granules with the beta cell plasma membrane .

Glucose enters the cell by facilitated diffusion mediated by a group of structurally related glucose transport proteins (GLUT), characterized by 12 hydrophobic helical domains. To date, at least 12 GLUTs have been described . In the pancreatic beta cell, glucose is transported by the glucose transporter 2 isoform (GLUT2).

Glucose is phosphorylated to form glucose 6 phosphate by glucokinase. This enzyme plays a critical role in glucose induced insulin secretion and is considered the glucosensor of the pancreatic beta cell. Due to its kinetic characteristics, glucokinase is a determining factor for glucose phosphorylation and hence for its metabolism through glycolysis and oxidation.

She continues:

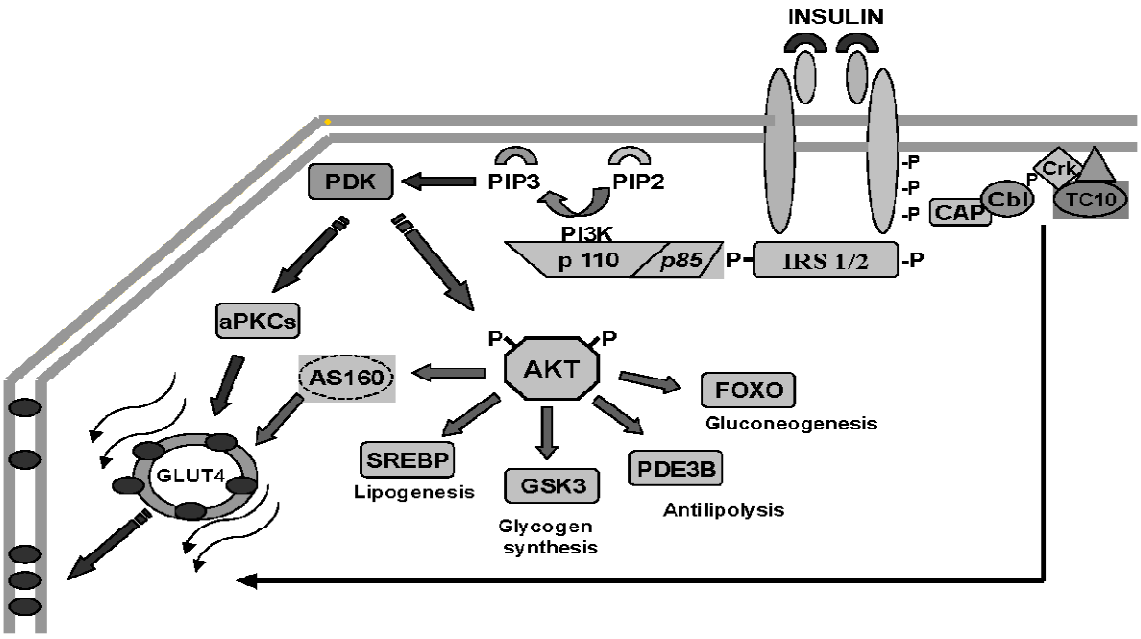
Insulin starts its action by binding to the insulin receptor; this leads to a cascade of events that involves protein and membrane phospholipid phosphorylation, scaffold and docking proteins, and cytoeskeleton activity (Fig. 2)… The insulin receptor belongs to a subfamily of receptors, all with protein tyrosine kinase activity. The insulin receptor is a heterotetrameric membrane glycoprotein consisting of two alfa subunits and two beta subunits. Insulin binds to the extracellular alpha subunit of the receptor and induces a conformational change that brings the alpha subunits closer together. This leads to a rapid auto phosphorylation of the receptor, and catalyzes the phosphorylation of intracelular proteins such as:

a) members of the insulin receptor substrate family,

b) Shc and

c) CbI. Upon tyrosine phosphorylation, these proteins act as docking sites for proteins that contain SH2 (Srchomology 2) domains, such as phosphoinositide 3 kinase, Grb 2 and SHP 2, resulting in a diverse series of signaling pathways.

I show here diagram below which is what we presented before but with more detail:



She continues with the other functions of Insulin which we summarize in the following Table.

Function	*Action*
Insulin mediated glycogen synthesis	Insulin stimulates glycogen accumulation through a coordinated increase in glucose transport and glycogen synthesis. The hormone activates glycogen synthase by promoting its dephosphorylation, through the inhibition of kinases such as PKA or GSK 3 , and activation of protein phosphatase 1 (PP1). Insulin, via PI3K/Akt, phosphorylates and inactivates GSK 3, decreasing the rate of phosphorylation of glycogen synthase, thus increasing its activity state.
Insulin mediated lipid synthesis	Insulin induces the transcription of critical enzymes of lipid synthesis. The transcriptional factor, sterol regulatory element binding protein I c (SREBP 1c), has a pivotal role on lipogenic gene expression, and has been proposed as a key mediator of insulin transcriptional effects . Insulin stimulates the transcription of SREBP 1c , this effect of insulin on SREBP 1c appears to involve PI3K/Akt pathway
Insulin repression of glucose output	Insulin inhibits the production and release of glucose by the liver by blocking gluconeogenesis and glycogenolysis. This occurs through a direct effect of insulin on the liver, as well as by indirect effects of insulin on substrate availability, such as free fatty acids, lactate and aminoacids . Insulin inhibits the transcription of the gene encoding phosphoenolpyruvate carboxylase, the rate limiting step in gluconeogenesis . The hormone also decreases transcription of the genes encoding fructose 1, 6 bisphosphatase and glucose 6 phosphatase. The mechanism is produced via phosphatidylinositol 3 kinase (PI3K) and Akt through phosphorylation of the transcription factor Foxo 1 .
Insulin repression of lipolysis	The hormone strongly inhibits lipolysis in adipocytes, through the inhibition of the hormone sensitive lipase . Insulin inhibits the activity of the lipase primarily through reductions in cAMP levels, owing to the activation of a cAMP specific phosphodiesterase 3B by the serine threonine kinase Akt . The low concentration of insulin required to inhibit the hormone sensitive lipase may explain why patients with mild type 2 diabetes and glucose intolerance are hyperglycemic in the absence of significant elevations of plasma free fatty acids or ketone bodies.

In the paper by Taubes the author states:

"Insulin is the primary regulator of fat, carbohydrate, and protein metabolism; it regulates the synthesis of glycogen, the form in which glucose is stored in muscle tissue and the liver, and it inhibits the synthesis of glucose by the liver. It stimulates the synthesis and storage of fats in fat depots and in the liver, and it inhibits the release of that fat. Insulin also stimulates the synthesis of proteins and of molecules involved in the function, repair, and growth of cells, and it functions as a signaling molecule conveying information on fuel availability from the periphery to the brain and central nervous system."

There are two theories now about how Diabetes evolves, (i) the lipid overload theory and (ii) the inflammation theory. As Taube states:

"....1. Fat overload

In the mid 1970s, endocrinologists focused on the insulin receptor itself as a likely key to the puzzle. They assumed that resistance was caused either by down regulation of the insulin receptor—a normal desensitization process—or by a defect in the receptor itself or the binding of insulin to the receptor. By the mid 1980s, Jerrold Olefsky, now at the University of California, San Diego, had demonstrated that the primary defect was downstream in the signaling pathway, not in the receptor itself.

Since the early 1990s, the observation that insulin resistance is associated with elevated levels of free fatty acids in the bloodstream has led researchers to focus on lipid overload as the precipitating event. Several observations support the hypothesis.

The single best predictor for the presence of insulin resistance in young, lean offspring of type 2 diabetics, according to Gerald Shulman, an endocrinologist at Yale University, is the accumulation of fat inside muscle cells. Shulman and his colleagues have also studied sedentary populations of lean, healthy, elderly subjects and obese, insulin resistant adults and children. In all those cases, he says, "the more fat inside the muscle cells, the more insulin resistant they are." ....

2. Inflammation

Competing with the lipid overload hypothesis is the theory that inflammation is to blame. The idea was sparked in the mid 1990s, when Gökhan Hotamisligil of the Harvard School of Public Health and Bruce Spiegelman of Harvard Medical School reported that the inflammatory cytokine TNF α was overexpressed in animal models of obesity.

They demonstrated that they could induce insulin resistance in fat cells in vitro by exposing them to TNF α. They also showed that they could protect obese strains of mice from insulin resistance by knocking out the genes either for TNF α itself or for TNF α receptors.

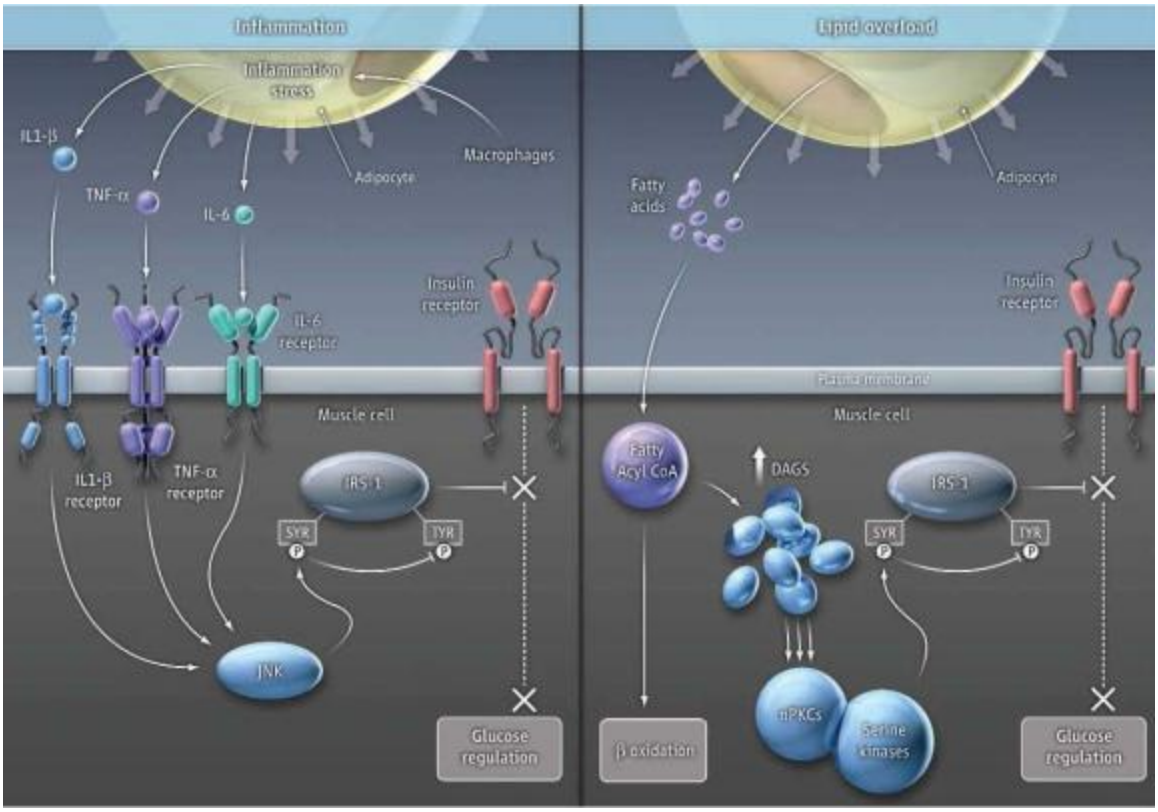
The hypothesis began to gain wide acceptance after Steven Shoelson of the Joslin Diabetes Center reported in 2001 that he could make cells insulin resistant by

overexpressing IKK β, a molecule that works in signaling pathways to activate the inflammatory mediator NF κB.

Among the compounds that inhibit IKK β are salicylates, aspirin like compounds that are used at high doses to treat rheumatoid arthritis and rheumatic fever, both inflammatory conditions. "That struck a chord with me," says Shoelson, because "among the list of things that can cause low blood sugar are salicylates."

One obvious implication, he says, is that "inflammation is a potential pathogenic mediator of both insulin resistance and type 2 diabetes." "

Taube also presents the following two pathway options, the one for inflammation and the one for lipid overload.



Thus the full details as to what causes the breakdown of the process has yet to be detailed. However we do know that by reducing the glucose load, with a reduced insulin capacity, we can reduce the overload of glucose in the blood, and by definition reduce the Diabetic state.

3.2 DEFINITION

The NIH defines Type 2 Diabetes as follows[4]:

[4] http://diabetes.niddk.nih.gov/dm/pubs/overview/

The most common form of diabetes is type 2 diabetes. About 90 to 95 percent of people with diabetes have type 2. This form of diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities. About 80 percent of people with type 2 diabetes are overweight.

Type 2 diabetes is increasingly being diagnosed in children and adolescents, especially among African American, Mexican American, and Pacific Islander youth.

When type 2 diabetes is diagnosed, the pancreas is usually producing enough insulin, but for unknown reasons the body cannot use the insulin effectively, a condition called insulin resistance. After several years, insulin production decreases. The result is the same as for type 1 diabetes—glucose builds up in the blood and the body cannot make efficient use of its main source of fuel.

The symptoms of type 2 diabetes develop gradually. Their onset is not as sudden as in type 1 diabetes. Symptoms may include fatigue, frequent urination, increased thirst and hunger, weight loss, blurred vision, and slow healing of wounds or sores. Some people have no symptoms.

Type 2 Diabetes is diagnosed as follows according to NIH:

The fasting blood glucose test is the preferred test for diagnosing diabetes in children and non-pregnant adults. The test is most reliable when done in the morning. However, a diagnosis of diabetes can be made based on any of the following test results, confirmed by retesting on a different day:

1. *A blood glucose level of 126 milli grams per deciliter (mg/dL) or higher after an 8 hour fast. This test is called the fasting blood glucose test.*

2. *A blood glucose level of 200 mg/dL or higher 2 hours after drinking a beverage containing 75 grams of glucose dissolved in water. This test is called the oral glucose tolerance test (OGTT).*

3. *A random—taken at any time of day—blood glucose level of 200 mg/dL or higher, along with the presence of diabetes symptoms.*

There is also a condition termed pre diabetes and the NIH classifies it as follows:

People with pre diabetes have blood glucose levels that are higher than normal but not high enough for a diagnosis of diabetes. This condition raises the risk of developing type 2 diabetes, heart disease, and stroke.

Pre diabetes is also called impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on the test used to diagnose it. Some people have both IFG and IGT.

IFG is a condition in which the blood glucose level is high—100 to 125 mg/dL—after an overnight fast, but is not high enough to be classified as diabetes. The former definition of IFG was 110 mg/dL to 125 mg/dL.

IGT is a condition in which the blood glucose level is high—140 to 199 mg/dL—after a 2 hour OGTT, but is not high enough to be classified as diabetes.

Pre diabetes is becoming more common in the United States. The U.S. Department of Health and Human Services estimates that at least 57 million U.S. adults ages 20 or older had pre diabetes in 2007. Those with pre diabetes are likely to develop type 2 diabetes within 10 years, unless they take steps to prevent or delay diabetes.

The ADA Expert Committee in 2003 stated:

Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)

This form of diabetes, previously referred to as non insulin dependent diabetes, type 2 diabetes, or adult onset diabetes, is a term used for individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency (18 –21). At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes, and it is likely that the proportion of patients in this category will decrease in the future as identification of specific pathogenic processes and genetic defects permits better differentiation among them and a more definitive sub-classification.

Although the specific etiologies of this form of diabetes are not known, autoimmune destruction of cells does not occur, and patients do not have any of the other causes of diabetes listed above or below. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance (22,23). Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region . Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection (25–27).

This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes (28 –30). Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications (30 – 34).

Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their cell function been normal . Thus, insulin

secretion is defective in these patients and insufficient to compensate for the insulin resistance.

Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal (36– 40). The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity (29,41). It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups (29,30,41). It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes (42,43).

However, the genetics of this form of diabetes are complex and not clearly defined…

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

The terms IGT and IFG refer to a metabolic stage intermediate between normal glucose homeostasis and diabetes, now referred to as pre diabetes.

This stage includes individuals who have IGT and individuals with fasting glucose levels 110 mg/dl (6.1 mmol/l) but 126 mg/dl (7.0 mmol/l) (IFG).

The term IFG was coined by Charles et al. (115) to refer to a fasting plasma glucose (FPG) level 110 mg/dl (6.1 mmol/l) but 140 mg/dl (7.8 mmol/l).

We are using a similar definition, but with the upper end lowered to correspond to the new diagnostic criteria for diabetes.

A fasting glucose concentration of 109 mg/dl (6.1 mmol/l) has been chosen as the upper limit of "normal." Although it is recognized that this choice is somewhat arbitrary, it is near the level above which acute phase insulin secretion is lost in response to intravenous administration of glucose (116) and is associated with a progressively greater risk of developing micro and macro vascular complications (117– 121).

Note that many individuals with IGT are euglycemic in their daily lives (122) and may have normal or near normal glycated hemoglobin levels (123). Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized OGTT. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes and cardiovascular disease (117).

IFG and IGT are associated with the insulin resistance syndrome (also known as syndrome X or the metabolic syndrome), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high triglyceride and/or low HDL type, and hypertension (124). Insulin resistance is directly involved in the pathogenesis of type 2 diabetes. IFG and IGT appear as risk factors for this type of diabetes at least in

part because of their correlation with insulin resistance. In contrast, the explanation for why IFG and IGT are also risk factors for cardiovascular disease is less clear. The insulin resistance syndrome includes well recognized cardiovascular risk factors such as low HDL levels and hypertension. In addition, it in includes hypertriglyceridemia, which is highly correlated with small dense LDL and increased plasminogen activator inhibitor 1 (PAI 1) levels.

The former is thought to have enhanced atherogenicity, perhaps as a result of its greater vulnerability to oxidation than normal LDL. PAI 1 is a cardiovascular risk factor probably because it inhibits fibrinoloysis. Thus, the insulin resistance syndrome contains many features that increase cardiovascular risk. IFG and IGT may not in themselves be directly involved in the pathogenesis of cardiovascular disease, but rather may serve as statistical risk factors by association because they correlate with those elements of the insulin resistance syndrome that are cardiovascular risk factors.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

The new criteria The diagnostic criteria for diabetes mellitus have been modified from those previously recommended by the NDDG or WHO . The revised criteria for the diagnosis of diabetes are shown in Table 3. Three ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day, by any one of the three methods given in Table 3. For example, one instance of symptoms with casual plasma glucose 200 mg/dl (11.1 mmol/ l), confirmed on a subsequent day by 1) FPG 126 mg/dl (7.0 mmol/l), 2) an OGTT with the 2 h postload value 200 mg/dl (11.1 mmol/l), or 3) symptoms with a casual plasma glucose 200 mg/dl (11.1 mmol/l), warrants the diagnosis of diabetes. For epidemiological studies, estimates of diabetes prevalence and incidence should be based on an FPG 126 mg/dl (7.0 mmol/l).

This recommendation is made in the interest of standardization and also to facilitate field work, particularly where the OGTT may be difficult to perform and where the cost and demands on participants' time may be excessive. This approach will lead to slightly lower estimates of prevalence than would be obtained from the combined use of the FPG and OGTT (Table 4).

The Expert Committee recognizes an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered altogether normal. This group is defined as having FPG levels 110 mg/dl (6.1 mmol/l) but 126 mg/dl (7.0 mmol/l) or 2 h values in the OGTT of 140 mg/dl (7.8 mmol/l) but 200 mg/dl (11.1 mmol/l).

Thus, the categories of FPG values are as follows:

1. *FPG 110 mg/dl (6.1 mmol/l) normal fasting glucose;*

2. *FPG 110 (6.1 mmol/l) and 126 mg/dl (7.0 mmol/l) IFG; FPG 126 mg/dl (7.0 mmol/l) provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).*

The corresponding categories when the OGTT is used are the following:

1. *2 h postload glucose (2 h PG) 140 mg/dl (7.8 mmol/l) normal glucose tolerance;*

2. *2 h PG 140 (7.8 mmol/l) and 200 mg/dl (11.1 mmol/l) IGT;*

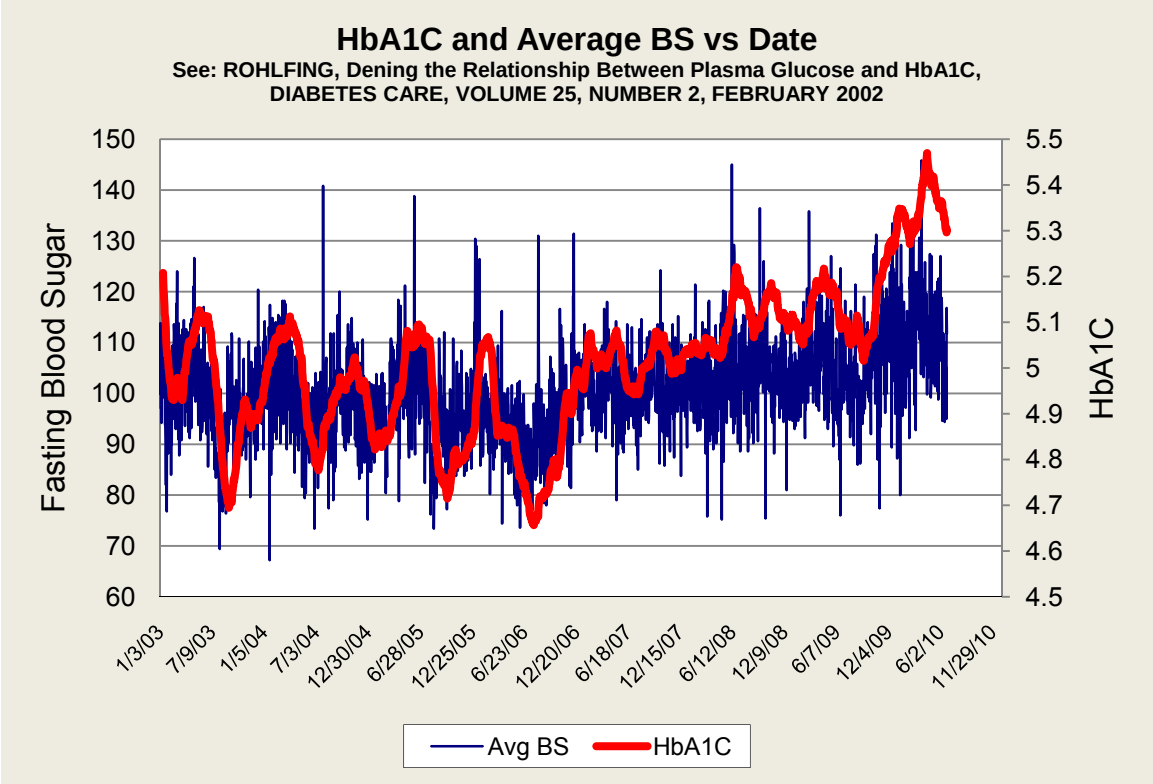
3. *2 h PG 200 mg/dl (11.1 mmol/l) provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).*

Because the 2 h OGTT cutoff of 140 mg/dl (7.8 mmol/l) will identify more people as having impaired glucose homeostasis than will the fasting cutoff of 110 mg/d (6.1 mmol/l), it is essential that investigator always report which test was used.

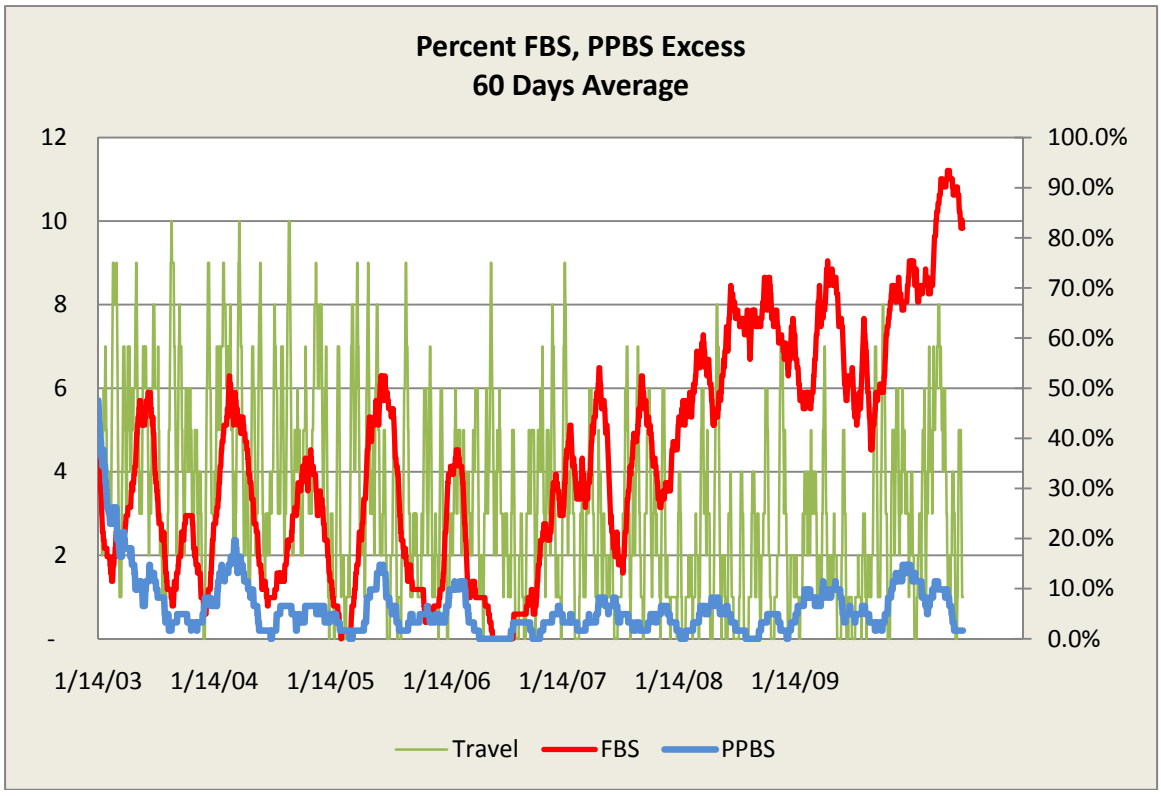
These two diagnostic criteria are similar but there are some subtle differences. The problem is that FPG at one time can change dramatically day to day. For example in our studies a single patient can see the FPG range over a 30 day period from 87-142. Thus any single sample is meaningless. HbA1c is an integrate 90 day number but that too can hide problems.

3.3 A SAMPLE PATIENT

Here we show specific results from a sample patient. This patient has a family history of Type 2 Diabetes on both sides and had a BMI of 31.0 and TG level of 455. The patient reduce weight to BMI of 22.5 and held it within 25.0 or less for this period. The chart depicts the HbA1c results from daily readings. No medication is used.

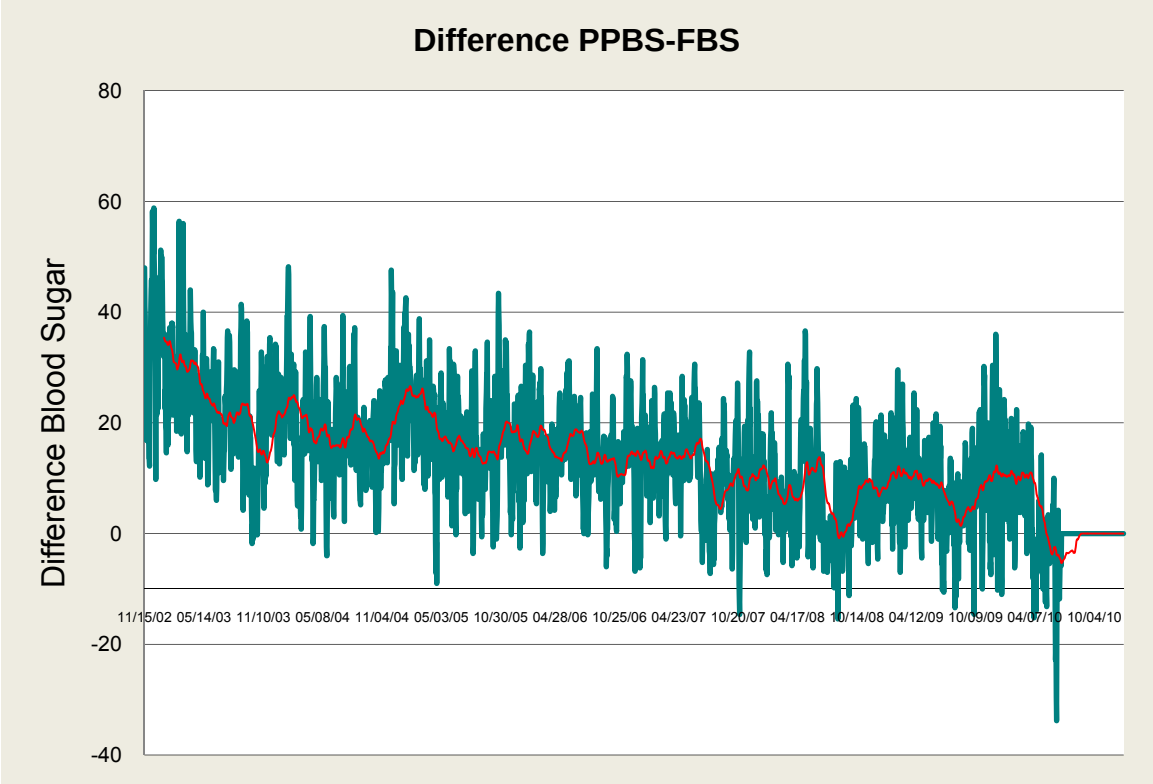


Now we also plotted the FP in excess of 100 and the PPPG in excess of 140 at 2 hour PP. The results are below:



Here we see the beginning of IFG syndrome over a two year period. One suspects that this patient, a heavy traveler as well, has been consuming excess carbs which we often see in IFG. The PPPG is well controlled, with infrequent spikes.

In fact we show the plot of FPG (FBS) less PPPG (PPBS) below.



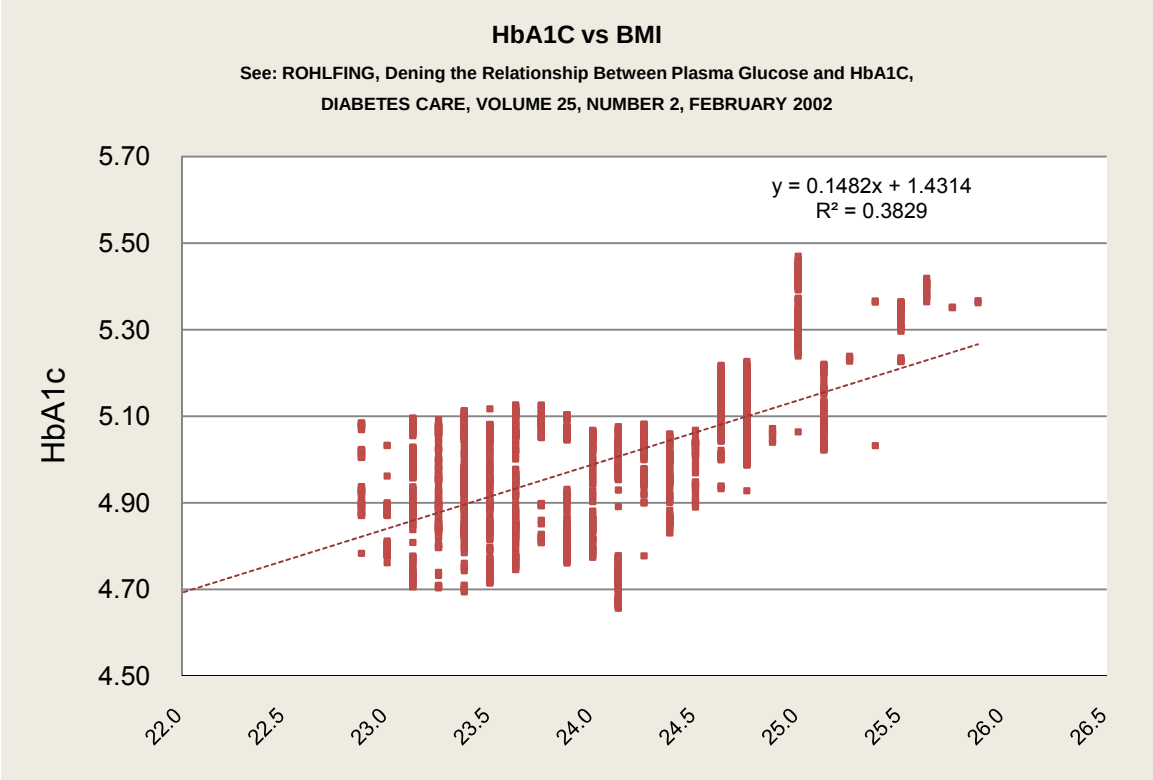
Note that what has happened is the IFG numbers clearly show FPG is often greater than PPPG. This we have seen often in IFG syndrome. We also believe it is controllable by stricter carbohydrate control post dinner meals.

4 CAUSALITY: OBESITY AND TYPE 2 DIABETES

The primary cause of Type 2 Diabetes is excess weight[5]. It commences as a breakdown of the pancreas' β cells to produce adequate amounts of insulin which in turn results in excess glucose in the blood stream[6]. It appears that when the body has excess weight that pancreas cannot generate the insulin fast enough and has a "run down" result.

It just stops generating insulin totally. There is however a social stigma to telling a Type 2 Diabetes patient that they are the cause of their disease due solely to their weight and their inability to control it. This is the distinct opposite to what had happened in cigarette smoking. Any attempt to modulate behavior related to caloric consumption is viewed as politically incorrect in today's environment which we believe is the main reason that we shall see an epidemic of Type 2 Diabetes especially in the young.

We start with a simple example. The chart below is from a patient who records FPG and PPPG on a daily basis for ten years. The patient had reduced BMI from 31.o to 22.5 and remained below 25.o Note the relationship between HbA1c and the BMI. There is a clear and strong correlation. This we shall show in detail herein.



[5] See the paper by Lazar. This is an exceptionally good summary of the obesity argument placed within a genetic and evolutionary context.

[6] See the paper by Marx for a recent summary of the status of the causes of Diabetes.

4.1 CAUSALITY STUDIES

We now will survey the results of four seminal studies on the causative effect of obesity on Type 2 Diabetes.

The first approach to better understanding the cause was proposed and studied by Taylor (2008). The Taylor approach is to take someone who has Type 2 Diabetes and then eliminate the putative cause. In this case what Taylor did was assume that weight was the cause and he then took patients and had them reduce the weight, mainly through gastric bypass surgery, and he then observed the results. Not surprisingly he noted the elimination of the Type 2 Diabetes as the BMI dropped to normal ranges.

Taylor states in the introduction of his paper:

Puzzles are oftenmost easily solved backwards. Isaac Newton exemplified this by using his newly invented and secret tool of calculus to establish the answer to unsolved mathematical problems, then presenting the proof in conventional mathematical terms having worked backwards to the question…. The same technique can be applied to unravelling the pathogenesis of disease, but there is a snag—a cure for the disease has to be discovered so that the pathogenesis may be observed, step by step, in reverse. However, it is now possible to achieve a cure in groups of people with type 2 diabetes. What happens during the period of return to normal insulin sensitivity and normal beta cell function?

This is the inverse approach and it is almost Popperian in that it has proven that one cannot find a case to disprove it. Taylor then continues the study. Note the key observation that in groups with Type 2 Diabetes a "cure" is achievable. This has been seen by every physician who has treated Type 2 Diabetes, get the weight off and all too often the disease disappears, at least the symptoms defining the disease.

Taylor has a compelling tale about fois gras, the fatty liver consumed heavily by the French. He states:

Fois gras in man and beast

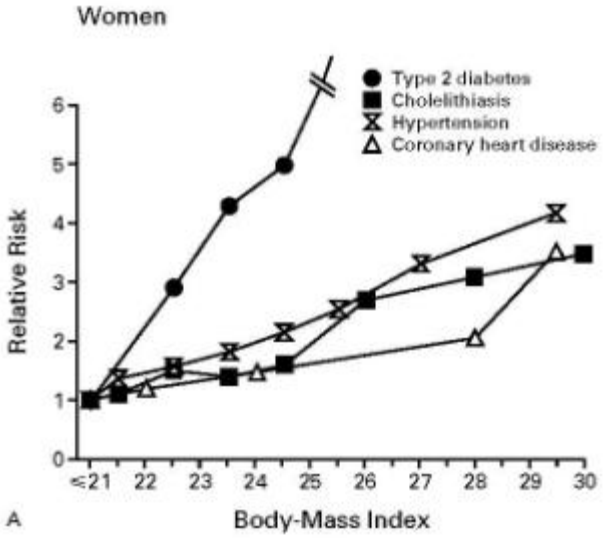
Obesity is strongly related to non alcoholic fatty liver disease . This is true in early life as well as in adulthood. An autopsy study has demonstrated a dose relationship between the degree to which children are overweight and the presence of fatty liver . In adolescence, 30% of obese individuals have fatty liver and the extent of liver fat accumulation is inversely proportional to habitual daily physical activity, both in type 2 diabetic and non diabetic individuals . But which comes first? Are individuals with fatty liver more prone to insulin resistance and weight gain, or do lifestyle factors initiate and underlie fatty liver?

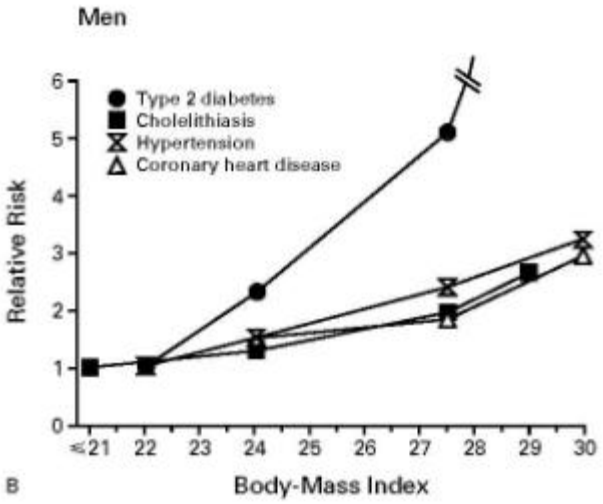
Farmers are the supreme experts at the practical manipulation of nature. The production of fatty liver in ducks and geese has been honed over at least 2,500 years . Currently, the birds are allowed increasing access to high carbohydrate feed over a 12 week free range period. During this phase, rapid weight gain occurs and the livers become fatty, enlarging to 50% of their final size. This is equivalent to severe fatty liver for man. In the final 12 days, gavage is used to administer a large, high fat energy overload and exacerbate the hepatic fat excess. However, the first phase of fois gras production gives all the necessary clues to the genesis of fatty liver in man. Prolonged intake of energy in excess of requirement will bring about intra hepatic triacylglycerol deposition.

Taylor Summarizes the forward and reverse path of the pathogenesis of Type 2 Diabetes.

Steps in the pathogenesis of type 2 diabetes	*Approximate time scale*
Reverse pathogenesis	
• ***Negative energy balance***	
• ***Decrease of liver fat***	Days
• ***Increase in insulin suppression of liver glucose production***	Days
• ***Improvement of glucose stimulated insulin secretion***	Days
• ***Decrease in plasma glucose***	Days to weeks
• ***Decrease in plasma triacylglycerol***	Days to weeks
Natural history	
• ***Positive energy balance***	
• ***Accelerated progression of insulin resistance***	Lifelong or years
• ***Increased liver fat***	Years
• ***Increased plasma triacylglycerol***	Years
• ***Unrestrained liver glucose production***	Few years
• ***Initial elevation of plasma glucose***	Few years
• ***Excess exposure of islets to fatty acid***	Months to years
• ***Decreased insulin secretion in response to glucose***	Months to years
• ***Hyperglycaemia***	Months
• ***Irreversible beta cell loss and dysfunction***	>2 years

Another forward looking correlative data source is in the paper by Willett et al where they summarize guidelines for weight in women based upon the Nurses' Study in the late 1990s. They present the following set of graphs shown relative risks as a function of BMI. These are clear indicators of correlation if not outright causality.





In the paper by Lazar he states:

"Type 2 diabetes stems from the failure of the body to respond normally to insulin, called "insulin resistance", coupled with the inability to produce enough insulin to overcome this resistant state. This common form of diabetes is often associated with obesity, and the current epidemics of these two conditions are seemingly related."

There is a strong relationship between Type 2 Diabetes and chronic inflammation, stresses that wear out the body's cells. As Lazar further states:

"*The close relationship between inflammation and diabetes is supported by the observation that stimulation of the innate immune response [by bacterial endotoxin during sepsis, for example] results in insulin resistance that contributes to the high mortality of critical illness. The interaction between inflammation and insulin signaling is*

also suggested by the ability of aspirin to improve insulin resistance, in part by preventing the antagonistic effects of fatty acids and cytokines."

Lazar continues:

"Why is obesity an inflammatory state and why does inflammation cause diabetes? The search for answers to these questions takes us again to evolutionary considerations. Perhaps the response to infection is more effective when glucose is shunted from muscle to the inflammatory cells involved in the immune response and tissue repair.

A potentially unifying view is that the body's ability to survive major stress, including infection and starvation, is enhanced by peripheral insulin resistance that preserves the brain's glucose supply.

This hypothesis might explain why cortisol, the major stress hormone, causes insulin resistance and stimulates the innate immune response, even though chronic cortisol exposure is anti inflammatory because of down modulation of the acquired immune response. The stress connection may extend to individual cells, as it has recently been shown that intracellular stress induces insulin resistance in a manner that is exacerbated by obesity, potentially through adipocyte secreted factors.

Moreover, chronic metabolic stress impairs the ability of pancreatic beta cells to secrete sufficient insulin to overcome insulin resistance, which is a hallmark of type 2 diabetes."

In the paper by Marx the author states:

"Although insulin resistance and the resulting impairment in glucose tolerance are early signs of diabetes, malfunction or even death of the insulin producing βcells also contributes to the disease. Ultimately about a third of diabetes 2 patients end up having to take insulin. Several factors seem to be involved in β cell dysfunction, including some of the same culprits implicated in insulin resistance.

For example, in experiments performed on the Zucker rat, a rodent model of obesity and diabetes, Unger's group at UT Southwestern has found that fatty acids can trigger a form of cell death called apoptosis in βcells. The fatty acids work indirectly, the UT Southwestern team found: They are first converted in βcells to toxic compounds known as ceramides.

That suggests to Unger that the β cell loss can be prevented. "If we block that [ceramide producing] pathway, we can block apoptosis," he says. Unger also suggests that this fatty acid toxicity may result from the body's insensitivity to leptin. In his view, that hormone's job is to keep fatty acids from accumulating in cells that aren't designed to handle them, such as βcells and muscle. But βcells don't have to die to contribute to diabetes 2 pathology: They can simply fail to secrete the insulin needed to handle all the glucose the body takes in.

At least in mouse models, researchers can duplicate that type of malfunction. For example, a team led by Ronald Kahn of the Joslin Diabetes Center in Boston and Mark Magnuson of Vanderbilt University School of Medicine in Nashville, Tennessee, found that they could prevent the increase in insulin secretion that normally occurs in response to glucose ingestion by specifically inactivating the insulin receptor in the β cells of mice. As a result of the consequent block in insulin activity, glucose can't get inside the cells to trigger release of the hormone."

The four studies above, Taylor, Lazar, Marx and Willett all point to obesity being the causative factor. The Taylor approach removes the factor and the disease goes away, the Willett's approach is correlative, the Marx study looks at details in rodent models, and the Lazar study relates it to inflammatory states as well. This completes the ring that demonstrates the truly causative effect.

4.2 GENES AND DIABETES

Unlike obesity and its putative genetic cause, Type 2 Diabetes has arguably a stronger basis for genetic causes. However there must be pre-disposing factors such as obesity and the inflammatory state created therefrom to set the genes in action.

There are several studies which link certain genetic markers to Type 2 Diabetes. Several of these are shown below are from Marx.

SOME CANDIDATE DIABETES 2 GENES

Mutated Gene	*Function*	*Effect*	*Linked to*
HNF 4 α, HNF 1 β Transcription IPF 1, NeuroD1	Insulin→ factors	MODY (human) secretion	
HNF 1 α factor	Transcription secretion	Insulin→ Oji Cree diabetes	MODY
Glucokinase metabolism	Glucose secretion	Insulin→	MODY
Calpain 10	Protease	Unknown Mexican and African Americans	Diabetes 2 in
PPAR γ factor	Transcription sensitivity	Insulin→	Diabetes 2
Insulin receptor insulin signals into cell	Transmits sensitivity and secretion	Insulin→ (rare); mouse models	Human diabetes
IRS1 and 2 signaling	Insulin sensitivity	Insulin→	Mouse models
Akt2 signaling	Insulin sensitivity	Insulin→	Mouse models
11 β HSD synthesis	Glucocorticoid lipids,	Blood → insulin sensitivity	Mouse models
UCP2	ATP → synthesis	Insulin→ secretion	Mouse models
Resistin	Fat cell "hormone"	Insulin→ sensitivity →	Mouse studies
Adiponectin	Fat cell "hormone"	Insulin sensitivity	Mouse, human studies

The current approach to treating Type 2 Diabetes is all too often the use of medications[7].

4.3 INFLAMMATION

Recent results have been confirming the role of inflammation being a major driver for Type 2 Diabetes. Inflammation is the result of obesity and the cytokines and other molecules release from the adipocytes. However the link between obesity and Type 2 Diabetes now seems clear via the inflammation pathways. We review two recent papers here to demonstrate the link.

[7] See the paper by DeFronzo and the one by Padwal. The DeFronzo paper is exceptionally good as a review of the various types of medications and their effective means of reducing insulin overload and maintaining proper insulin production.

In the paper by Rajala the author looks at the adipocyte as a source of inflammatory responses. He states:

Obesity is associated with an increase in TNF production in adipose tissue . The locally elevated TNF directly interferes with proper insulin signal transduction through specific phosphorylation of critical serine residues in the insulin receptor and insulin receptor substrate 1, thereby leading to a local desensitization to insulin signaling . In addition to local increases in TNF, a systemic increase in inflammatory markers has been shown to be associated with obesity.

C reactive protein (CRP) is an unspecific acute phase reactant that serves as an excellent indicator of systemic inflammation . Insulin resistance is not only associated with a significant increase in CRP, but a whole host of additional acute phase reactants that are elevated as well. Many of these additional factors including IL 6, 1 acid glycoprotein, and serum amyloid A (SAA) are expressed in adipose tissue . All of these proteins (with the exception of CRP) are up regulated in adipose tissue in the insulin resistant state. Increased serum IL 6 is predictive of future cardiovascular problems .

SAA can effectively compete for binding of apolipoprotein A I on high density lipoprotein particles, thereby altering trafficking of these particles . Additional acute phase reactants produced in adipocytes include the pentraxin family member PTX 3 , which is closely related to CRP, as well as the lipocalin 24p3 , whose roles in the innate immune response and as an iron binding protein have recently been established (81, 82).

Additionally, ceruloplasmin and macrophage migration inhibitory factor have also been identified as secretory products of adipocytes, albeit it is not known whether expression of these proteins is altered with the development of insulin resistance (83, 84). Interestingly, the antiinflammatory factor IL 1 receptor antagonist (IL 1Ra) is also expressed in adipose tissue where it is significantly up regulated in obesity, concomitant with an increase in systemic IL 1 receptor antagonist levels .

Rajala continues also to link this inflammatory response to cancer as follows:

Epidemiological studies have identified obesity as one of the major risk factors for cancer.

A recent prospective study on 900,000 adults in the United States by Calle et al. showed an association between increased BMI and risk of death from all cancers over a period of 16 yr.

The conceptual importance of the critical cross talk between cancer cells and the surrounding stromal cells has become increasingly accepted (100, 101). These contributions may be particularly prominent in adipocyte rich environments, such as mammary gland or bone marrow, as obesity has been established as a significant risk factor for the development of breast cancer in postmenopausal, but not premenopausal women (102).

A unique feature about early stage breast cancers that arise from ductal epithelial cells is the fact that they critically depend on an adipocyte enriched milieu for survival and growth.

Elliott and colleagues (103) showed that adipocyterich environments facilitate SP1 (a murine mammary carcinoma cell line) growth after injection into mice. Subcutaneous injection of the SP1 cells alone did not result in malignant foci formation. Iyengar et al. (104) have recently defined the specific effects that adipocyte derived secreted factors have on breast cancer cells and demonstrated that adipocyte conditioned medium promotes tumorigenesis, including increased cell proliferation, invasive potential, survival, and angiogenesis.

This observation was found in both estrogen dependent as well as estrogen independent breast cancer cell lines. It appears clear that adipocyte secreted proteins may play an important and possibly necessary role for the development of some types of breast cancers.

For example, type VI collagen, a soluble extracellular matrix protein abundantly expressed in adipocytes (105), was shown to be upregulated in adipocytes during tumorigenesis and to be critical

Pradhan (2007) states:

Compelling evidence linking inflammation to insulin resistance derives from both epidemiological studies and experimental data in humans and animal models. It is well known that the prevalence of diabetes, obesity, and MetS all increase with age.[2,5] In a cross sectional study of 70 healthy individuals aged 21– 94 years, advancing age was negatively correlated (r–0.38, P0.001) with whole body glucose disposal (WBGD) and positively correlated (r0.64, P0.001) with plasma concentrations of tumor necrosis factor alpha (TNF).[9]

Furthermore, a significant negative association was noted between WBGD and plasma TNF , independent of age, sex, body fat, and waist to hip ratio.[9] In 439 non diabetic women followed in the Women's Health Study, fasting insulin was strongly associated with plasma concentrations of the acute phase reactant C reactive protein (CRP), with a smaller, non significant trend for the pro inflammatory cytokine, interleukin 6 (IL 6).[10]

Similar findings were noted in the Insulin Resistance Atherosclerosis Study. In an analysis of 1,008 non diabetic men and women, a strong association was identified between plasma CRP concentration and insulin sensitivity. Furthermore, a linear rise in CRP levels was noted with increasing numbers of MetS components (dyslipidemia, abdominal obesity, insulin resistance, hypertension).[11]

Using the ATP III definition of MetS (Table 1),[12] similar results were reported among 14,719 non diabetic women enrolled in the Women's Health Study; median CRP concentrations increased from 0.68 mg/L in women with no characteristics of MetS, to 5.75 mg/L in those with five characteristics.[13]

Inflammation is also a corollary of obesity. In recent years, it has rapidly become apparent that obesity is marked by a broad inflammatory response.

The first molecular link between obesity and inflammation was elucidated just over a decade ago by Hotamisligil et al.[14] in seminal work demonstrating that the inflammatory cytokine TNF is constitutively expressed in adipose tissue and over expressed in rodent models of obesity. In humans, TNF mRNA expression is 2.5 fold higher in adipose tissue extracted from obese individuals relative to lean controls, with a strong correlation between TNF mRNA expression and hyperinsulinemia.[15]

Body weight reduction in obese individuals is also associated with a reduction in both TNF mRNA expression and in improved insulin sensitivity.[15] Interestingly, TNF expression in obese adipose tissue may originate from macrophage infiltration rather than adipocytes themselves.

In a recent paper by Maier et al (2010) they have studied in some detail the impact of inflammation on Diabetes and note:

In both type 1 and type 2 diabetes, pancreatic islet dysfunction results in part from cytokine-mediated inflammation. The ubiquitous eukaryotic translation initiation factor 5A (eIF5A), which is the only protein to contain the amino acid hypusine, contributes to the production of proinflammatory cytokines.

We therefore investigated whether eIF5A participates in the inflammatory cascade leading to islet dysfunction during the development of diabetes. As described herein, we found that eIF5A regulates iNOS levels and that eIF5A depletion as well as the inhibition of hypusination protects against glucose intolerance in inflammatory mouse models of diabetes.

We observed that following knockdown of eIF5A expression, mice were resistant to β cell loss and the development of hyperglycemia in the low-dose streptozotocin model of diabetes. The depletion of eIF5A led to impaired translation of iNOS-encoding mRNA within the islet….

Diabetes is a disorder of glucose homeostasis that afflicts over 200 million people worldwide. Dysfunction or destruction of islet β cells appears to underlie all forms of diabetes.

Whereas type 1 diabetes results from the autoimmune destruction of islet β cells, ***type 2 diabetes is thought to develop as β cell insulin release is unable to compensate for an increasing insulin demand . Emerging data suggest that in both forms of diabetes the release of proinflammatory cytokines is central to triggering pathways that initiate β cell dysfunction and eventual death.***

In the case of type 1 diabetes, a complex interplay between β cells and cells of the immune system leads to the recruitment of activated CD4+ T cells and macrophages into

the vicinity of the islet, resulting in local release of proinflammatory cytokines (IL-1β, TNF-α, IFN-γ) .

In the case of type 2 diabetes, systemic insulin resistance leads to increased circulating proinflammatory cytokines , and exogenous administration of IL-1 receptor antagonist (IL-1Ra) has been demonstrated to reduce glycemia and improve β cell function in mice with diet-induced hyperglycemia and in human subjects with type 2 diabetes *...*

In both type 1 and type 2 diabetes, a key feature of islet dysfunction is thought to emanate from inflammatory cascades triggered by cytokine signaling. *The subsequent production of iNOS and the generation of nitric oxide, among other mediators, has been suggested to cause defects in insulin release . In this report, we identify eIF5AHyp as a proximal regulator of iNOS production and show that eIF5A depletion as well as the inhibition of hypusination preserves islet glucose responsiveness in the presence of cytokineinduced stress. eIF5A, previously known as eIF4D and IF-M2Ba, is a highly conserved 17-kDa protein that was originally characterized as a translation initiation factor, promoting the formation of the first peptide bond in mRNA translation in vitro .*

However, interest in its role in translation initiation has diminished over the years, as studies using yeast mutants show that eIF5A is not essential for general translation but instead probably necessary for the translational elongation of specific transcripts . More recently, eIF5A has been thought to function in the translation of mRNAs that encode proteins essential for the G1-S transition of the cell cycle , for cytotoxic stress responses , and for the propagation of human immunodeficiency virus . ***Thus, eIF5A is best positioned as a factor that controls the balance between cellular proliferation and death, depending upon the nature of cellular stress.***

5 SEQUELAE

We now briefly discuss the various sequelae to Type 2 Diabetes. Unlike smoking, where when one gets lung cancer the life span is in months, and generally one even gets lung cancer when under 65, Type 2 Diabetes sequelae are chronic, they start often in middle age and continue for decades becoming ever so more costly.

As Mankiw has stated in the opinion piece:

"Sometimes, advocates of "sin" taxes contend that consumers of certain products impose adverse budgetary externalities on the rest of us — that if the consumption induces, say, smoking or obesity related illness, it raises health care costs, which we all pay for through higher taxes or insurance premiums.

Yet this argument has a flip side: If consumers of these products die earlier, they will also collect less in pension payments, including Social Security. Economists have run the numbers for smoking and often find that these savings may more than offset the budgetary costs. In other words, smokers have little net financial impact on the rest of us. It may seem grisly to consider the budgetary savings of an early death as a "benefit" to society. But when analyzing policy, economists are nothing if not cold blooded. If one uses budgetary costs to justify taxing particular consumption goods, the accounting needs to be honest and complete.

There is, however, an altogether different argument for these taxes: that when someone consumes such goods, he does impose a negative externality — on the future version of himself. In other words, the person today enjoys the consumption, but the person tomorrow and every day after pays the price of increased risk of illness."

The implication of Mankiw is that smoking and obesity sequelae are comparable. They clearly are not. We detail that herein.

Some of the typical end points detailed by the ADVANCE Study are:

Primary End Points

1. Combined major macrovascular and microvascular events
2. Major macrovascular events
3. Nonfatal MI
4. Nonfatal stroke
5. Death from cardiovascular causes
6. Major microvascular events
7. New or worsening nephropathy
8. New or worsening retinopathy

Secondary End Points

1. Death from any cause

2. Major coronary events
3. All coronary events
4. Major cerebrovascular events
5. All cerebrovascular events
6. Heart failure
7. Peripheral vascular events
8. All cardiovascular events
9. New onset microalbuminuria
10. Visual deterioration
11. New or worsening neuropathy
12. Cognitive decline
13. Dementia
14. Hospitalization

The CDC list the following data on sequelae[8]:

1. Heart disease and stroke

- In 2004, heart disease was noted on 68% of diabetes related death certificates among people aged 65 years or older.
- In 2004, stroke was noted on 16% of diabetes related death certificates among people aged 65 years or older.
- Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes.
- The risk for stroke is 2 to 4 times higher among people with diabetes.

2. High blood pressure

- In 2003–2004, 75% of adults with self reported diabetes had blood pressure greater than or equal to 130/80 millimeters of mercury (mm Hg), or used prescription medications for hypertension.

3. Blindness

- Diabetes is the leading cause of new cases of blindness among adults aged 20–74 years.
- Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year.

4. Kidney disease

- Diabetes is the leading cause of kidney failure, accounting for 44% of new cases in 2005.
- In 2005, 46,739 people with diabetes began treatment for end stage kidney disease in the United States and Puerto Rico.

[8] http://www.cdc.gov/diabetes/pubs/pdf/ndfs2007.pdf

- In 2005, a total of 178,689 people with end stage kidney disease due to diabetes were living on chronic dialysis or with a kidney transplant in the United States and Puerto Rico.

5. Nervous system disease

- About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, erectile dysfunction, or other nerve problems.
- Almost 30% of people with diabetes aged 40 years or older have impaired sensation in the feet (i.e., at least one area that lacks feeling).
- Severe forms of diabetic nerve disease are a major contributing cause of lower extremity amputations.

6. Amputations

- More than 60% of nontraumatic lower limb amputations occur in people with diabetes.
- In 2004, about 71,000 nontraumatic lower limb amputations were performed in people with diabetes.

7. Dental disease

- Periodontal (gum) disease is more common in people with diabetes. Among young adults, those with diabetes have about twice the risk of those without diabetes.
- Persons with poorly controlled diabetes (A1c > 9%) were nearly 3 times more likely to have severe periodontitis than those without diabetes.
- Almost one third of people with diabetes have severe periodontal disease with loss of attachment of the gums to the teeth measuring 5 millimeters or more.

8. Complications of pregnancy

- Poorly controlled diabetes before conception and during the first trimester of pregnancy among women with type 1 diabetes can cause major birth defects in 5% to 10% of pregnancies and spontaneous abortions in 15% to 20% of pregnancies.
- Poorly controlled diabetes during the second and third trimesters of pregnancy can result in excessively large babies, posing a risk to both mother and child.

9. Other complications

- Uncontrolled diabetes often leads to biochemical imbalances that can cause acute life threatening events, such as diabetic ketoacidosis and hyperosmolar (nonketotic) coma.
- People with diabetes are more susceptible to many other illnesses. Once they acquire these illnesses, they often have worse prognoses. For example, they are more likely to die with pneumonia or influenza than people who do not have diabetes.
- Persons with diabetes aged 60 years or older are 2–3 times more likely to report an inability to walk one quarter of a mile, climb stairs, do housework, or use a mobility aid compared with persons without diabetes in the same age group.

We will focus on the resulting impact on several key systems.

5.1 CEREBROVASCULAR DISEASE

Stroke is one of the primary causes of morbidity and mortality in the US. It is a costly disease leaving the patient often unable to care for themselves and frequently in a state requiring ongoing and very costly care. The current costs for a stroke victim may easily exceed $1000 per day!

The ADVANCE Collaborative Group reported in NEJM the following:

The prevalence of diabetes is increasing worldwide, and most people with diabetes will die or be disabled as a consequence of vascular complications.

Prospective studies have shown continuous associations of blood glucose and glycated hemoglobin levels with the risks of major vascular events.

However, previous randomized trials evaluating the effects of glycemic control in patients with diabetes have provided inconsistent evidence of effects on vascular disease.

Nevertheless, current guidelines recommend a target glycated hemoglobin level of 7.0% or less for most patients with diabetes.

In the paper by Davis et al, the authors provide a detailed analysis of stroke and Type 2 Diabetes. They state:

The incidence of cardiovascular disease is increased 2- to 3-fold in patients with type2 diabetes mellitus, and this increase cannot be explained by the presence of classic risk factors for atherosclerosis, such as smoking, hypertension, and dyslipidemia.

In patients with cerebrovascular disease, the presence of type 2 diabetes increases the risk of ischemic cerebral infarction, which accounts for more than three quarters of all strokes, but is not associated with an increased risk of cerebral hemorrhage.

The crude incidence of stroke among patients with type 2 diabetes can be more than 3 times that in the general population, with particularly high rates reported in Sweden and the southeastern United States.8,15 The relative risk of stroke in patients with type 2 diabetes reaches a maximum in the 40- to 60- year-old group, and women comprise a greater proportion of patients with stroke than in the nondiabetic population. ...

Studies of diabetic patients have consistently identified hypertension as the major risk factor. Associations have been found between stroke and other manifestations of atherosclerosis, cardiac failure, and non-rheumatic atrial fibrillation, but in diabetic patients, inadequate glycemic control, dyslipidemia, obesity, smoking, and microvascular disease have not been identified as independent risk factors.

Many studies, however, have used relatively small numbers of selected patients from cross-sectional studies and a limited number of risk factors in the assessment of stroke in patients with type 2 diabetes….

An evaluation of the effect of changes in blood pressure and antihypertensive treatment from the time of diagnosis on stroke incidence was beyond the scope of the present study and has been reported recently elsewhere.

Nevertheless, given the difficulty in achieving acceptable blood pressure control in diabetic patients with hypertension, it is not surprising that the blood pressure at the time of diagnosis was a strong predictor of the occurrence of stroke.

Other features of the "metabolic syndrome," including obesity, hyperinsulinemia, and dyslipidemia, were not associated with stroke in our patients, consistent with previous studies of type 2 diabetes. A recent meta-analysis has indicated that hypertension, but not elevated blood cholesterol levels, is related to the incidence of stroke in the general population.

5.2 CARDIOVASCULAR STATUS

The cardiovascular problems created by Type 2 Diabetes are significant to an extreme. The inflammatory characteristics of the adipocytes are one of the most significant drivers of this process, and it is then compounded in the presence of Type 2 Diabetes. We discuss here some of the current research.

In the paper by Bonow and Eckel the authors state:

The growing prevalence of obesity and type 2 diabetes in the United States has attracted the attention and concern of the medical profession, the media, policymakers, and the American public.

Recent statistics from the Centers for Disease Control and Prevention indicate that nearly two thirds of American adults are overweight (body mass index [the weight in kilograms divided by the square of the height in meters], greater than 25) and more than

30 percent are frankly obese (body mass index, greater than 30), that nearly 8 percent are diabetic, and that 24 percent have the metabolic syndrome.

The metabolic syndrome is an ominous combination of visceral obesity, atherogenic dyslipidemia (low levels of high density lipoprotein [HDL] cholesterol and elevated levels of triglycerides), hypertension, and glucose intolerance that contributes to insulin resistance and a heightened risk of diabetes and cardiovascular disease.

In the paper by Gaede et al they state:

"Patients with type 2 diabetes mellitus have a risk of death from cardiovascular causes that is two to six times that among persons without diabetes, and among white Americans, the age adjusted prevalence of coronary heart disease is twice as high among those with type 2 diabetes as among those without diabetes. The cardiovascular events associated with type 2 diabetes and the high incidence of other macrovascular complications, such as strokes and amputations, are a major cause of illness and an enormous economic burden.

Multiple modifiable risk factors for late complications in patients with type 2 diabetes, including hyperglycemia, hypertension, and dyslipidemia, increase the risk of a poor outcome. Randomized trials that investigated the effect of intensified intervention involving a single risk factor in patients with type 2 diabetes demonstrated benefits in terms of both macrovascular and microvascular complications in kidneys, eyes, and nerves.

On the basis of the results of these trials, recent guidelines from the American Diabetes Association and other national guidelines recommend an intensified multifactorial treatment approach, although the effect of this approach has not been confirmed in long term studies."

Clearly cardiovascular problems are significant and as we shall demonstrate later they are one of the most costly sequelae.

5.3 OCULAR

One of the most debilitating sequelae is the retinopathy and other ocular disorders of Type 2 Diabetes. Again the inflammatory nature of the disease is a prime driver.

In the paper by Sheetz (2002) the author states:

Diabetic retinopathy occurs in three fourths of all persons with diabetes after more than 15 years of the disease. It is the most common cause of blindness in the industrialized world in persons between the ages of 25 and 74 years. Diabetic retinopathy is diagnosed by the appearance of retinal vascular lesions of increasing severity, culminating in the growth of new vessels (proliferative diabetic retinopathy [DR]).

A loss of vision can result through either a nonclearing vitreous hemorrhage or through fibrosis causing traction retinal detachment. In addition, retinal vessels can leak at any stage of retinopathy and produce macular edema with potentially irreversible loss of central vision.

Early in the course of diabetes, hyperglycemia is responsible for many of the functional retinal vascular changes, including impairment of retinal blood flow, increased leukocyte and monocyte adhesion in the retinal microvessels, and capillary closure resulting in localized hypoxia. In addition, retinal neuronal function, as assessed by electroretinography, may also exhibit abnormalities early in the course of the disease.

One of the earliest and most specific retinal changes induced by hyperglycemia is the death of microvascular contractile cells (pericytes). The death of pericytes and the loss of vascular intercellular contacts may predispose to endothelial cell proliferation, facilitating the development of microaneurysms.

Alterations in hemodynamics and vascular autoregulation that are characteristic of the diabetic state can produce venous dilation and beading as well as intraretinal microvascular abnormalities that represent dilated small vessels. Impairments of vascular cell to cell contacts and altered barrier permeability function can lead to small intraretinal hemorrhages and fluid leakage. When water is reabsorbed, the plasma lipids and proteins precipitate as hard exudates.

In the paper by Frank, the author states:

Diabetic retinopathy is the most severe of the several ocular complications of diabetes. Advances in treatment over the past 40 years have greatly reduced the risk of blindness from this disease, but because diabetes is so common (affecting approximately 6 percent of the U.S. population), retinopathy remains an important problem… Proliferative diabetic retinopathy involves the formation of new blood vessels that develop from the retinal circulation. Untreated, the process carries an ominous prognosis for vision.

New vessels can extend into the vitreous cavity of the eye and can hemorrhage into the vitreous, resulting in visual loss, and they can cause tractional retinal detachments from the accompanying contractile fibrous tissue. Late in the course of the disease, new blood vessels may form within the stroma of the iris and may extend, with accompanying fibrosis, into the structures that drain the anterior chamber angle of the eye.

This development blocks the outflow of aqueous humor, causing neovascular glaucoma, with a devastating elevation of the intraocular pressure.

Proliferative retinopathy may occur in up to 50 percent of patients with type 1 diabetes and in about 10 percent of patients with type 2 diabetes who have had the disease for 15 years. The prevalence of proliferative retinopathy is somewhat higher among those with type 2 diabetes who require insulin to control their disease and is lower among those who do not.

Needless to say, Diabetic Retinopathy is just one more chronic sequela to Type 2 Diabetes.

5.4 NEPHROLOGICAL

Kidney failure is a major sequela to Type 2 Diabetes. It becomes a chronic and costly disorder to treat. We summarize some of the recent research in this area.

In the paper by Sheetz the author states:

Diabetic nephropathy is a major cause of end stage renal disease. It is first characterized by glomerular hemodynamic abnormalities that result in glomerular hyperfiltration, leading to glomerular damage as evidenced by microalbuminuria. As glomerular function continues to decline, overt proteinuria, decreased glomerular filtration rate, and end stage renal failure will result.

Hyperglycemia induced glomerular hyperfiltration is the result of the dilation of the afferent glomerular arteriole to a greater extent than dilation of the efferent glomerular arteriole. This increases the glomerular hydrostatic pressure, forcing an increase in the passage of fluid through the glomerular filtration apparatus. These hemodynamic abnormalities are thought to be mediated by an increase in the production of vasodilatory prostanoids and nitric oxide.

The dysfunction of the glomerular filtration apparatus is manifested by microalbuminuria and has been attributed to changes in the synthesis and catabolism of various glomerular basement membrane macromolecules, such as collagen and proteoglycans, leading to an increase in glomerular basement membrane thickness.

Another possible mechanism to explain the increase in permeability of the glomerulus is the increase in renal VEGF levels that are observed in preclinical models of diabetes, since VEGF is both an angiogenic and a permeability factor.

In the paper by Mitch, the author states:

"Economic issues sometimes seem to be the primary considerations in discussions of treatment for nephropathy in patients with type 2 diabetes. But in the end, the economics of treatment are driven by clinical issues, many of which have yet to be resolved. For example, in the United States, type 2 diabetes is the leading cause of end stage renal disease; it accounted for approximately 40 percent of cases in patients who began dialysis between 1994 and 1999.

Worse yet, the worldwide incidence of end stage renal disease among patients with type 2 diabetes is expected to double by 2010.

These depressing data are compounded by estimates that 11 percent of adults in the United States have chronic kidney disease. Consequently, Medicare costs associated with end stage renal disease are projected to increase from $12.7 billion in 1999 to $28.0 billion in 2010. Regardless of the exact dollar figures, the increase in the rate of diabetic nephropathy will undoubtedly strain the economies of all countries."

In the 2002 NEJM paper by Remuzzi et al the authors state:

Nephropathy associated with type 2 diabetes is the most frequent cause of end stage renal disease in the United States, Europe, and Japan. In the United States, the incidence of diabetic nephropathy has increased by 150 percent in the past 10 years, a trend also seen in Europe. [1,2] In North America, 40 percent of patients starting dialysis in 1998 had diabetic nephropathy.

Among patients who require dialysis, those with diabetes have a 22 percent higher mortality at one year and a 15 percent higher mortality at five years than patients without diabetes. In 1998, the estimated cost of care for a diabetic patient undergoing dialysis was $51,000 per year, which was about $12,000 more than the cost for a nondiabetic patient…. Early recognition of renal changes increases the chance to prevent the progression from incipient to overt nephropathy. A routine dipstick urinalysis should be performed at the time of diagnosis, because of the difficulty in precisely dating the onset of type 2 diabetes.

If the test is positive for protein, analysis of a 24 hour urine sample is recommended for quantification of urinary protein excretion (Fig. 1).

Since a negative dipstick test for protein does not rule out microalbuminuria, a more sensitive method should be used (e.g., the Micral test or radioimmunoassay for albumin) and repeated every year, if the result is negative. If the result is positive, microalbuminuria can be confirmed and quantified by measuring the ratio of albumin to creatinine in a morning urine sample or by measuring the rate of albumin excretion in a 24 hour or overnight urine sample.

Overnight samples can be used to distinguish true microalbuminuria from postural or exercise proteinuria, which are common in young patients. Isolated microalbuminuria or macroalbuminuria usually indicates the presence of diabetic nephropathy, but the presence of other abnormalities on urinalysis suggests another renal disease. Screening for and monitoring of background or proliferative retinopathy are especially important in all patients with urinary abnormalities. [3] If retinopathy is present, albuminuria can be attributed with confidence to diabetic nephropathy; if there is no evidence of retinopathy, one should look for other causes of albuminuria.

Kidney failure is insidious. It starts with microalbuminuria, leakage of albumin, protein, through the nephrons, and then progresses to end stage renal disease. This requires dialysis and kidney transplants. The kidney disease also leads to a swath of other secondary problems.

5.5 NEUROLOGICAL

Type 2 Diabetes has a plethora of neuropathies. They are generally painful and are highly debilitating. They may be burning pain, piercing pain, or many other types of neurological pain as well as the total absence of feeling. The absence of feeling often leads to injury, infection and amputation.

Sheetz states:

About half of all people with diabetes have some degree of diabetic neuropathy,[17] which can present as either a polyneuropathy or a mononeuropathy.[18] [19] Our brief description will focus on changes in peripheral sensation in myelinated and nonmyelinated nerves.

Diabetic peripheral neuropathy can produce positive symptoms such as those assessed by the Total Symptom Score 6, including pain, burning, and allodynia, as well as eventually lead to negative symptoms (ie, loss of sensation) as the disease progresses.

The most common form of diabetic neuropathy is a polyneuropathy characterized by the loss of peripheral sensation, which, when coupled with impaired microvascular and macrovascular function in the periphery, can contribute to nonhealing ulcers, the leading cause of nontraumatic amputation in the United States.[20] Distal symmetric sensorimotor polyneuropathy is manifested clinically by paresthesia, dysesthesia, pain, impaired reflexes, and/or decreased vibratory sensation. Anatomically, diabetic peripheral polyneuropathy is characterized by a thickening of axons (sometimes attributed to increased axonal intracellular fluid early in the course of diabetes), a decrease in microfilaments, and capillary narrowing involving small myelinated or nonmyelinated C fibers.[21] As the syndrome progresses, there is axonal loss.[22]

Diabetic neuropathy is thought to occur both from direct hyperglycemia induced damage to the nerve parenchyma and from neuronal ischemia brought about indirectly by hyperglycemia induced decreases in neurovascular flow.[23] Abnormalities of microvessels, such as endothelial cell activation and proliferation, pericyte degeneration, basement membrane thickening, and monocyte adhesion, have all been described.[24]

In the paper by Boulton et al on somatic neuropathies they state:

The neuropathies are among the most common of the long term complications of diabetes, affecting up to 50% of patients (1–4). Their clinical features vary immensely, and patients may present to a wide spectrum of specialties, from dermatology to podiatry, for example, or from urology to cardiology. Neuropathies are characterized by a progressive loss of nerve fibers, which may affect both principle divisions of the peripheral nervous system.

This review will focus on the somatic neuropathies; those affecting the autonomic division were recently reviewed by Vinik et al. . There is increasing evidence that

measures of neuropathy, such as electrophysiology and quantitative tests, are predictors of not only end points, including foot ulceration, but also of mortality .

The epidemiology and natural history of diabetic neuropathy (DN) remain poorly defined, partly because of poor patient selection and the variable criteria for what constitutes a diagnosis of DN. These aspects, as well as the pathogenesis of DN, will be covered in detail in this review. Studies have confirmed the major contribution of prolonged hyperglycemia in the etiopathogenesis of neuropathy and neuropathic pain (7–9,10), and this and other putative mechanisms will be discussed.

The clinical features, diagnosis, and management of the focal and multifocal neuropathies will be described. A major portion of this review will discuss the clinical features, assessment, and management of the patient with the most common form of DN, diabetic distal sensory polyneuropathy (DPN). The late sequelae of DPN and their prevention will also be described.

Finally, practical guidelines for the screening of DPN in clinical practice will be provided. For further details on this topic, please refer to recent reviews (11–18).

In the paper by Vinik et al on autonomic neuropathies they state:

Diabetic autonomic neuropathy *(DAN) is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of DAN has not been fully appreciated.*

The reported prevalence of DAN varies widely depending on the cohort studied and the methods of assessment. In randomly selected cohorts of asymptomatic individuals with diabetes, approximately 20% had abnormal cardiovascular autonomic function. DAN frequently coexists with other peripheral neuropathies and other diabetic complications, but DAN may be isolated, frequently preceding the detection of other complications.

Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure. DAN may affect many organ systems throughout the body (e.g., gastrointestinal [GI], genitourinary, and cardiovascular).

GI disturbances (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence) are common, and any section of the GI tract may be affected. Gastroparesis should be suspected in individuals with erratic glucose control. Upper GI symptoms should lead to consideration of all possible causes, including autonomic dysfunction. Whereas a radiographic gastric emptying study can definitively establish the diagnosis of gastroparesis, a reasonable approach is to exclude autonomic dysfunction and other known causes of these upper GI symptoms. Constipation is the most common lower GI symptom but can alternate with episodes of diarrhea.

The general classifications of diabetic neuropathies are from Boulton et al:

"Numerous classifications of the variety of syndromes affecting the peripheral nervous system in diabetes have been proposed in recent years. Some have been based on presumed etiology, topographical features, or pathological features. However, until we have a clear understanding of the etiopathogenesis of neuropathy, classifications based on the clinical manifestations are most commonly used.

Rapidly reversible hyperglycemic neuropathy.

It has been recognized for many years that rapidly reversible abnormalities of nerve conduction may occur in patients with recently diagnosed or transiently poorly controlled diabetes; these abnormalities may be accompanied by distal uncomfortable sensory symptoms (11,23,24). Such changes are unlikely to be caused by structural abnormalities, as recovery soon follows restoration of euglycemia. It remains unknown whether these temporary abnormalities result in a greater risk of developing other chronic neuropathies in later life.

Generalized symmetrical polyneuropathies.

Chronic sensorimotor neuropathy is the most common form of DN that is discussed in detail below. It is usually of insidious onset and may be present at the diagnosis of type 2 diabetes in >10% of subjects. Whereas up to 50% of patients may be asymptomatic, 10–20% may experience troublesome sensory symptoms that require specific treatment. Sensorimotor neuropathy is often accompanied by autonomic dysfunction. Late sequelae of neuropathy, which include insensate foot ulceration, Charcot (neuropathic) arthropathy, and occasionally even amputation, are also discussed below.

Acute sensory neuropathy is a distinct variety of the symmetrical polyneuropathies with an acute or subacute onset characterized by severe sensory symptoms, usually with few if any clinical signs. The natural history is one of gradual improvement of these symptoms with establishment of stable glycemic control.

Autonomic neuropathy is also common, though rarely severely symptomatic. Autonomic neuropathy was a topic of focus in a recent technical review by Vinik et al. (5) and will not be further described here.

Focal and multifocal neuropathies.

All the neuropathies under this heading are recognized as being more common in older type 2 diabetic patients. Focal limb neuropathies are often, but not always, due to entrapment (e.g., carpal tunnel syndrome), indicating the greater susceptibility of diabetic nerve to compression. Recent data suggest that there is a threefold risk of having diabetes in 514 patients with carpal tunnel syndrome compared with a normal control group (28).

Among the cranial nerves, those supplying the external ocular muscles are most commonly involved. Thoracolumbar radiculoneuropathies may present with girdle like pain, occasionally with motor weakness of abdominal wall muscles. Proximal motor neuropathy (amyotrophy) may be unilateral or asymmetrically bilateral with pain, wasting, and weakness that may be relatively acute in onset. All of these focal/multifocal neuropathies are discussed in greater detail below.

It seems probable that chronic inflammatory demyelinating polyneuropathy (CIDP) occurs more commonly in people with diabetes (24,29), although a case control study has not been performed. Its features, differential diagnosis, and management will be discussed in more detail below.

This is a description with some overall details of just a few of the major sequelae from Type 2 Diabetes. Our argument this far has demonstrated:

1. Obesity is primarily a choice driven result.

2. Obesity is the primary cause of Type 2 Diabetes

3. The sequelae of Type 2 Diabetes are minion and have a chronic and costly impact on the overall health care system, in many ways totally unlike cancers which often have short durations and are non chronic.

We now proceed to examine the incidence and prevalence and then the costs.

6 INCIDENCE AND PREVALENCE

The incidence and prevalence of Type 2 Diabetes is dramatically increasing. We briefly review the data on these two factors.

Type 2 Diabetes has become a pandemic in all societies. It leads to kidney failure, blindness, nerve damage, vascular damage, heart attacks, and a vast panoply of other tertiary diseases. It has started to creep down in age in incidence. It consumes almost 10 12% of the total health care costs in the United States alone. It also is an almost totally preventable disease. It is in almost all cases a disease of life style. It presents a case study for handling the delivery of health care in the United States. For we argue herein that this disease, which in many ways is akin to the disorders related to smoking, is a totally preventable disorder. It is a disease which can be modulated and reduced by economic means.

Type 2 Diabetes is a disease of insulin production[9]. The pancreas no longer produces adequate insulin to transport the glucose produced by sugar and carbohydrate consumption and the net result is an excessive rise of glucose in the blood stream. In simple terms this excess glucose catalyzes many reactions which in turn cause the circulatory, renal, optic, and neurological damage. The excess of glucose in simple terms wears down these systems in rapid order.

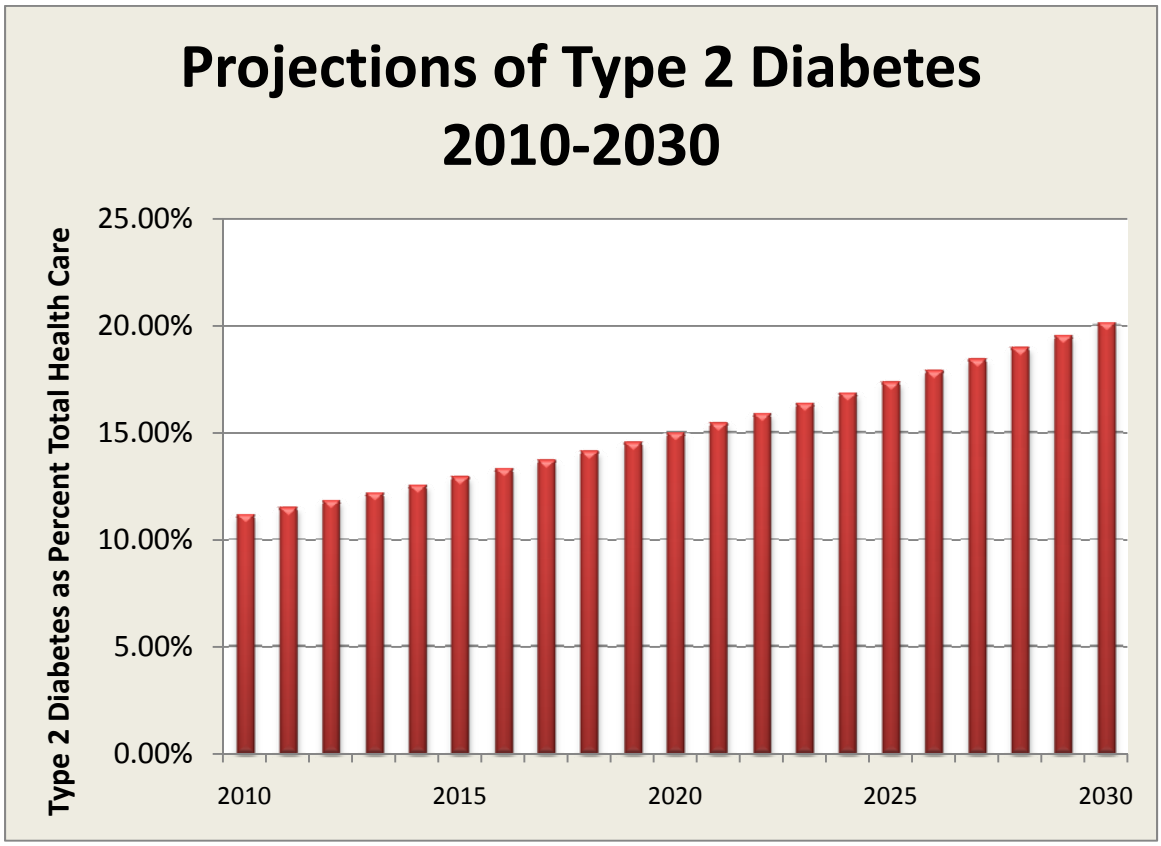
The primary drive of this process leading to Type 2 Diabetes is excess consumption of carbohydrates and generally this excess is directly exhibited in overweight individuals. Weight impact on health is measure by the Body Mass Index calculation. If the BMI is less than 25 and greater than 20 then this is a healthy range. Overweight is defined as BMI greater than 25 and less than 30. Obese is defined as anything greater than 30. Thus a 6'3" male of 250 lbs is obese, where as if he is greater than 210 he is overweight. The most predisposing factor, and many believe causative factor of Type 2 Diabetes if being overweight, not just being obese. This now applies for any age, children included.

In 1997 about 4.7% of people were Type 2 Diabetics. In 2008 that has increased to 5.9%. By 2020 the number is anticipated to increase to 15%. The total expenditures for Type 2 Diabetes in 2008 are in excess of $250 billion, about 12% of all health care expenditures. This combination results in an expenditure of $12,500 per Type 2 Diabetic per annum.

However the problem is explosive. With health care growing at 6% per annum in excess of inflation and Type 2 Diabetes prevalence growing at 3% per annum, and the overall population growing at 1% per annum, the net result is costs growing at in excess of 10% per annum! That exceeds rate of the health care costs alone. It is conceivable that Type 2 Diabetes will reach 20% of all health care costs by 2030.

We present this growth picture in the following Figure.

[9] See Porte et al and LeRoith et al.



6.1 INCIDENCE

The following is a summary of the NIH review of Type 2 Diabetes. The incidence of Diagnosed Diabetes in People Younger than 20 Years of Age, United States, 2002 to 2003 is as follows:

Based on 2002 to 2003 data, 15,000 youth in the United States were newly diagnosed with type 1 diabetes annually, and about 3,700 youth were newly diagnosed with type 2 diabetes annually.

The rate of new cases among youth was 19.0 per 100,000 each year for type 1 diabetes and 5.3 per 100,000 for type 2 diabetes.
Non Hispanic white youth had the highest rate of new cases of type 1 diabetes.

Type 2 diabetes was extremely rare among youth aged <10 years. While still infrequent, rates were greater among youth aged 10 to 19 years compared with younger children, with higher rates among U.S. minority populations compared with non Hispanic whites.

Among non Hispanic white youth aged 10 to 19 years, the rate of new cases of type 1 diabetes was higher than for type 2 diabetes.

For Asian/Pacific Islander and American Indian youth aged 10 to 19 years, the opposite was true—the rate of new cases of type 2 was greater than the rate for type 1 diabetes.

Among African American and Hispanic youth aged 10 to 19 years, the rates of new cases of type 1 and type 2 diabetes were similar.

6.2 PREVALENCE

Prevalence of Diagnosed Diabetes in People Younger than 20 Years of Age, United States, 2007. About 186,300 people younger than 20 years have diabetes—type 1 or type 2. This represents 0.2 percent of all people in this age group. Estimates of undiagnosed diabetes are unavailable for this age group.

Prevalence of Diagnosed and Undiagnosed Diabetes in the United States, All Ages, 2007

Total: 23.6 million people—7.8 percent of the population—have diabetes.
Diagnosed: 17.9 million people
Undiagnosed: 5.7 million people

Prevalence of Diagnosed and Undiagnosed Diabetes among People Aged 20 Years or Older, United States, 2007

Age 20 years or older: 23.5 million, or 10.7 percent, of all people in this age group have diabetes.

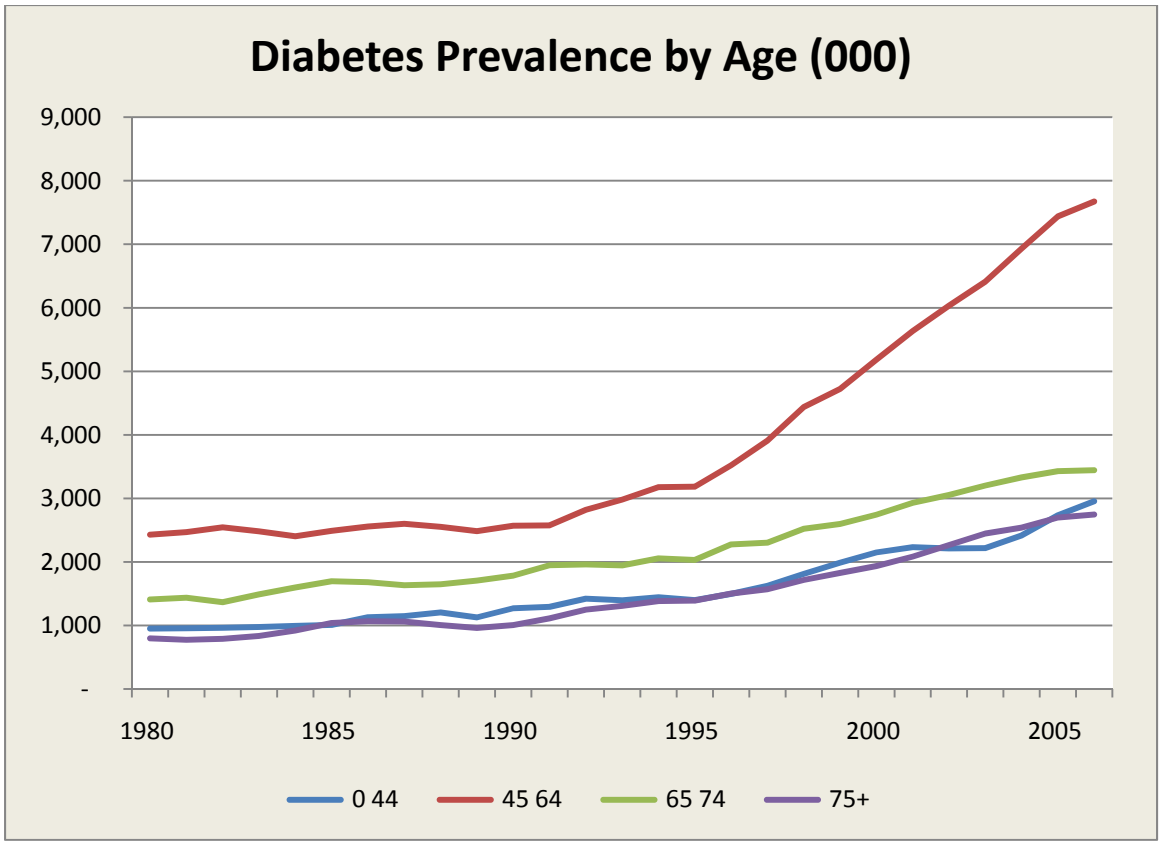
Age 60 years or older: 12.2 million, or 23.1 percent, of all people in this age group have diabetes.

Men: 12.0 million, or 11.2 percent, of all men aged 20 years or older have diabetes.

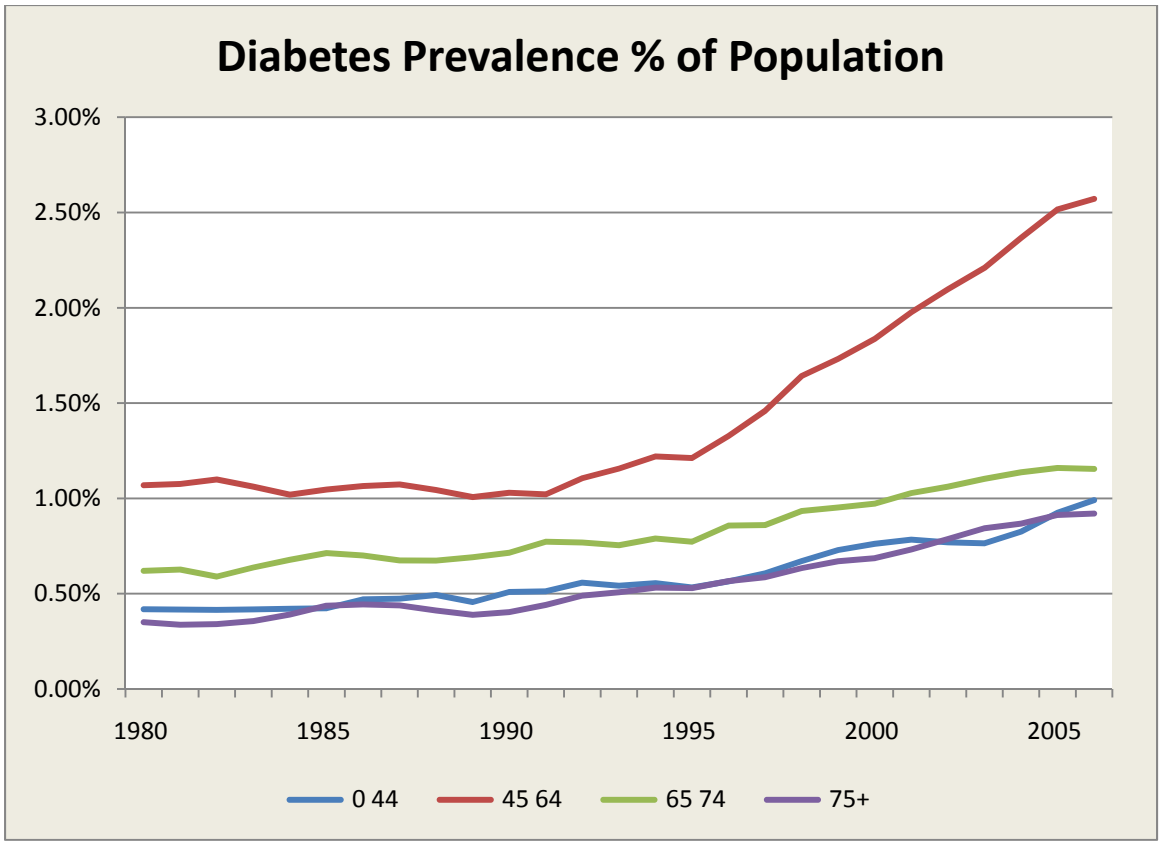
Women: 11.5 million, or 10.2 percent, of all women aged 20 years or older have diabetes.
Non Hispanic whites: 14.9 million, or 9.8 percent, of all non Hispanic whites aged 20 years or older have diabetes.

Non Hispanic blacks: 3.7 million, or 14.7 percent, of all non Hispanic blacks aged 20 years or older have diabetes.

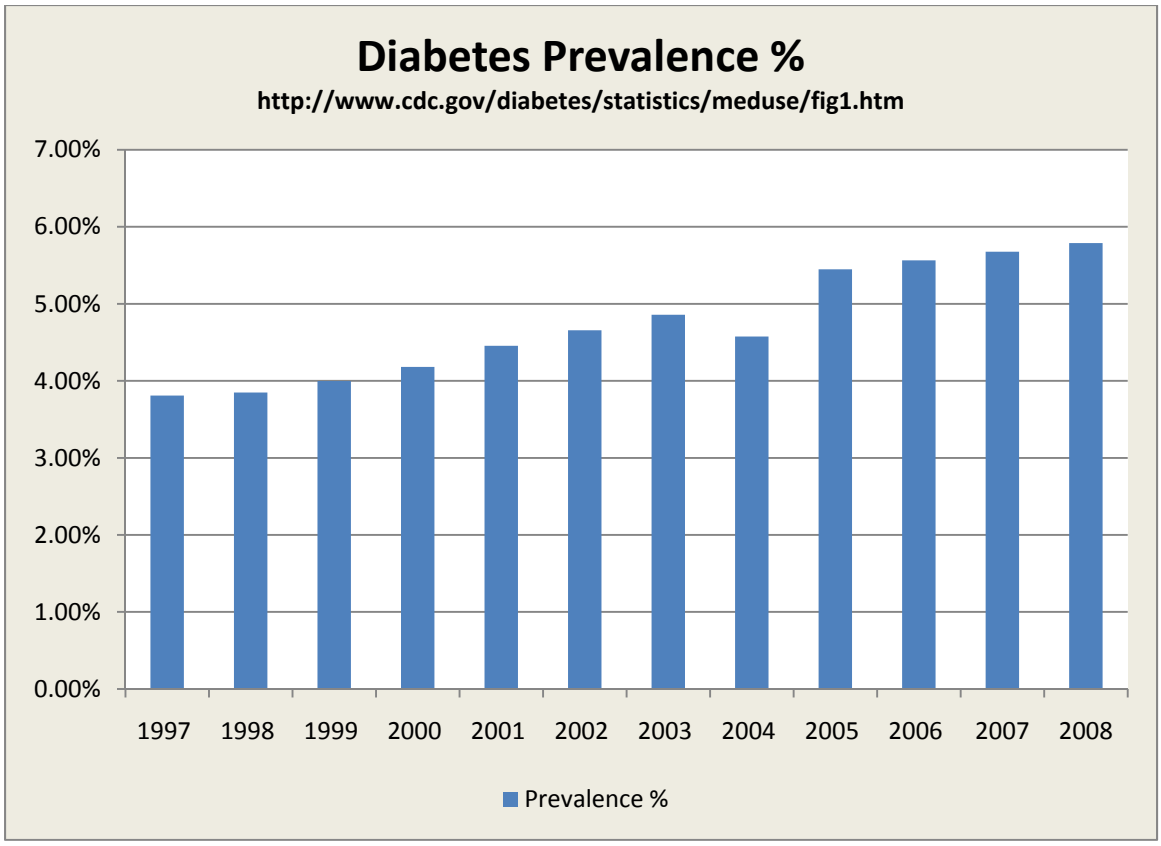
The following Figures depict prevalence over the past 25 years broken out by age group. There is an explosive growth amongst the 45 64 age group. This will of course spread as they age and create significant chronic health care costs.



The following shows the same data but now as percent of the population. Note that as before the 45 64 age group grows from 1% to over 2.5% of the total population. This is truly a worrisome factor. These are the baby boomers. They are



The overall combined prevalence is shown in the following Figure. This is a summary of the previous Figure but it rolls up all of the age categories.


Diabetes Prevalence %
http://www.cdc.gov/diabetes/statistics/meduse/fig1.htm
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Prevalence %

7 COSTS

We can now assess the costs associated with Type 2 Diabetes. We rely upon a study performed by Brandle et al entitled "*The Direct Medical Cost of Type 2 Diabetes*", from the Division of Endocrinology & Metabolism, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan. This is a seminal study which can become the basis for many other such analyses. Brandle looks at all the sequelae of Type 2 Diabetes and then develops detailed costs for each.

This is an interesting study of benchmarking prevalence and costs by treatment type. We rely upon this data and we have updated it from 2000 cost numbers to 2008 cost numbers as well as incorporating a total US prevalence. It should be noted that certain procedures have not been costed in the model so that the actual costs are estimated to be 10-15% higher than calculated herein.

Our approach is to use the Brandle methodology, then to use update prevalence and cost numbers and then to combine this in a going forward model for the costs.

7.1 SECONDARY DISORDERS: THE SEQUELAE

Type 2 Diabetes leads to many secondary disorders, sequelae. The key ones we have briefly discussed before but they are as follows:

1. Retinopathy status
    a. Nonproliferative retinopathy
    b. Proliferative retinopathy
    c. Macular edema
2. Nephropathy status
    a. Microalbuminuria
    b. Proteinuria
    c. ESRD with dialysis
3. Neuropathy status
    a. Neuropathy
    b. Amputation
4. Cerebrovascular disease
5. Cardiovascular status
    a. Angina
    b. MI
6. Peripheral vascular disease
7. High blood pressure BP 140/90 mmHg

In the study by Brandle the team determined the prevalence of each of these and then went and determined the costs of treatment. We shall rely on and modify the Brandle work herein as a basis for estimating the current and projected costs. The following Table

presents the statistics of the study group and the prevalence of the above common secondary effects.

Factor	*Range*	*Mean*	*Percent*
Sample Size *N*	1,364	1,364	100.0%
Age (years)	66 (54–72)	66	4.8%
Diabetes duration (years)	8 (4–16)	8	0.6%
Sex			
Male	681	681	49.9%
Race			
White	1,005	1005	73.7%
African American	176	176	12.9%
BMI (kg/m2)	30.7 (27.1–36.1)	31	2.3%
HbA1c (%)	7.1 (6.3–8.2)	7.00	0.5%
Education			
Not a high school graduate	244	244	17.9%
High school graduate	397	397	29.1%
Some college	383	383	28.1%
College graduate	133	133	9.8%
Any postgraduate work	153	153	11.2%
Missing*	54	54	4.0%
Household income			0.0%
$40,000	903	903	66.2%
$40,000–69,999	289	289	21.2%
$70,000	172	172	12.6%
Diabetes treatment			0.0%
Diet or exercise only	69	69	5.1%
Oral antidiabetic medication	870	870	63.8%
Insulin	425	425	31.2%
Retinopathy status			0.0%
Nonproliferative retinopathy	170	170	12.5%
Proliferative retinopathy	41	41	3.0%
Macular edema	29	29	2.1%
Missing	248	248	18.2%
Nephropathy status			
Microalbuminuria	99	99	7.3%
Proteinuria	207	207	15.2%
ESRD with dialysis	6 (0.4)	6	0.4%
Missing	248	248	18.2%
Neuropathy status			
Neuropathy	544	544	39.9%
History of amputation	25	25	1.8%
Cerebrovascular disease			
Cerebrovascular disease	199	199	14.6%
Missing	217	217	15.9%
Cardiovascular status			0.0%
Angina	58	58	4.3%
History of MI	363	363	26.6%
Missing	205	205	15.0%
Peripheral vascular disease			0.0%
Peripheral vascular disease	538	538	39.4%
Missing	248	248	18.2%
High blood pressure status			0.0%
BP 140/90 mmHg without treatment	481	481	35.3%

Factor	*Range*	*Mean*	*Percent*
Treated with medication	416	416	30.5%
Missing	253	253	18.5%
Cholesterol status			0.0%
LDL 100 mg/dl without treatment	386	386	28.3%
Treated with medication	404	404	29.6%
Missing	248	248	18.2%
Cigarette smoking			0.0%
Current smoker	233	233	17.1%
Missing	17	17	1.2%
Total cost	3,715 (1,894–7,719)	$3,715	

This above Table will be used again in the costing process.

7.2 PROCEDURE AND COSTS

Using the Brandle data we again take the secondary factors and the incorporate the Brandle data using the 2000 year costs and the prevalence and then update to 2008 populations and escalated health care costs.

The following Table details the analysis of providing the 2008 costs. These costs can then be projected forward in time using the same process of scaling.

	Baseline cost	*$1,684*	$2,977
Disease status	*Increment SE in log10 scale*	*Multiplier (2000)*	*Amount (2008)*
Sex			
Female	0.095 0.025	1.25	$3,722
Age	‡		$0
Race			
African American	0.088 0.036	0.82	$2,442
Duration			
Every 1 year after onset	‡		$0
BMI (kg/m2)			
Every unit 30 kg/m2	0.004 0.002	1.01	$3,007
Diabetes intervention			
Oral antidiabetic medication	0.040 0.056	1.10	$3,275
Insulin	0.200 0.058	1.59	$4,734
High blood pressure			
Treated blood pressure	0.092 0.028	1.24	$3,692
Retinopathy			
Nonproliferative retinopathy	‡		$0
Proliferative retinopathy	‡		$0
Macular edema	‡		$0
Nephropathy			
Microalbuminuria	0.067 0.048	1.17	$3,484
Proteinuria	0.113 0.036	1.30	$3,871
ESRD with dialysis	1.023 0.183	10.53	$31,353
Neuropathy			
Clinical neuropathy	‡		$0
History of amputation	‡		$0
Cerebrovascular disease	0.113 0.035	1.30	$3,871
Cardiovascular disease			
Angina	0.239 0.061	1.73	$5,151
History of MI	0.278 0.029	1.90	$5,657
Peripheral vascular disease	0.116 0.028	1.31	$3,900

Finally there are three major events that Brandle notes and they are shown below, each requiring hospitalization. We have also updated their costs and their prevalence.

	Subjects who survived first year (n)	*Total costs for 1 year after onset of acute event for subject who survived first year (2000 Dollars)*	*Costs in 2008 Dollars*	*Incidence*
Acute event			1.77	
Stroke	88	$26,600 (15,400–44,900)	$47,031	6.45%
Acute MI	84	$24,500 (15,000–50,000)	$43,318	6.16%
Amputation	47	$37,600 (23,300–62,200)	$66,480	3.45%

7.3 TOTAL ANNUAL COSTS

Now taking the above data we can then combine the result to estimate total costs of Type 2 Diabetes in 2008. This is accomplished in the following Table. Here we have provided the data for only the secondary factors.

Disease status	*Prevalence %*	*Total Prevalence*	*Unit Cost*	*Total Cost ($000,000)*
Diabetes intervention			$0	
Oral antidiabetic medication	3.32%	584,622	$3,275	$1,915
Insulin	1.45%	254,687	$4,734	$1,206
High blood pressure				
Treated blood pressure	35.26%	6,206,452	$3,692	$22,915
Retinopathy				
Nonproliferative retinopathy	12.46%	2,193,548	$0	$0
Proliferative retinopathy	3.01%	529,032	$0	$0
Macular edema	2.13%	374,194	$0	$0
Nephropathy				
Microalbuminuria	7.26%	1,277,419	$3,484	$4,450
Proteinuria	15.18%	2,670,968	$3,871	$10,339
ESRD with dialysis	0.44%	77,419	$31,353	$2,427
Neuropathy				
Clinical neuropathy	39.88%	7,019,355	$0	$0
History of amputation	1.83%	322,581	$0	$0
Cerebrovascular disease	14.59%	2,567,742	$3,871	$9,939
Cardiovascular disease				
Angina	4.25%	748,387	$5,151	$3,855
History of MI	26.61%	4,683,871	$5,657	$26,498
Peripheral vascular disease	39.44%	6,941,935	$3,900	$27,077
Acute Illnesses				
Stroke	6.45%	1,135,484	$47,031	$53,403
Acute MI	6.16%	1,083,871	$43,318	$46,951
Amputation	3.45%	606,452	$66,480	$40,317
Total		39,278,018		$251,291

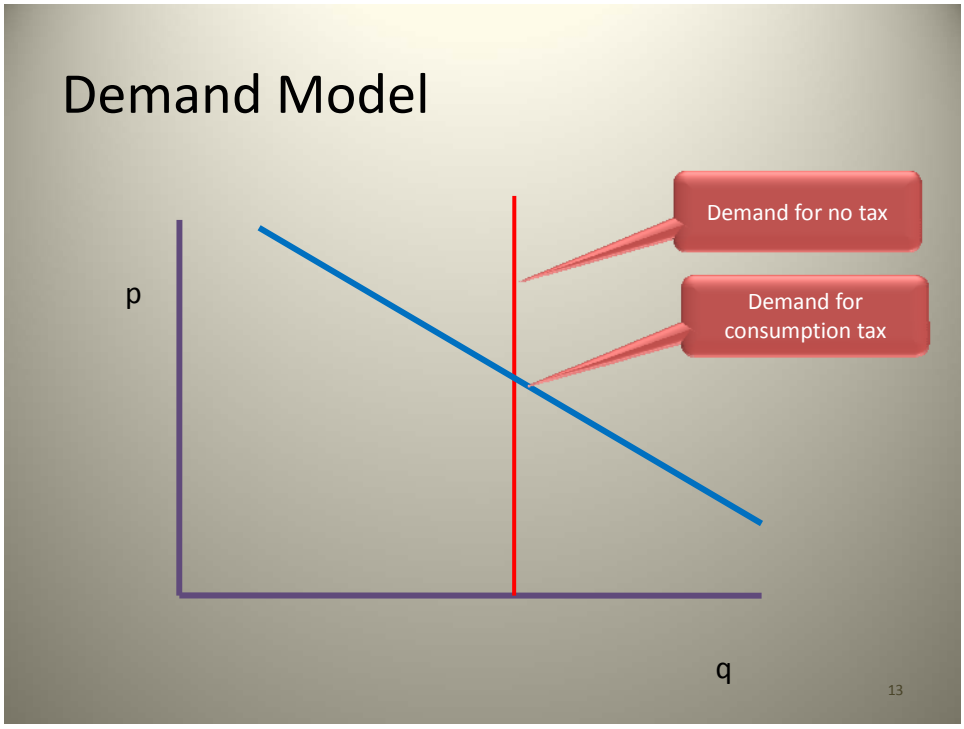
The result is that we estimate that Type 2 Diabetes costs $251 billion in 2008. This does not include the retinopathy costs which were lacking. We estimate that they add an additional 10%, raising the total to $275 billion, exceeding 12% of all 2008 health care expenditures.

8 THE ECONOMIC IMPLICATIONS

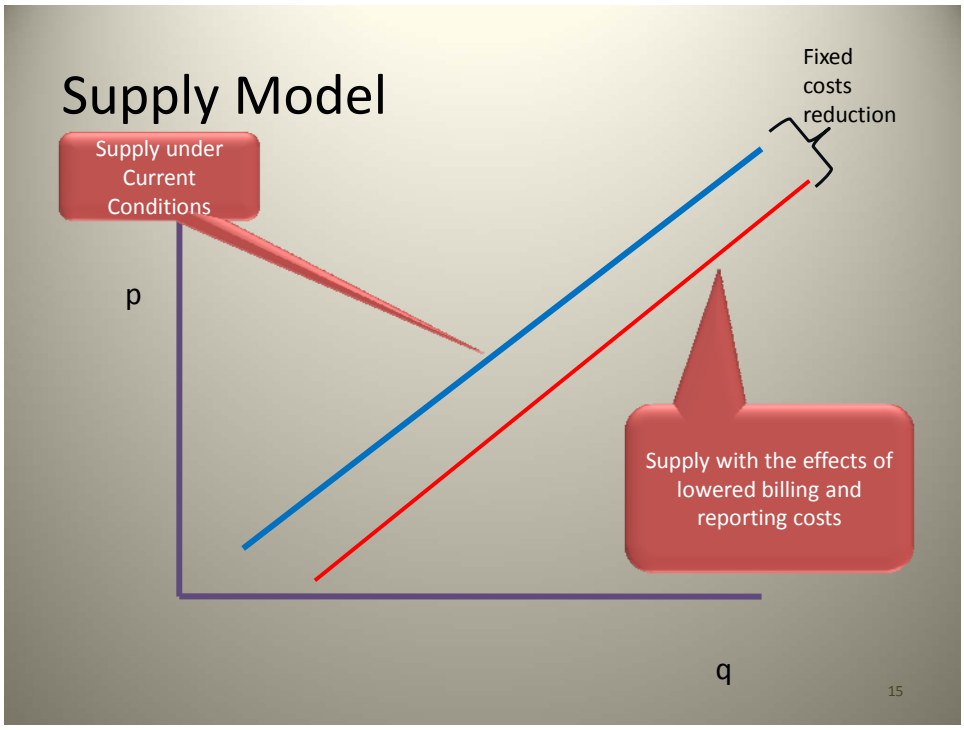
We can now examine in simple economic terms what the impact of the proposal to address obesity and carbohydrate consumption will be. We proceed through five steps; demand, supply (three steps) and market stability. The approach here is to look at the market and recognize that the supply curve can be modulated, reduced, my certain efficiencies which we have discussed elsewhere (McGarty, Health Care, 2009). The demand side is what we address here with some thought. We do not look at the Pigou tax approach since we comment on that in the Conclusions.

8.1 AN ECONOMIC MODEL

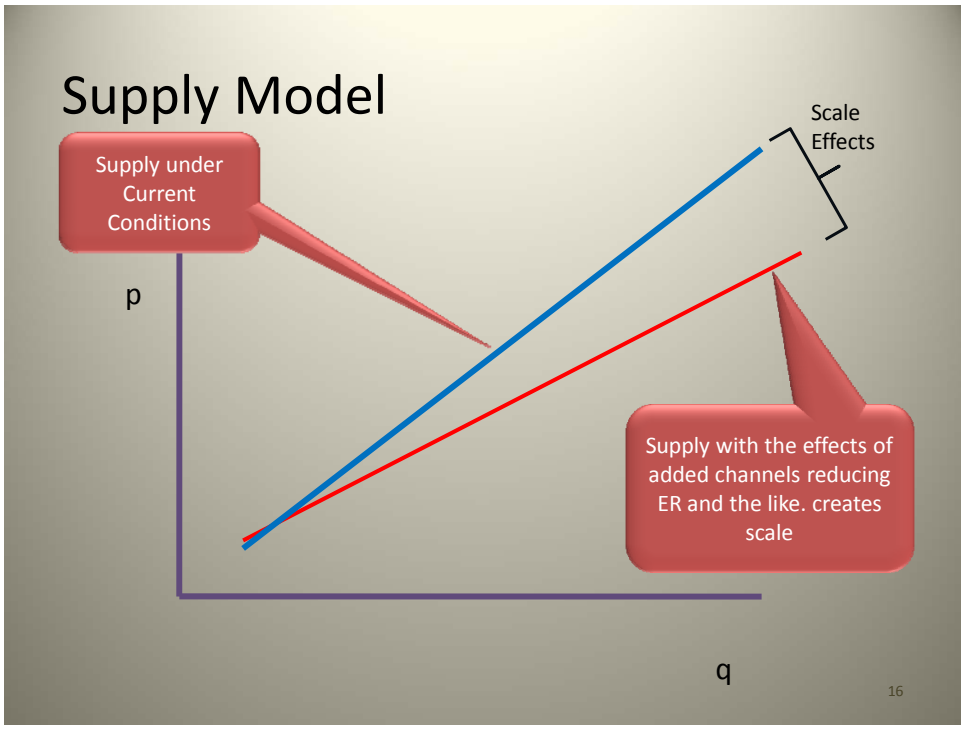
Consider first the demand. Here we plot demand on a price, p, and quantity, q, and diagram common to all economics. Currently demand is independent of price. The current demand is a vertical line that is fixed and independent to any costs. This is more than simplistic since we generally accept anyone into the ER and in states like California illegal immigrants are provided care independent of any status. Now if we apply to the system some "tax" for bad foods or behavior and also provide costs incentives for excessive use then we get a more normal demand curve, namely price or cost sensitivity.



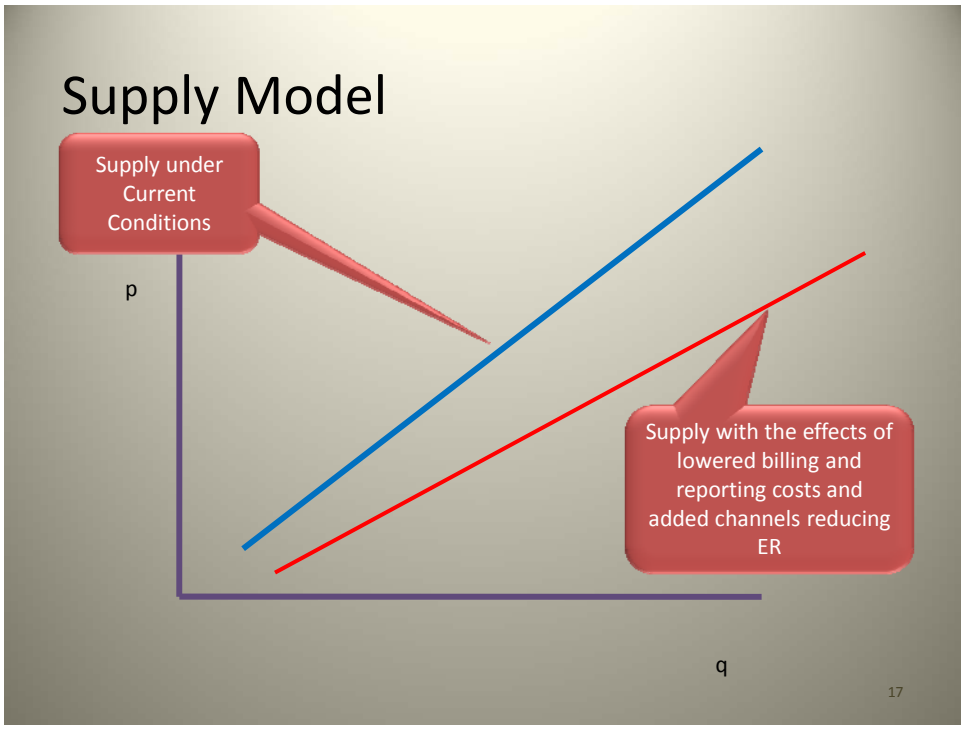
Now the first step in the supply curve will be to drive out costs which are overhead costs. Thus is we reduce the cost of billing and that of report management on a per patient basis this would represent a shift in the supply curve downward as shown in the following. This is the first step in cost reduction.



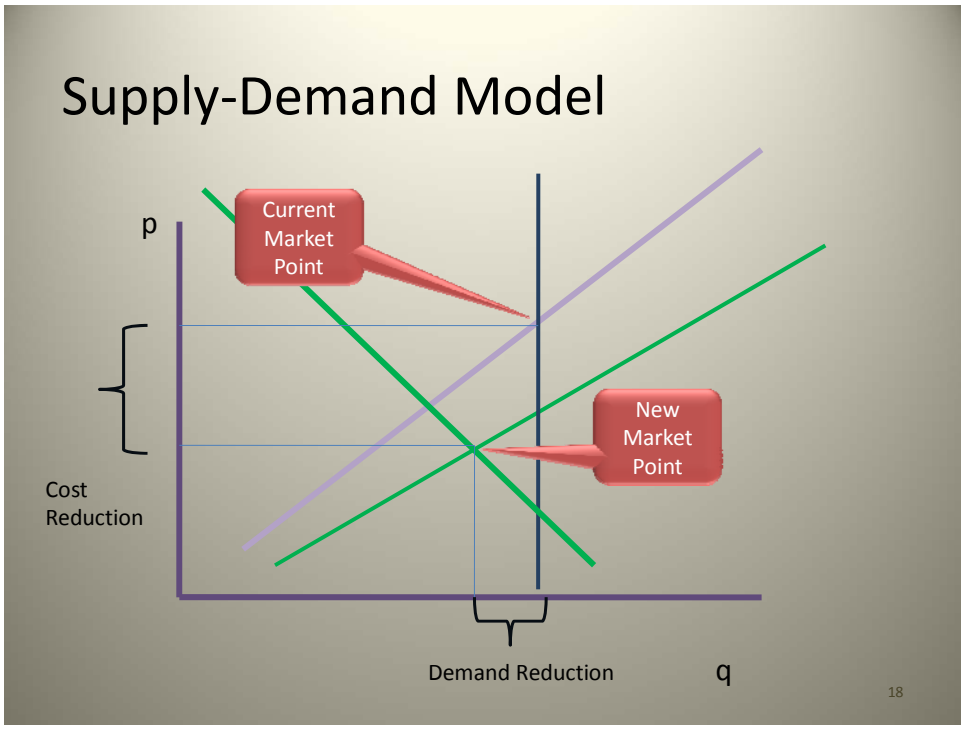
The alternative would be to create scale economies in the delivery, namely making it less costly the more service that are delivered. We argue herein that using a Public Health delivery system would do so by alleviating other more costly means such as the ER. There are many more examples of such an approach. The following Figure depicts what would happen in this event. Namely we see a decline of the supply curve the larger the demand becomes, clear scale effects.



We can then combine the two effects of reducing overhead and achieving scale to create a compound new supply curve as shown in the following Figure



Finally we can combine the Demand and the Supply curves to show what the total effect would be. This is done in the following Figure.



We note that we reduce the costs significantly while have a small but measurable decrease in the supply by means or reallocation while keeping the overall quality high. This above graphic is in essence what we propose in the plan.

Specifically if we can achieve cost reductions via certain market restructuring then by demand reduction especially in the area of obesity we can achieve dramatic overall cost reductions.

8.2 THE PIGOU TAX

There has been a great deal of discussion regarding the Pigou tax as a way to modify behavior which has negative externalities. For example if trains cause sparks as the run on rails and if the sparks cause fires on corn fields, and if the corn crop is destroyed, then perhaps we tax the train companies as a disincentive to cause the sparks. The problem here is that the train company will just raise prices and the corn will still burn. This approach was used to some degree on cigarettes, where now in New York City it will cost $10.00 or more per pack. That has driven smoking rates down.

The debate on cap and trade, which we detailed a year ago, is also predicated on the so called Pigou Tax and externalities.

Th principle is that if the actions of a person has a cost external to a specific transaction and that costs impacts society as a whole, such as the putatively generate CO2, then the Government taxes the person as a disincentive to use more.

This is just a tax. If the person has no alternative than other than freezing to death in the winter.

Let me give another example. Take the carb tax. That is something which we have discussed herein. An obese person, and there are quite a few in the current Administration, except those who smoke, has a cost to society which can be statistically calculated to the penny. Type II diabetes and its sequelae cost $325 billion in 2010 alone. To solve that but still allowing people to est and have the resulting morbidity associated with it we can use a Pigou Tax but put the money in a Fatty Fund to pay for the added costs. I can actually calculate by grams of carbs what the tax should be! One can still pork up but now the costs are covered. It costs those not indulging nothing and in fact saves them by having the consumers of excess carbs pay.

Now back to cap and trade. Here there is no alternative to heating or driving to work. The Government just taxes and spends! What stupidity.

As Prof Glaeser at Harvard in the NY Times states[10]:

Following the great English economist Arthur Cecil Pigou, economists have long argued that such externalities can be treated with a tax equal to the size of the externality. In this case, the right tax would equal the worldwide economic damage wrought by emitting carbon or other greenhouse gases. So why is the Kerry-Lieberman climate change bill, the grandly named American Power Act, 987 pages long?

This bill is a behemoth for three reasons. First, it tries to do far more than just charge for carbon emissions. The bill starts by providing "incentives for the growth of safe domestic nuclear and nuclear-related industries." It supports carbon capture in coal plants, expands offshore drilling, establishes an Office of Consumer Advocacy and promotes "clean energy career development." Standard economics suggests that many of these interventions would be unnecessary if we had the right tax on carbon emissions; if companies pay the full social costs of their actions, they have the right incentives to invest in greener technologies without any further help from Uncle Sam.

The second reason that the bill is so big is that it uses a complicated cap-and-trade system rather than a simple Pigovian tax. In theory, a permit system can be identical to a tax. Selling permits to emit carbon at $50 a ton is equivalent to taxing carbon emissions at $50 a ton. But tradeable permits, typically and as promulgated in the American Power Act, differ from a tax for two reasons: the quantity of permits is relatively fixed, and many permits will be given away rather than sold.

Well this is no surprise. The Markey-Waxman bill of 2009 which we wrote about in detail then had the same problems. It gave credits to a whole swath of friends to be doled out by Congress!

[10] http://economix.blogs.nytimes.com/2010/05/18/making-the-simple-complicated/

The solution to this CO2 problem is economically viable and competitive alternative sources of energy, not taxing those who cannot pay to begin with. Demand will not decrease, at least for energy! It is akin to rationing water. This makes no sense. The solution is improved efficiency and better technology. Can the Government do this? Frankly the Government qua Government has shown no ability to ever do so. One need look no further than the DoE electric car project of 40 year duration or even better the ancient air traffic control system.

On the other hand there have been successes in the past, look at the MIT Rad Lab in WW II or the Manhattan Project. The common thread, focus and non Governmental employees.

So where is there a focus on achieving new alternatives? Nowhere, they are swamped with favors for friends as Glaeser says, though not very well. Will this tax, the Pigou Tax, work? No, not really, it will just get added to the VAT, the inheritance, the rich persons tax and whatever else is added on.

To summarize, the Pigou approach works if the externalities are quantifiable, if there is an alternative, and if the fees charged pay for the costs of the externalities and no more or less. This is the Coase argument. In a transaction costless environment, one should let the parties clear the market. The railroad should pay the farmer for the loss of the crops caused by sparks from the train. The Government should not have its hand out in the process and take from both parties.

The Agency for Healthcare Research and Quality has released its 2009 report on health care[11]. This is worth the read. The trends reflect the limited improvements in the system. It is a reflective report and does not really look forward.

They state:

Despite the data limitations, we find that health care quality in America is suboptimal. *The gap between best possible care and that which is routinely delivered remains substantial across the Nation. Receipt of quality health care also varies widely. For example, caregivers reported that 95% of hospice patients received the right amount of pain medication, but only 8% of patients needing care for alcohol problems received such treatment at a specialty facility. Across the core report measures tracked in the NHQR, the median level of receipt of needed services was 58%. We can and should do better.*

Moreover, despite efforts to transform the U.S. health care system to focus on effective preventive and chronic illness care, it continues to perform better when delivering diagnostic and therapeutic care in response to acute medical problems. Our system achieves higher performance on hospital measures, such as acute treatment for heart

[11] http://www.ahrq.gov/qual/nhqr09/nhqr09.pdf

attacks, than on outpatient measures, such as cancer screening and diabetes management. *For example, between the 2008 and 2009 reports, five measures attained overall performance levels exceeding 95%. Four of these five measures relate to hospital care for heart attack. In addition, all 10 of the worst performing process measures tracked in this NHQR are measures of outpatient care, and 6 of these relate to preventive services.*

One of the concerns is that much of the concern about prevention is truly a patient duty and we continue to disconnect the patient from the outcome. Patients who smoke, who are obese, who fail to get the proper tests especially if family history tells them they should are as much to blame as is the system. A physician can only deal with a patient and their propensity to get ill if the patient shows up and then follow through.

9 CONCLUSIONS

The intent herein was to demonstrate that the research and knowledge to date is adequate to show that obesity is primarily caused by excess carbohydrates, that obesity in turn is the primary cause of Type 2 Diabetes, and that Type 2 Diabetes has sequelae of chronic diseases that resulting long term and high intensity care and thus costs, and that the total costs of these sequelae are now more than 12% of the total health care expenditures and are growing at an almost exponential rate for the foreseeable future in the US and worldwide.

We believe that we have achieved that goal, by use of primary research, and that the conclusion is both obvious and readily extensible. There are other issues that we wish to note as well starting with the Pigou taxing issue which we introduced earlier.

9.1 PIGOU AND HIS TAX

As we had indicated at the beginning, we had started this task because of Prof Mankiw's assertions regarding the tax on soda and that such a tax would have de minimis effect on the costs resulting therefrom. In addition Mankiw asserts that we should be taxing fuel as a means to control both consumption and reduce green house gases.

We contend that to the contrary, the costs of controlling Type 2 Diabetes far exceed those of all energy usage and indeed the costs of Type 2 Diabetes are growing at a substantially greater rate. Furthermore we contend that the taxing of carbs, in reality the establishment of a fee on carbs which will then be used to pay for the sequelae of excess use, is a more fait tax and in fact can be done extra the Government as agent and furthermore can be done in a pure Coasian manner, in direct contrast to Pigou and Prof Mankiw.

Let us compare the two taxes that Mankiw proposes in light of what we have demonstrated about Type 2 Diabetes. We compare a tax on Energy paid to the Government versus a fee on carbohydrates paid to a fund to pay the expenses for Type 2 Diabetics and their sequelae. This comparison is highly enlightening in view of the current cap and trade proposals as well as how the new health care plan functions in its total disregard for demand control. The approaches by both parties seem to be, if one assumed Mankiw is representative of the Republicans having been in the Bush administration, one of having the Government control everything either directly or via a tax. Both are excerpts from the Progressive movements of a century ago. One can see this by comparing the proposal herein for Type 2 Diabetes control and the Mankiw tax on energy.

Factor	*Type 2 Diabetes*	*Energy*
Factor sought to control	1. Exploding costs of health care 2. General welfare of citizens	1. CO2 emissions and argued global warming 2. Reliance on foreign oil
Value of Current Expenditures	$300 B and growing at 15% pa due to prevalence of obesity.	$233 B and declining[12]
Target of Tax	Direct payment of costs of behavior.	Tax applied and collected by Government for redistribution purposes
Impact of Tax	Pays for specific costs resulting from consumption.	Takes capital from the economy reducing investment and increasing redistribution
Personal Choice	Can decide to consume or not but cost assigned	Little choice since most if not all uses are non discretionary
Basis of Tax	Specific costs of specific disorders	Arbitrary value at a level intended to reduce consumption.
Elasticity Effects	Consumer consumption highly elastic and is based on displaceable choice, lower carb or no carb, and possible lower costs	Consumer consumption is highly inelastic because consumer needs fuels for heating and travel to and from work. There are no alternatives for most consumers.
Negative Consumer Externalities	Raises costs to the segment who have excess consumption	Raises costs to consumer
Theoretic Methodology	Coase, Hayek	Pigou, Marx

Professor Mankiw is a respected economist and was the head of the Council of Economic Advisors under President George W Bush. yet I cannot understand what logic or reason drives this irrational tendency to support this Pigou club. Let me explain why I fell thus.

The Pigou Club alleges to be believers in the Pigovian Tax. This is a tax on things we do not want people to do. This means that using the economists terms there are negative externalities to these specific actions society wishes to eliminate. Let me give a few examples.

1. Smoking Causes Lung Cancer. Thus was tax cigarettes at an astronomical rate to get people not to smoke. Today that me be $7.00-$10.00 per pack! But people have an alternative. They can give up smoking even if it is a trying experience. They are not deprived of anything by not smoking. The externality is the risk of lung cancer. Mankiw dismisses this because patients with cigarette caused lung cancer generally do not live long and all too often they come down with this disease before they turn 65 so that there is a de minimis burden on the society as a cost.

[12] http://www.eia.doe.gov/emeu/international/oiltrade.html

2. Carbs make you fat and fat leads to Type 2 Diabetes.: Thus we would or should tax carbs or perhaps weight. The $0.05 tax per 12 oz can of soda is an example. We could tax all empty carbs, we could tax high fructose corn syrup, if that made sense, and people would not have a major life change. In fact they may get a little nervous from a lack of a sugar rush but that is all. The difference here as we have observed is that Type 2 Diabetes has sequelae which are costly and are chronic lasting many decades.

Now consider a few Mankiw type Pigou charges, ones that he finds compelling.

3. Driving causes congestion. Apparently Mankiw dislikes traffic. Then again he is in Cambridge and I am in New York, most of the time, so he wants to tax people at say $1.00 per gallon in addition to what is there to get them to stop driving. There is a negative effect. People need to drive, they do so to go to work. There are real people who do not work at Harvard who have to drive say to Lynn, or Lowell, or some other place where they cannot get public transportation. There is thus a burden on these people because unlike the sugar or tobacco case they have money taken from them and given to the Government and they then lower their standard of living. This is true, I see this in West Virginia, Kentucky, and many other states. Perhaps not in Massachusetts.

4. Carbon Dioxide is Bad and Cap and Trade Reduces it: Well let's go along with the CO2 issue for a moment. Yet as a commercial horticulturalist I could do with warmer weather, I lost a good percent of my seedlings to an overly cold winter, but I digress. Facts are so annoying. Mankiw supports the plan proposed by Congressman Ingliss. Simply Ingliss proposes the same Cap and Trade as does the Administration but he says that the Government should give the money back to the taxpayer. Has he gone out of his mind. Has the Government ever given anything back. Just look at Social Security, we pay and they take. Then they complain they cannot meet their obligations. At least the current Administration is not a dreamer. They just want to tax and take away for what they believe is in their best interests.

Consider a simple Cap and Trade calculation.

1. In electrical power today there are 2.4 BmTn of CO2 emitted from electrical power generation.

2. Ingliss proposes a $10 to $100 tax per mTn. This is a tax of $24 B to $240 B.

3. There are 300M people and 80M HH in the US

4. This is a tax of $300 to $3,000 per HH per year.

5. There are current 35M people over 65 collecting Social Security with about 1.5 people per HH. This means that there are 24 M HH of those over 65. They collect $12,000 per person per year.

Thus we will tax the old at a rate of 25% of their gross income! What a great idea Congressman and you too Professor. This will soon take care of the Medicare problem, they will all just freeze to death. I have not included auto taxes on top of this.

Thus the Pigou Club has a strange idea. If there is some bad unintended consequence, a negative externality to be correct in the jargon of the economist, then we tax the user no matter if the result is another unintended consequence to them, such as their death! Only economists can create such a logic!

9.2 THE SUGAR TAX

There has been a growing debate on the sugar tax, with the focus on soda as a major source. The problem is that a 12 oz bottle has about 180 kcal. It will take 20 bottles to add a pound of fat. Thus the question is should we target soda or carbs. The following is a recent example of the dynamics of that debate.

The Ethicist of the New York Times has entered the battle of taxing carbs[13]. First the mere thought that the Times has an ethicist is an oxymoron if I ever saw one. Is it that they need one or is it that they believe that they can opine on what is right. But back to what was said. The article begins:

"*Proposals to tax sugary drinks as a way to fight obesity and finance health care reform have found support from medical experts and some interest from President Obama while meeting resistance from the beverage industry in general and the Coca-Cola C.E.O. Muhtar Kent in particular. "I have never seen it work where a government tells people what to eat and what to drink," he told the Rotary Club of Atlanta last month. "If it worked, the Soviet Union would still be around." Is this sort of argument so dubious, and does it come from the maker of products so damaging, that Muhtar Kent should be dragged off in handcuffs — or worse*?"

One would expect the CEO of Coke to say as such. But there is an example. It is the tax on cigarettes. It has worked and continues to work. We have shown that many times and it is detailed in our book, Health Care Policy: Politics vs Reality.

He goes on to state:

"*Assuredly, many factors affect our weight. But it doesn't follow that because a policy fails to address all of them, it should not address any. That the feds devote few resources to going after counterfeiters who mint fake quarters doesn't mean they should decline to pursue those who run off $20 bills.*
What's more, the multiple causes of a problem need not share equal significance. Studies suggest that sugary beverages are a key contributor to obesity. In its analysis, the Center on Budget and Policy Priorities notes that "Americans consume about 250-300 more daily calories today than they did several decades ago, and nearly half of this increase

[13] http://ethicist.blogs.nytimes.com/2009/09/21/an-anti-tax-argument-thats-hard-to-swallow/

reflects greater consumption of high-sugar soft drinks." So there's a case to be made for giving serious consideration to a soda tax even if other steps are not taken."

To build upon the above let us recall the simple relationships:

1. It requires 3500 kcal for each added pound.

2. A BMI between 25 and 30 is overweight and over 30 is obese. Obesity is the primary cause of Type 2 Diabetes which costs us $275 Billion in 2007, and it is growing.

3. The extra 300 kcal per day equals 2100 kcal per week, or 109200 kcal per year or 31.2 pounds per year!

We want to reduce health care costs so here is the target. It is not ethical it is economic.

In a recent NEJM article the authors state:

"*Economists agree that government intervention in a market is warranted when there are "market failures" that result in less-than-optimal production and consumption. Several market failures exist with respect to sugar-sweetened beverages. First, because many persons do not fully appreciate the links between consumption of these beverages and health consequences, they make consumption decisions with imperfect information. These decisions are likely to be further distorted by the extensive marketing campaigns that advertise the benefits of consumption. A second failure results from time-inconsistent preferences (i.e., decisions that provide short-term gratification but long-term harm). This problem is exacerbated in the case of children and adolescents, who place a higher value on present satisfaction while more heavily discounting future consequences.*

Finally, financial "externalities" exist in the market for sugar-sweetened beverages in that consumers do not bear the full costs of their consumption decisions. Because of the contribution of the consumption of sugar-sweetened beverages to obesity, as well as the health consequences that are independent of weight, the consumption of sugar-sweetened beverages generates excess health care costs. Medical costs for overweight and obesity alone are estimated to be $147 billion — or 9.1% of U.S. health care expenditures — with half these costs paid for publicly through the Medicare and Medicaid programs.""

Our analysis presents a substantially greater number but they are within a factor of two which is not bad for this type of analysis. The NEJM authors then go on to discuss how the taxes would work. Let us look at this in a more general manner. We see the following mechanisms:

1. Tax at Point of Sale/Consumption: This is akin to the cigarette tax. We know that the cigarette tax works but it took many years and many tax increases to get it to function. Also there is a one to one mapping between tobacco and cancer for example. That is if you stop tobacco usage as in cigarettes you stop lung cancer. This is not the case with sugar. It is total kcal which must be modulated. Thus we would have to tax cookies,

cakes, candies, and the like. It is more complex.

2. Tax at Point of Result: This is the proposal that everyone must be weighed each and every year and they get taxed on excess BMI. Thus, for example, you get weighed and pay $1,000 per point over 25 if you are between 25 and 30 and say $2000 for every point above 30. After all you get your car inspected each year and all you would then do is do the same for yourself! Thus if you desire to gain weight you can but you get taxed.

These two proposals look at extremes. One looks at one particular element and the second looks at the result. One attempts to modify behavior and the other penalizes the results. We feel that neither accomplishes the desired result and that the carb issue is more complex than tobacco but it worth continued study.

In a recent article in Science the author does a wonderful job in providing an up to date review of just where the research is on Type 2 Diabetes and obesity[14].

The author concludes:

"*One observation that seems indisputable is that when individuals lose weight, they become more insulin sensitive. If nothing else, this has given researchers the confidence to assume that excess body fat—particularly in the abdomen and around the internal organs— is a fundamental cause of insulin resistance. But that still avoids the question of what causes insulin resistance in lean individuals. This is something few researchers will even address, although one possibility is that they, too, simply can't store fat safely in subcutaneous pads.*

"The biggest question in the whole field of insulin resistance is still this direction of causality," says O'Rahilly. "Does obesity make you insulin resistant? Or does underlying factor x cause both obesity and insulin resistance?""

Yet the remaining fact is that Type 2 Diabetes is prevalent in obese people 100 to 1 more times in those not and the article does articulate the fact that fat is the primary cause of inflammation which in turn is a causative factor in the insulin collapse chain.

9.3 THE POSNER APPROACH

Richard Posner is a Judge in the Federal Courts and on the faculty at the University of Chicago. In a recent blog entry by Judge Posner regarding the calorie or carb tax[15] he states:

"*I am skeptical, because the author ignores the possibility of substituting untaxed sugar-sweetened foods or beverages. People who crave sugar will find no dearth of substitutes*

[14] http://www.sciencemag.org/cgi/reprint/325/5938/256.pdf

[15] http://www.becker-posner-blog.com/archives/2009/05/a_soda_or_calor.html

for sugar-sweetened sodas. Moreover, most consumers of these sodas are not and never will be obese. They may well be overweight, but all that that means is that they are heavier than the "ideal" weight calculated by physicians....

There are many obese Americans, in the sense of ones who are grossly overweight (with some being morbidly obese), and we should consider whether society should be concerned with obesity if not with mere overweight. Obesity impairs health, and, in most segments of the population it diminishes social and professional success as well, and so it can be regarded as self-destructive behavior. Some of it is involuntary....

As to whether by increasing obesity the sale of sugar-flavored sodas imposes costs on other people besides the buyers, the evidence is mixed. Obese people have more health problems than the non-obese and hence higher annual medical costs; they also lose more time at work because of illness. Their poorer health increases the medical costs of other people in their insurance pools and reduces the productivity of their employers, assuming realistically that employers cannot selectively reduce the wages or health benefits of their obese employees.

Cutting the other way, obese people have a reduced life expectancy, and the shorter a person's life, the less an above-average annual cost of medical care translates into an above-average total (lifetime) cost. But assuming nevertheless that the net social costs of obesity are positive, this would be a ground for arguing for taxing obesity, but such a tax would be unacceptable as well as cruel. ..."

Unfortunately Judge Posner fails to deal completely with all the facts. We have shown herein that:

1. It costs over $275 B today of our total $2.5T health care costs. That is 12% of the total costs.

2. It will grow to 25% by 2020.

3. Type 2 Diabetes in 95% of the cases is due solely to obesity. Keep the BMI at 22.5 or lower and you keep the HbA1c at 5.0 or lower and no Diabetes! That means keep the weight down.

4. Diabetes is a carbohydrate disorder. It is not a fat or protein disorder. Thus we want low carbs, and our old friend Pigou had this tax idea, tax things we do not want people to do, like smoking, and it works! Just look a lung cancer in males. It is down 50% from twenty years ago! High taxes on cigarettes. So tax carbs, not just soda. Education may help, but how many physicians have "educated" their patients to lower BMI, less than 0.1%!

Thus if the Judge had examined the facts in some detail he would see that taxing is not only a good plan but that it is the only one we know works!

Robert Solow of MIT wrote a critique of the most recent Posner book in the New York Review of Books. Solow is a Nobel Prize winner and I have come to know and respect him personally[16]. He states:

"Judge Posner evidently writes the way other men breathe. I have to say that the prose in this book often reads as if it were written, or maybe dictated, in a great hurry. There is some unnecessary repetition, and many paragraphs spend more time than they should on digressions that seem to have occurred to the author in mid-thought. If not exactly chiseled, the prose is nevertheless lively, readable, and plainspoken. The haste may have been justified by the pace of the events he aims to describe and explain. Posner has an extraordinarily sharp mind, and what I take to be a lawyerly skill in argument. But I also have to say that, in some respects, his grasp of economic ideas is precarious. In his book on public intellectuals, Posner blames the decline of the species on the universities and their encouragement of specialization. I may be acting out that conflict. Remember that even hairsplitting is not so bad if what is inside the hair turns out to be important."

As Posner's economics grasp may be precarious to Solow, his grasp of medicine is almost totally lacking to me!

9.4 OBESITY AND THE INTERVENTION

It is interesting to see how the Europeans view this obesity phenomenon, since it is starting to come forth there as well. In a recent paper by Brunello et al the authors state[17]:

"*From an economic viewpoint, a relevant policy question is whether public intervention that would* ***reduce obesity can be justified on the basis of equity or efficiency*** *considerations.*

Consider equity first. Both Baum and Ruhm (2009) and Brunello, Michaud and Sanz-de-Galdeano (2009) provide evidence that ***individuals' BMI is generally inversely related to their mothers' educational attainment in the US and in Europe; BMI is higher among those with less educated mothers****. However, establishing whether such correlation purely reflects causality, which would imply that individuals' BMI is at least partly determined by circumstances beyond their control, is a complex empirical task that remains on the research agenda.*

The second rationale for public intervention on economic grounds is efficiency. Cawley (2004) rightly argues that ***if individuals were perfectly rational and their decisions about food and weight imposed no costs on others in society, if information about the consequences of obesity were accurate and readily available and if markets were perfectly competitive, there would be no market failure and no reason for government intervention****.*

[16] http://www.nybooks.com/articles/archives/2009/may/14/how-to-understand-the-disaster/

[17] http://www.voxeu.org/index.php?q=node/4061

In Brunello, Michaud and Sanz-de-Galdeano (2009), we provide cross-country evidence on the relevance of the inefficiencies related to obesity and we organise them around four categories of market failures: productive inefficiencies, limited information, limited rationality, and health insurance externalities."

The conclusion seems to be, if you have a dumb mother you will be fat! You are fat because you eat too much! You may have had a goat for a mother, who cares, you still eat too much. It is a fundamental law of nature:

Net Accumulation = Input - Output!

Where did these ideas come from? It is still 3500 kcal per pound and if your BMI is 2000 and you consume 2500 than every 7 days you gain a pound! Your mother could have been a flea! Just stop eating.

The authors continue:

"*We estimate the difference in lifetime expenditures using a micro-simulation approach both in the US and Europe.* ***We find that an obese American at age 55 faces, on average, an additional $22,251 in health expenditures, which represents 10% of a non-obese person's lifetime health expenditures****. Since a 55 year old can expect to live approximately 29 years, the expected loss in income/consumption (using a 3% real interest rate) is close to $1166 per year. In Europe, the difference in lifetime health expenditures is slightly lower, at $13,840 or 11.1% of a non-obese person's lifetime expenditures, reflecting mostly the differences in average costs across countries but also better baseline health in Europe.*

Given that in both the US and Europe obese individuals face larger lifetime health expenditures, ***the next question is whether a subsidy exists or these additional expenditures are born by individuals themselves****. The fraction of individuals covered by a public health scheme is likely to be a good proxy for the degree of risk pooling. This is because public insurance schemes seldom allow for risk rating of premiums for equity reasons but also because expenses are financed either through a flat contribution rate or through taxation. Except for the US, public health schemes are predominant in OECD countries. In the US, about a fourth of the population, mostly the elderly, is covered by public insurance. Only 44% of total health expenditures are financed through the public system and 60% of the population rely solely on private health insurance*."

This statement contains several good nuggets. First, it is not clear what the basis of this assertion is, but they state that the lifetime costs of health care to an individual is $225,000 in current dollars. If that is correct, then many interesting statistics flow from it. One is that half of that is spent from birth to 65 and the remaining half from 65 to death. The second observation that make is regards to the costs of the European system but if one looks at OECD data on obesity in Europe it is lower than the US except for the UK. The authors conclude:

"*But the existence of a subsidy is not necessarily inefficient.*

If one thinks of obesity as a trait that individuals inherit, then there is nothing inefficient about risk pooling, i.e. the subsidy is a pure transfer that can be undone, if desired, on equity grounds.

It is the change in behaviour induced by the subsidy that may be inefficient. In other words, the subsidy must affect the propensity of individuals to gain more weight. There is little evidence in the literature that this behavioural response is important.

In fact, one can make the conservative assumption that the behavioural response to the subsidy is similar across countries. In that case, despite being small, one would expect the insurance externality to be higher in Northern European countries than in the US The fact that obesity is higher in the US provides a rough indication that the behavioural response ought to be small; i.e. Europeans are not fatter in spite of the fact that they face a larger insurance subsidy.

Hence, a conclusion from our study is that the obesity externality, although more likely to be important in Europe than in the US, is unlikely to be a good reason for public intervention."

The first paragraph makes no sense. Individuals do not inherit weight. The accumulate it by individual choice. They eat! It is a free choice, in all except a very few rare circumstances. Thus the taxing of weight due to the costs associated with its negative health benefits and costs to those not obese if not only a worthy disincentive it is an imperative.

When one reads articles of this type one wonders if anyone has had a thought of rationality or is this the result of some social mind meld to excuse those who have made negative and costly choices.

9.5 BANTING AND BEST REDUX

Banting and Best who are noted as the discoverers of insulin, along with MacLeod, at Toronto, having been awarded the Nobel Prize for the achievement, accomplished the task with minimal resources in a brief period of time and under less than supportive conditions. Banting was clearly a driven man with the ability to survive the pressures from the external environment. The example of this team is that a small focused group can achieve wonders.

In a recent article in Nature Genetics and it is on the determination of some several genes related to glycemic control in humans with Type 2 Diabetes[18]. Like so many articles of

[18] http://www.nature.com/ng/journal/v42/n2/abs/ng.520.html?lang=en

this type it states:

Levels of circulating glucose are tightly regulated. To identify new loci influencing glycemic traits, we performed meta-analyses of 21 genome-wide association studies informative for fasting glucose, fasting insulin and indices of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) in up to 46,186 nondiabetic participants.

Follow-up of 25 loci in up to 76,558 additional subjects identified 16 loci associated with fasting glucose and HOMA-B and two loci associated with fasting insulin and HOMA-IR. These include nine loci newly associated with fasting glucose (in or near ADCY5, MADD, ADRA2A, CRY2, FADS1, GLIS3, SLC2A2, PROX1 and C2CD4B) and one influencing fasting insulin and HOMA-IR (near IGF1).

***We also demonstrated association of ADCY5, PROX1, GCK, GCKR and DGKB-TMEM195 with type 2 diabetes**. Within these loci, likely biological candidate genes influence signal transduction, cell proliferation, development, glucose-sensing and circadian regulation.*

***Our results demonstrate that genetic studies of glycemic traits can identify type 2 diabetes risk loci, as well as loci containing gene variants that are associated with a modest elevation in glucose levels but are not associated with overt diabetes**.*

Interesting but there were some 176 authors! The list of authors was longer than the abstract! This is an amazing trend in research papers which I find disturbing. I see this even at the graduate level where there are so many authors one wonders who really did the work. In the past, say 40 years ago, there was a single author. We knew who made the contribution and we knew who made the mistake. In the biological sciences the need to publish and the need to extend the reach of involvement, possibly for later plausible deniability, has it appears gone to the extreme.

If from experiments of this type a great discovery occurs, then we will not have a Banting and Best, Watson and Crick, and the like. We will just have a large bunch of folks. Pity.

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11 APPENDIX: MANKIW ARTICLE (NY TIMES)[19]

"As governments large and small face sizable budget shortfalls, policy makers are looking for ways to raise tax revenue that will do the least harm and, perhaps, even a bit of good. One idea keeps popping up: a tax on soda and other sugary drinks.

The city council in Washington recently passed such a tax. Gov. David A. Paterson has sought one in New York. And a national soda tax was briefly considered by the Senate Finance Committee as a way to help pay for President Obama's health care overhaul.

But is a soda tax a good idea?

Economists have often advocated taxing consumption rather than income, on the grounds that consumption taxes do less to discourage saving, investment and economic growth. Hence the case for broad based consumption taxes, like a value added tax. The main issue for the soda tax, however, is whether certain forms of consumption should be singled out for particularly high levels of taxation.

One argument for specific taxes is that consuming certain products has an adverse impact on bystanders. Economists call these effects negative externalities.

Taxes on gasoline can be justified along these lines. Whenever you go out for a drive, you are to some degree committing an antisocial act. You make the roads more congested, increasing the commuting time of your neighbors. You increase the likelihood that other drivers will end up in accidents. And the gasoline you burn adds to pollution, including the greenhouse gases thought to cause global climate change.

Many economists advocate gasoline taxes so that drivers will internalize these negative externalities. That is, by raising the price of gasoline, a tax would induce consumers to take into account the harm they cause after making their purchases. One prominent study added up all the externalities associated with driving and concluded that the optimal gasoline tax is over $2 a gallon, about five times the current level (combining the federal and a typical state's levies) and about the tax rate in many European countries.

Applying that logic to other consumer goods, however, is not as straightforward. Consider cigarettes. They are among the economy's most heavily taxed products, as governments try to discourage people from smoking. Yet the case for such a policy cannot rely on a conventional externality argument.

When a person sits at home and smokes two packs a day, the main adverse impact is on his or her own health. And even if second hand smoke is a concern, that problem is most naturally addressed within the household, not at the state or federal level.

[19] http://www.nytimes.com/2010/06/06/business/06view.html

Sometimes, advocates of "sin" taxes contend that consumers of certain products impose adverse budgetary externalities on the rest of us — that if the consumption induces, say, smoking or obesity related illness, it raises health care costs, which we all pay for through higher taxes or insurance premiums.

Yet this argument has a flip side: If consumers of these products die earlier, they will also collect less in pension payments, including Social Security. Economists have run the numbers for smoking and often find that these savings may more than offset the budgetary costs. In other words, smokers have little net financial impact on the rest of us. It may seem grisly to consider the budgetary savings of an early death as a "benefit" to society. But when analyzing policy, economists are nothing if not cold blooded. If one uses budgetary costs to justify taxing particular consumption goods, the accounting needs to be honest and complete.

There is, however, an altogether different argument for these taxes: that when someone consumes such goods, he does impose a negative externality — on the future version of himself. In other words, the person today enjoys the consumption, but the person tomorrow and every day after pays the price of increased risk of illness.

This raises an intriguing question: To what extent should we view the future versions of ourselves as different people from ourselves today?

To be sure, most parents have no trouble restricting a child's decisions on the grounds that doing so is in the young person's best interest. Few teenagers are farsighted enough to fully incorporate the interests of their future selves when making decisions. As parents, we hope that someday our grown up children will be grateful for our current restrictions on their behavior.

But people do not suddenly mature at the age of 18, when society deems us "adults." There is always an adolescent lurking inside us, feeling the pull of instant gratification and too easily ignoring the long run effects of our decisions. Taxes on items with short run benefits and long run costs tell our current selves to take into account the welfare of our future selves.

IF this is indeed the best argument for "sin" taxes, as I believe it is, we are led to vexing questions of political philosophy: To what extent should we use the power of the state to protect us from ourselves? If we go down that route, where do we stop?

Taxing soda may encourage better nutrition and benefit our future selves. But so could taxing candy, ice cream and fried foods. Subsidizing broccoli, gym memberships and dental floss comes next. Taxing mindless television shows and subsidizing serious literature cannot be far behind.

Even as adults, we sometimes wish for parents to be looking over our shoulders and guiding us to the right decisions. The question is, do you trust the government enough to appoint it your guardian?"

By N. Gregory Mankiw is a professor of economics at Harvard.

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