It’s a pleasure to be here to talk to you about our work on asthma disparities as it pertains to the root causes and potential solutions. So asthma, as most of you know, is the most common chronic disease of childhood. It poses enormous cost, in 2007 about $15.5 billion were spent in direct costs for asthma, most of those are related to prescription and severe exacerbations, ED visits or hospitalizations. Asthma is a disease characterized by airway inflammation, air flow obstruction that is often but not always reversible and increasing responsible to nonspecific stimuli such as cold air and allergies.

Whereas asthma affects 9% of children in this country, there are profound disparities in the prevalence, morbidity and mortality from asthma across ethnic groups. So this slide illustrates this. When you compare prevalence, ED visits or mortality those are much higher in non-Hispanic blacks than in whites in this country. When you look at Hispanics you could think that it’s not that different from whites, but that belies a profound and tragic mistake made in biomedical research over the last few decades and caused by the U.S. census. And by that I mean that this is a term coined by the United States census and nobody else. Nobody in Latin American would know what Hispanic means. As defined by the U.S. census Hispanic refers to people who can trace their ancestry to countries that were previously under Spanish control. That includes Mexico, large parts of Central and South America, some islands in the Caribbean and of course Spain. These 5 individuals would be classified as Hispanic by the U.S. census. Rigoberta Menchu, who is a Mayan Indian from Guatemala and won the Nobel Peace Prize in 1992, two players of my favorite team, the Red Sox, Mike Lowell who is Puerto Rican of Cuban descent and Big Puppy David Ortiz from the Dominican
Republic, Alberto Fujimori who was born to Japanese parents but who is Peruvian would be considered Hispanic by the U.S. census and Shakir Rems from my home town and is half Lebanese, half Columbian would also be classified as Hispanic.

In this country Hispanics come largely from Mexico, two-thirds, 9% are Puerto Ricans, 4% are Cubans, 13% are Central and South American and others compose 11%. So you could ask the question who are these others? Those people would be Spaniards, Dominicans and Hispanics who have been in this country for 400 years, so people who live in (inaudible) County near Albuquerque, New Mexico check the both other Hispanics, they have a genealogical society and have been there since the 1500s.

When you decompose this Hispanic aberration by subgroups a completely different picture emerges. You have Puerto Ricans rank at the top of asthma prevalence among children in this country with blacks second and the group that has the lowest prevalence is Mexicans. This phenomenon is known as the Hispanic paradox. Puerto Ricans have the greatest prevalence, morbidity and mortality from asthma of all ethnic groups in the United States. Mexicans consistently have been shown to have the lowest prevalence, morbidity and mortality from all ethnic groups in the United States. You will observe these paradoxical findings not only for asthma but also for chronic obstructive pulmonary disease and for prematurity. Puerto Rican women deliver the most premature babies in this nation, a Mexican woman the fewest.
This is an editorial that Dr. Eric Forno, who is faculty here, showing the costs or potential costs of these disparities in asthma and those include factors at the individual level and at the community level. The individual level we can start with ancestry and genetics, socioeconomic status and fortunately for historical reasons race and poverty are tightly linked in this country, indoor exposure to pollutants including allergens and second hand smoke, potentially vitamin D status, and we’ll talk about that, exposure to stress and violence, the epidemic blighting our cities and this is very timely given the events of yesterday, barriers in access to healthcare and delivery of it. And once these are overcome there is still barriers related to literacy and cultural beliefs. At the community level you have socioeconomic status, housing conditions, sociocultural factors, exposure to stress and violence, outdoor air pollution and education.

So let’s start by talking about racial ancestry. This is a paper published by Rush Kumar in the New England Journal in 2001. These are data for African-American adults, these are healthy adults where they reviewed data from pulmonary function test databases. If you plot African ancestry assessed by genetic markers, not by self report, in these African-Americans you’ll find profound variability. But what’s most interesting is that African ancestries are linearly and inversely related to lung function, where you look at these in adult men or adult women. If you in fact use the generic predicted reference values to assess what percent of normal FEV1 an African-American has there will be misclassification as this racial ancestry varies.
We asked the question with Dr. John Brehm also faculty here as to what about children and what about Puerto Rican children? African American adults have on average 75 to 80% African ancestry, Puerto Ricans are on average a quarter African, could we see a similar effect? This is racial ancestry now where children assess by snips from GWAS we performed, so 85,000 snips are used to assess markers. These are our kids. These are groups from the Human Genome Project. In our children their ancestry lies between European and African predominantly, with some Native American ancestry. The Taino Indians were wiped out of Puerto Rico in the 1600s so our kids are on average 25% African, 12% Native American with the remainder being European. In these children African ancestry is linearly and (inaudible) related to both FEV1 and enforced by L capacity after you account for potential confounders of this relationship such as household income. We already referred to poverty, use of medications, health insurance, etc. So these are school aged kids 6 to 14, for every 20% increase in African ancestry their FEV1 is 152 ml lower.

I’m going to now move you to Costa Rica. This one thing that I’ve learned in my 25 years here is that geography is not a strong suit of North Americans, so when I was faculty at Harvard and I said I wanted to do research in Costa Rica there was a Harvard professor who stood up and said well if you are going to do anything in Costa Rica you have to talk to me, I practically own that island. So Costa Rica is between Nicaragua and Panama, it’s in Central America. It’s citizens have enjoyed universal healthcare since 1948, much earlier than this nation, largely because they abolished their army, they just have a police force. So with Wei Chen and John Brehm here we used GWAS data to assess the racial ancestry of participants in this study. These are adolescents and adults and they are
related to individuals with chronic obstructive pulmonary disease. Now the ancestry of these subjects is very different from the Puerto Ricans, they lie predominantly between European, marked in blue, and Native American with minimal African ancestry; however Costa Ricans have a very high prevalence of both childhood asthma and COPD. And we asked the opposite question, what about Native American ancestry? The observation was made 20 years ago by John Sammut, a mentor of mine, that Hispanics in New Mexico had a lower risk of COPD, and those Hispanics in New Mexico are predominantly European and Native American.

So what about Native American ancestry? It turns out that in these Costa Ricans Native American ancestry is positively associated with lung function, both FEV1 and FVC. Now shown here is also associated with lower rates of chronic obstructive pulmonary disease and we showed in another study in New Mexico that Native American ancestry is associated with lower rate of declining lung function among individuals who smoke and lower rates of COPD. So we come to this Hispanic paradox and have to now say that perhaps in part these paradoxical findings are due to underlying differences in racial ancestry, that is populations who have Hispanic populations with greater Native American ancestry have lower risk of asthma and COPD in part because of their Native American ancestry. And those populations of African ancestry have a higher risk of asthma and COPD morbidity because of their African ancestry. An enormous amount of work remains to be done because ancestry, racial ancestry not only is a marker for genetic variation but also for culture and lifestyle. It is thus possible that in early life even in utero there is some practices that are related to ancestry or some exposures that underlie these findings.
What about genetics? Well one problem that plagues human genetics, and particularly genetics of complex diseases is that whereas we should all do unto others as you would have them do unto you, the reality is that in genetics it was a white man’s world. Most GWAS of diabetes, asthma, COPD included whites, and this happened for several years.

This landmark paper done in Japanese challenged this idea of the whites only research. It’s a study in Asian populations, at this point there were 20 GWAS of diabetes mellitus and none had detected this gene, KCNQ1. This data involved about 20,000 Asians, originally done in Japanese then in Han Chinese and Koreans and across all populations this was the strongest signal.

The historical data was reviewed for GWAS of diabetes type II in Scandinavians. It was found that there was a signal but it wasn’t either as strong or as significant and it would have never been detected in whites. This has to do with the fact that alleles vary in frequency across ethnicity and also that because of environmental covariates the effects may be stronger in some populations than others. Thus there are human variants for disease that are ethnic specific.

So across those lines we participated in this very large metaanalysis called the EVE Consortium where the idea was to try to find some genes that would have variants that would be cosmopolitan, that is that affect all ethnic groups, and some that would be specific. And in fact when you look at the associations that were replicated there were four, Interleukin 1 receptor, thymic stromal
lymphopoietin, Interleukin 33 and these very highly replicated locus on 17q21 that would replicate across all populations. But it was one gene, the PYHIN1 that was only found in African Americans and Afro Caribbeans, and in fact that remains a subject of active investigation.

So what have the asthma-susceptibility loci consistently replicate and identify by all of these GWAS efforts? There is this highly replicated 17q21 locus that includes 4 genes that cross regulate and it’s very hard to try to identify one that stands out. Most work has been done on this one, it has to do with integrity of the airway epithelium but others may contribute. This is a main contributor to childhood onset asthma as opposed to adult onset asthma. The key is (inaudible) gene which we originally reported on in 2008 in Costa Ricans. It turned out to be a cosmopolitan gene. IL33 and the IL1 are one receptor, but again there is this African or ethnic specific gene.

Now the opposite question could be asked, is it good business for our government to invest in research in minorities since these things may not be applicable to the majority population? So I’m going to show you the opposite example. Dr. Steve Shapiro, the Chief Medical Officer of UPMC, did this landmark work in 1997 where he showed that in a mouse model of emphysema, emphysema that was caused by smoking in mice was dependent on matrix metalloproteinases. The knockout mouse for this gene did not develop emphysema.

A few years later Jack Elias who is now the Chair of Medicine at Yale showed that in fact this, if you have a mouse that over-expresses an interleukin that is critical in asthma, IL13, and those mice
are exposed to smoke you can also show that that mechanism of over-expression of IL13 dependent emphysema is ultimately dependent on MMPs.

So based on that we asked the question could this gene that has been shown in murine models to influence emphysema and where an interleukin that is implicating asthma plays a role be involved in high risk of COPD? We did this with Matt Hornyak who is at Brigham in Boston. And in fact with work that is starting on minority population in Costa Rica we went on to show that two variants in these gene influence lung function in children with asthma, not only Costa Rican but also white children, and also individuals at risk for COPD. Moreover in a longitudinal study of adults followed for 30 years with multiple PFTs we show that these variants predicted a lower risk of COPD over time. So the point of showing you this is that actually studying minorities makes sense when it comes to genetics.

So now I’m going to switch gears from ancestry and genetics to vitamin D. This work led mostly by John Brehm here in our group. This child, this is a picture taken in San Jose, Costa Rica on one of my trips, this child is doing everything he can to increase his vitamin D levels. He’s doing everything right. He’s wearing short sleeves, short pants in a sunny day, 15 minutes on those conditions will give you enough vitamin D. He’s also drinking milk. So one of the points of justifiable skepticism about this vitamin D hypothesis as a potential cause of asthma or asthma morbidity is well you are telling us that vitamin D may be implicating asthma but there are all these countries near the Equator with plenty of sun for vitamin D insufficiency it should be rare, they have
a lot of sun. In fact in this study of 616 Costa Rican children with asthma 28% of participants had levels under 30 ng/mL. And we showed in this work the first report of vitamin D insufficiency and asthma morbidity that vitamin D levels are inversely related to multiple measures of asthma morbidity or severity, that is the lower the vitamin D the greater the asthma severity in these children.

We then on to a longitudinal study of 1,000 kids in North America, and more recently a study in Puerto Rico, so again now this is an island, unlike Costa Rica, and this is the Port of Elmora. And one thing, I know the reason for skepticism about this vitamin D hypothesis is well here you have vitamin D and you have severity, and you could say to me well is it possible that the kids who have worse asthma are just not going out that much therefore you know they are having low vitamin D? So this is sort of a chicken and egg phenomenon or reverse causation. I never believed that to be the case, first because as most people in pulmonary know severe asthma in children is rare. We have difficult to treat asthma but severe asthma is rare; and secondly because we have shown before that after adjusting for multiple markers of severity this association persisted, but that’s still possible.

You could also say to me well you have shown us that African ancestry is related to lung function, what if African Ancestry explains low vitamin D levels? And again this is just a mediator, right? These are (inaudible). African ancestry heavy individuals have darker skin, they have lower vitamin D levels, they have worse asthma because of their African ancestry and their vitamin D.
So we went on to test this hypothesis in this study of children, these are 351 Puerto Rican children with asthma, 6 to 14 years of age where low vitamin D levels confer a 2.6 greater risk of severe asthma exacerbation, meaning ED visits or hospitalizations requiring systemic corticosteroids. We adjusted the analysis for African ancestry, for time outdoors, for atopy and many other covariates and this very robust. So so far we have shown that vitamin D insufficiency is common even in tropical environments, in the study of Puerto Rico 44% of children had low vitamin D levels that is associated with increased rates of severe asthma exacerbations now in three populations, Costa Rica, North American and Puerto Rico. And we believe that the potential mechanisms for this based on both in vitro data and human data is through enhancing responsiveness to corticosteroids and/or immunomodulating viral illnesses which are the main cause of exacerbations in childhood. We are in fact after a tremendous struggle finishing a pilot of vitamin D and we again ask everybody for help to resubmit a large application for a clinical trial of vitamin D to prevent exacerbations this summer.

I’m going to now switch to psychosocial stress and exposure to violence, and this is work led by Wei Chen in our group. One thing that you have to be honest about is on this slide just to show you that the epidemic of asthma occur from at least the ’96 through the ‘90s there was a huge increase in prevalence in the western world. And you are not going to tell me that this is due to genetics, the rate of mutation in human populations is very, very low. So something had to change in the environment or lifestyle for this asthma epidemic to occur. Does this mean that genetics is not important? No, it does not, there are still susceptible populations that when the environment change
the effect of these things will occur, and that’s important but we cannot ever neglect environment or lifestyle in this pursuit.

And one of the hottest areas of research now is this whole idea of epigenetics. Epigenetics refers to heritable changes in gene expression that occur without any change in DNA sequence. I can test the DNA sequence of anybody in this audience from samples in any of their tissues, the hair, nails, blood, mouth, DNA sequence will be the same barring methodological errors; however if I were to assess the epigenome of somebody in this audience that would be entirely different across tissues and cell compartments. Epigenome is tissue specific, and it seems to inspire (inaudible).

We know that Puerto Ricans are often exposed to high levels of stress and violence, this is true in the island of Puerto Rico, this is true in the U.S. mainland. We also know that Puerto Ricans are very susceptible to posttraumatic stress disorder; the ethnic group with the highest rate of PTSD after 9/11, Puerto Ricans, the group with the highest risk of PTSD after war, Puerto Ricans. We were the first in the world to show that childhood abuse is associated with a two-fold increase rates of asthma and asthma morbidity in 2008 in Puerto Ricans, a finding that was replicated in December of 2013 in a longitudinal study of black women followed over 10 years. We have also shown that both paternal and maternal stress in early life are associated with greater risks of asthma symptoms and asthma morbidity up to age 3 years. The mechanisms for this remain unclear.
Talking about epigenetics the two – there are multiple mechanisms including microRNA, histone modifications and DNA methylations. And DNA methylation refers to the fact that if a gene – if the methylation is increased particularly in the promotor region its expression will be decreased. If methylation is decreased its expression will be increased. And again environment lifestyle can modify that.

Writing one of these grants I ran into this paper which in my view is one of the most important papers in biomedical research over the last decade. This is a paper by Kerry Ressler who will be here next May to give a talk, not this May, 2015. And he look at this gene called the adenylate-cyclase activating polypeptide I receptor, I’m going to call that ADCY for short, and showed very convincingly in a Nature paper this implicating the pathogenesis of PDSD in adults who were exposed to traumatic events. His same group showed a while later that this same snip that is implicated in PTSD is implicated in society in children of school age. But what made this paper in my view very, very different is that he showed that if you plotted a PTSD symptom scale that goes from 0 to 100, so this is a quantitative scale, and the methylation levels of this gene there was a linear relationship that was highly significant, the first demonstration of this phenomenon in the literature that I’m aware of.

So we asked the question well we have data on exposure to stress and violence, we have GWAS data, we can interrogate this in Puerto Rican children. And in fact we showed that for each one point increment in a different scale exposure to violence the methylation of this gene is increased in Puerto
Rican Children. We further showed that methylation of this gene is associated with asthma in these kids. And then we showed that the same snip that was implicating PTSD in adults and aside in children is associated with asthma in Puerto Rican children. It’s the first time to my knowledge to provide a potential genetic or epigenetic mechanism for the well known link between stress and asthma in childhood. There are studies that are longitudinal that are needed to further evaluate not only Puerto Rican but other populations that are often exposed to stress and violence like blacks, etc.

We were also interested in obesity and this work led by Eric Ford in our group and it’s no secret there are two parallel epidemics in this nation. I showed you the asthma epidemic and there is an obesity epidemic. There is no association in the literature except for second hand smoke as a strong or as consistently replicated as that between obesity and asthma in children or adults.

There was a study we published when I was in Boston, 15,000 Chinese adults all of whom had error responsiveness testing, and we showed even though this population is far leaner, this is rural China, than the U.S. that in fact there was an association both in men and in women. What’s interesting is that if you define asthma using objective testing there was no gender difference. This strongly suggests that this reported difference by gender is in part related to diagnostic bias. Adult women are more often diagnosed with asthma, adult men are more often diagnosed with COPD, particularly if they smoke.
We then interrogated the question could obesity be related to asthma morbidity through response to treatment? And we did it using a study of 1,041 North American children of several races, it’s called the Childhood Asthma Management Program. And in that population children were placed on Budesonide or placebo/Nedocromil and we have data on their BMI and we can then classify them as lean or not overweight and overweight or obese. And these are some of the characteristics of the children. As you would expect the children that were overweight or obese have lower vitamin D levels, that’s because vitamin D is lipophilic. They also have lower lung function, that’s been previously described. But what was really interesting is that we then assessed response to inhaled corticosteroids as it relates to overweight or obesity over a period of 4 years. And I’m just showing you data for FEV1 and FVC. In lean kids those who were on inhaled corticosteroids had a consistently higher FEV1 and FVC over the duration of the trial; overweight, obese, no difference in FEV1 and FVC between the two groups.

What’s more, if you look at the data as it relates to prevention of severe exacerbations among the lean kids use of inhaled corticosteroids was associated with a 44% reduction in severe asthma attacks that was highly significant. In overweight or obese kids there was difference at all in the rate of severe asthma attacks when you compare those who are using inhaled corticosteroids or those who did not. This suggests that obesity or overweight confers resistance to the effect of inhaled corticosteroids.
I’m going to take you back to Puerto Rico. Most of these studies of obesity and asthma have used body mass index, BMI. Whether adiposity indicators other BMI can predict asthma or asthma morbidity or the usefulness is largely unknown. In a recent study we showed there were other adiposity indicators in children including percent body fat, waist circumference and waist/hip ratio provide complementary information to that given by BMI.

But what was far more interesting about this study in my opinion was that Eric did what’s called a mediation analysis trying to determine what proportion of the effect, estimated effect of overweight or obesity on say severe asthma attacks is mediated by say allergy. And consistently in this population that ranges between 29 and 40%.

Sometimes you know Louis Pasteur says (inaudible), I’m a firm believer in that and this is just serendipity. Dr. Pauls had the good sense or kindness or (inaudible) on this paper which is another landmark paper by Dale Umetsu from Boston Children’s now at Genentech, this will become obvious in a minute. So Dr. Umetsu had this mouse model, high fat diet induced obesity mice and airway responsiveness. And he shows in this experiment that this obesity induced airway responsiveness is independent of TH2 mechanisms, and is dependent on innate immunity TH17 responses and inflaming the lung. This was very intriguing and interesting to me because we have shown this data for resistance to corticosteroids and TH17 immune responses have been associated with it.
So (inaudible) Eric looked at data for 2700 children participating in the National Health and Nutrition Examination Survey, these were school aged kids. And in these kids we have fractional exhaled nitric oxide, which is a measure of eosinophilic or allergic airway inflammation. And we divided the kids into those who had normal levels, that is they have no eosinophilic airway inflammation and those who have high levels. And very interesting the association between the indicators of adiposity or obesity and asthma was only seen among children with no allergic airway inflammation, consistent with Dr. Umetsu’s mouse model. But then we asked a different question, if we take the kids who have - who already have asthma would eosinophilic airway inflammation make them worse when they are obese? And the answer is a conclusive yes. So once asthma is established eosinophilic airway inflammation makes asthma, obese asthma more severe.

So from this we can say, and I didn’t show you this, but obese asthma is more common in ethnic kids, inner city children, not all obese asthma is the same, this is true for all of asthma. Our vast ignorance needs to be unraveled. And ongoing work by our group and others should identify sub-phenotypes of obese asthma. Regardless of all this research what is very, very clear to me is that weight management should be first and foremost in managing an obese child with asthma, they will get better.

So how can we improve asthma care in the context of these profound disparities? Well there was a speaker at the Grand Rounds recently talking about community interventions, we also had Dr. Bob Strong who was at St. Louis who spent a lot of time trying to do (inaudible) interventions, and I can
tell you that nothing replaces the effect of primary care physicians at properly prescribing controller medications to poor children. This has been shown over and over and over again, and we still don’t do it to the extent that we should.

There is a city-wide study in Hartford, Connecticut, the poorest city of its size in the U.S. northeast by my colleague Michelle Cloutier where she did a very simple protocol easy breathing where PCP’s simply fill a sheet of paper, three is a lot of asthma in Hartford, and according to that prescribe steroids. Rates of prescriptions of inhaled corticosteroids went from 30 some percent to 97 percent by PCPs over a 2 year period. And there was a profound reduction city-wide in hospitalizations and ED visits for asthma, which I’m not surprised about.

We recently examined temporal trends in asthma morbidity and mortality in Cost Rica, a country that again has universal access to healthcare. So my colleague, Manuel Soto-Martinez with whom I’ve worked now for 15 years was the first pediatric pulmonologist in Central America. He trained in Melbourne, Australia, and when he got to Costa Rica n the late 1980s he introduced to specialists the idea of inhaled corticosteroids, that is pulmonologists and allergists. And the government restricted use of inhaled corticosteroids to specialists up to 2003, when a National Asthma Program led by Manuel occurred throughout the country. There are 4 million Costa Ricans, they went to every town and city, again this is universal healthcare, government regulated, and people were educated and encouraged to use inhaled corticosteroids. And the effects on morbidity, you know this started here, there is only one tertiary pediatric hospital in Costa Rica, National Children’s Hospital,
look at what’s happening in all age groups. The effects have been more profound even in adults than in kids, that is because Manuel had started to work in kids earlier. I’m not showing the mortality data but it’s also very impressive. And look at what happened at prescription of inhaled corticosteroids in Costa Rica between 2004 and 2011. This is not any sophisticated inhaled corticosteroid, this is Beclomethasone, the cheapest inhaled corticosteroid you can get. It works, as long as people educate patients on the importance of using that and how to use them this works very well in most children.

It takes me back to this slide, so with Obamacare there are great expectations and we should all be very cautious about great expectations. Yes, it’s a major step in reducing disparities, not only in asthma but in other conditions. But we have to pay attention to many other things. The rate of health literacy by adults in this country is very low. I’m sure you’ve seen these studies estimated at least 50% in our not functional (inaudible) for healthcare. So you can try to provide healthcare to these people but if you don’t do it in a way they can understand you are going to fail. And there are cultural beliefs that are barriers also to care.

So with Christian Rosas-Salazar who was one of our Fellows now at Vanderbilt we did this study of parental numeracy. What is numeracy? It’s basic knowledge of mathematics needed to take care of yourself or your children. This was a questionnaire that had 3 very, very simple questions. One was your child was prescribed 40 mg of Prednisone, every tablet has 10 mg, how many tablets do you have to give to your child? Is it zero, 1, 2, 3, 4? Only 10% of participants, 10.5% got the three
questions right. And analysis that accounted for multiple variants, covariates including health insurance, use of medications, low parental numeracy was associated with 80% greater odds of at least 1 ED or urgent care visit for asthma in the prior year. This was very highly significant.

So I had the honor and the privilege of leading the writing committee of our major Respiratory Society, the American Thoracic Society, as it relates to defining respiratory health equality in the U.S. and the perspective of our society, an effort I’m very proud of. And this is just one slide of that paper, but to really do this well there are several things that have to be done. One is to pursue this concept of environmental justice. There are upstream factors. You cannot have health equality in this country when you have the tobacco companies selling menthol cigarettes to African Americans and promoting e-cigarettes. You cannot have health equality in this country if the poorest members of our society breathe dirty air. You have to do research and continue to do that and you have to implement excellent healthcare.

One thing I did not talk about that we mentioned in this paper is the fact that the representation of minorities in medical schools, particularly at higher levels, it’s very low. There is an article in JAMA 2013 showing a very, very, very poor job by the major medical schools in trying to encourage recruitment of medical students and their promotion through the ranks. Multiple studies including two recent studies showed that minority physicians are more likely to care for minority populations, so a better effort has to be made.
I told you about obesity, we have to get kids to exercise, this is no joke. Obesity has many detrimental health effects, I just showed you the ones on asthma.

So anybody who does work you know is blessed to have good collaborators and I do. These are some of the people who I’ve worked with not only here but also throughout the world. And I’m just representing our division. These people work very, very hard to care for individuals with respiratory and allergic diseases, they do so every day and I’m immensely proud of the work our faculty and staff do. And well you know I wouldn’t be here without David. So he does smile from time to time.

So at the end of the day this is a great book, you know it’s very inspiring, (inaudible) writes well. Most leaders in this country have – don’t have God to speak or whisper in their ear, and so this scenario is repeated day after day. People pick the prettiest boy or the prettiest girl, and then you have a 199th draft pick beat every record and win 3 Super Bowls because he’s hungrier and angrier than all the pretty boys. Picking the pretty boys is safe but you often miss the Tom Bradys of this world.

And then we are back here, so when looking at these slides some of you may say this is an unsurmountable challenge, this cannot be accomplished. You would all do well by remembering the words of Lyndon B. Johnson 46 years ago, this is what America is about, it is the uncrossed desert and the unclimbed ridge, it is the star that cannot be reached, and the harvest sleeping in the
unplowed ground. These (inaudible) we say farewell, it’s a new world coming, we welcome it and we shall bend it to the hopes of men. Thank you very much.