What I’d like to do today is to first of all tell you that when you went to medical school if it was more than about 10 years ago, everything has changed. There’s been such rapid progress understanding pancreatic disease that we just feel like we’re on the verge of some major advances and breakthroughs. I’m going to talk about a couple of those today.

I’d like to start by talking about acute pancreatitis. Acute pancreatitis is an acute inflammatory event that originates within the pancreas and is associated with a wide variety of local and systemic complications. About 20 percent of the patients have a severe clinical course with pancreatic necrosis, infections and the systemic inflammatory response syndrome, multiorgan system failure and death. The severity of pancreatitis is defined in many ways and that means we don’t really have a good definition for it. There’s the Atlanta criteria which is a combination of any of the other criteria and includes the Balthazar score and others. And each of these really reflects the inflammatory response. The overall accuracy of these are not very good, do not exceed 80 percent and they’re not possible until well into the time when the attack has been established. So what do we do?

Well, there’s a major problem here and what I’m going to try to focus on is really a conceptual change I’d like to see happen. These predictive models are not very good and even what they do tell us is not that helpful. So let me ask you if somebody came to your office with a stroke, if you waited for two days and did an assessment could you tell whether or not it was going to be a major event or a transient attack. It’s easy of course. How about a major attack, they come in with
crushing chest pain, you wait for two days or 48 hours to make your assessment, well you better have some accuracy.

Both of these diseases, stroke and acute heart attacks, the severity of the disease, the duration of the disease, the death has been markedly reduced when physicians act quickly to prevent serious complications from an acute injury. And this is what we have to do with acute pancreatitis. What I’d like to do is talk about how we’re approaching this and hope you understand acute pancreatitis better. Then we’ll talk about chronic pancreatitis and find out everything we taught in medical school is wrong and what you should know and what you should tell your patients.

Now, there’s a whole variety of things can cause acute pancreatitis and they’re not really that important unless you’re trying to prevent another attack. What we see is that each of these causes an acute injury. The injury is like an injury in any other tissue but the magnitude of the inflammatory response is out of proportion to that of all other organs. So if you have a small injury in your arm, your liver, your spleen, your leg, a little contusion, that’s it. You do that to the pancreas you end up in the intensive care unit.

The reason is that there’s activation of Trypsin which is a digestive enzyme and that seems to be the key trigger that causes this explosion of inflammation. Trypsin also directly cross-activates the immune system so it not only becomes active by the local injury to the pancreas but it directly activates the immune system as well.
So this is a diagram of trypsin and I’m going to show you a couple things, it explains a lot of what we know about why people get acute pancreatitis.

The first thing is that trypsin is the master enzyme that controls all the other digestive enzymes. The pancreas synthesizes all the digestive enzymes in inactive form except for lipase and amylase. And that’s why we measure those in the emergency room or in the office because the chemist can easily detect whether or not these enzymes are at elevated concentrations in the blood by doing a simple chemical test for activity. The others ones have to be activated by trypsin before you can detect them so they’re not used.

Trypsin itself is controlled by a molecule called SPINK1 that turns out to be quite important. It’s also called the pancreatic secretory trypsin inhibitor and it is a specific trypsin inhibitor shown in red that fits right inside of the jaws of the trypsin enzyme because it looks like a Pac man with a yellow and blue jaw and it bites and chews up proteins attacking an arginine or a lysine, those are the two amino acids it attacks. But SPINK when it’s present can fit inside the jaws, it’s a suicide inhibitor, it’s like a gag in the mouth and it just stops trypsin.

However, most of the time we don’t have SPINK present so it’s only there in cases of prolonged inflammation. Trypsin is usually controlled by itself and by calcium. There are two sites in which trypsin acts and two sites in which calcium binds. And if you look at this diagram you’ll see that
over on the right side here is a arm that sticks off to the side and that tells us it is inactive trypsinogen. It actually forms the first calcium binding pocket and when calcium goes into this arm it stabilizes it and now a second trypsin can come and cut the trypsinogen activation peptide off of the molecule, it now becomes trypsin and the end terminus turns and goes inside of the molecule like a key going into a lock and it turns trypsin on and trypsin just starts shredding any protein that has an arginine or lysine in it which is most proteins.

Now there’s a second site as well and it turns out that the side chain that’s connecting the two globular domains of the molecule is flexible and it has an arginine in the middle of it. And trypsin can attack the molecule here and actually cut trypsin in half and the two halves become unstable. And once this occurs there’s a second molecule chymotrypsin C which can attack a second place and now the molecule is destroyed and trypsin rapidly disappears. This site it turn out is also controlled by the second calcium binding site and when calcium is present it binds this flexible side chain to the site of the molecule and locks it in and protects it from being attacked.

So what we see is that when calcium levels are low you cannot activate trypsin and if it is activated it’s rapidly destroyed. So low calcium is protective and that’s exactly the environment inside of the acinar cells. If calcium levels are high as occurs in the pancreatic duct and in the duodenum then trypsin is easily activated and it cannot be inactivated. Amazingly, as it digests the food and begins moving down the digestive tract as it goes through the jejunum the calcium is all absorbed and the trypsin in unprotected and kills itself. And so active trypsin is normally in a very small location
within the body in the duodenum and jejunum, it’s very powerful but it’s protected in that area and it does a job of turning your meal into a liquid so you don’t have pieces of hamburger floating around in your bloodstream.

Now the amazing thing is that we found a whole bunch of mutations that affect acute pancreatitis and chronic pancreatitis. And all of them are associated with trypsin. So the susceptibility to chronic pancreatitis is really due to activation of trypsin. Now in this diagram what you see is, you see the inactive trypsinogen over here and if it becomes activated to trypsin which is facilitated by calcium and the breakdown is blocked by calcium, this is the bad one. Calcium if it’s gone it can’t activate it and it rapidly destroys it. If you have mutations in chymotrypsin C there’s a delay in breaking it down and trypsin can cause lots of injury. If you have a mutation in the calcium sensing receptor you get too much calcium, trypsin. If you have alcohol, alcohol messes up intracellular calcium regulation, you get too much trypsin, injury. If you secrete out of the duct, out of the acinar cell into the duct, the cystic fibrosis gene quickly flushes trypsin out. If you have mutations in this gene then you cannot flush trypsin out and you get pancreatitis.

If you get injury, injury causes an acute inflammatory response which increases SPINK1, SPINK1 then goes back and shuts off trypsin either inside the acinar cell or inside the duct cell but it is an acute phase protein. So it only is present during inflammation and as a matter of fact, it’s the champion of all acute phase proteins because it starts at the lowest level and rises to the highest level of any other acute phase protein in pancreatitis.
So chronic pancreatitis which we’ll talk about in a little bit is initiated by injury and acute pancreatitis and it progresses. SPINK is a disease modifier so if the SPINK is also mutated it doesn’t increase your risk of trypsin activation, it just means your body can never shut it off.

Environmental factors turn out to be important because they either block the duct or increase calcium levels to cause pancreatic disease. So it can occur either inside the acinar cell or inside the duct cell. Now just quickly summarize the risk for acute pancreatitis and it turns out that a lot of them are in the acinar cell and disrupt this normal process. If there is premature activation inside the acinar cell it can be caused by hypercalcemia due to a whole variety of reasons or trypsin related defects usually associated with mutations. If you have a problem with the SPINK then the inflammatory response is not shut off.

On the duct cell the biggest issue is the cystic fibrosis gene and we know that for people that have cystic fibrosis. Now where did the name cystic fibrosis come from? The term is cystic fibrosis of the pancreas. Because the pancreas is destroyed in utero because as the trypsin is slowly developing and normally flushed out to break down the meconium, it gets stuck and the baby has destruction of the pancreas in utero. Now it turns out that adults that don’t have severe mutations but have mild mutations are at risk of pancreatitis because they can’t flush the trypsin out.
You know what the most amazing thing is, we just discovered a whole class of cystic fibrosis mutations that only affect bicarbonate secretion because in the pancreas CFTR is used to transport bicarbonate and not chloride. And so these mutations put people at risk of getting acute pancreatitis and chronic pancreatitis but they’ve been totally ignored because all the cystic fibrosis doctors are what kind of doctors, pulmonologists. And if it’s above the diaphragm ___ they don’t care. Duct obstruction is the other cause. If you can’t get the trypsin out for any of these reasons you get acute pancreatitis and again SPINK aggravates any of these causes.

Now let’s talk about acute pancreatitis. Most of us can diagnose it very easily, it’s characterized by sudden onset of abdominal pain, elevation of amylase and lipase and it can be identified with a CT scan. Normally a CT scan is not needed for the diagnosis and there’s a theoretic danger and I think it’s more than theoretic if you use a contrast CT scan too early in the clinical course.

Now this is one of the most important things I want to talk about because acute pancreatitis is very dynamic and actually the damage is done within the first 24 hours and if you don’t figure out what’s going on with the patient and intervene, then you’re like somebody with a heart attack who comes in 2 days and you find the person is hypotensive and blue, you say they’re not going to do well. Well, anybody can do that and it’s too late to reverse it. The same way with a stroke, you come in 2 days later and they can’t move on one side, you say gee, they had a stroke. But if you catch them early you can intervene. Now what do we need to know and what’s the time table?
We know there’s a sequence of events. There’s injury, there’s a pro-inflammatory phase and then an anti-inflammatory phase, otherwise, you’d keep having inflammation forever. There’s an anti-inflammatory component of the immune system that shuts off the acute side and that’s activated and very important and then there’s resolution and healing.

Severity is measured in many ways, there’s organ damage, there’s high cytokine levels and interesting there’s sepsis physiology, the patient looks like they’re septic but they’re not. It’s the same thing as you get with major trauma and with burns of over 25 percent of the body, it is systemic activation of the immune system, it’s systemic inflammation and in some people it’s associated with a terrible outcome, in others they get better in 24 hours.

What we see is that there is a bunch of etiologies that all activate trypsin and trypsin causes injury. The tissue damage activates the immune system and the immune system goes through an early phase, a middle phase and a late phase. The early phase is pro-inflammatory and it actually calls in a bunch of really nasty white cells and other things that will cause early tissue damage. The tissue damage causes more inflammation and you have a feed forward effect and a rapid amplification especially if trypsin is causing more injury and now being released from all the cells and cross activating the immune system and that’s what we talked about with acute pancreatitis being so severe.
But very early there is a stage in which the antiinflammatory response which is lead by the acute phase protein, the mostly antiinflammatory proteins begin shutting down the proinflammatory phase and then it blocks further tissue injury and promotes healing. This is what normally happens. In some patients that are designated as severe, the proinflammatory phase spills out and you get a systemic inflammatory response and in some cases a vascular leak syndrome. A vascular leak syndrome is seen first by pulmonary edema and then by hypotension and shock. And it turns out if you have hypovolemia and abdominal pain the whole physiology of shock changes. The blood is shunted away from the viscera to maintain pressure in the extremities and so if you’re measuring the blood pressure and heart rate in somebody, you know, laying on a gurney, you may grossly underestimate that their abdomen is in shock.

The visceral shock leads to pancreas necrosis, acute renal injury and gut injury and the gut injury is the bad boy. This is what causes the severity of acute pancreatitis because it goes back and drives the SIRS and now the whole pancreas is being bypassed and it’s a leakage of bacterial products from the gut that’s driving the SIRS and causing the severe injury.

What you see on the far right is that there’s a timetable and there’s an opportunity to intervene, those are sort of the beginning of each of these features and they’re ballpark ideas for discussion, we’re trying to figure out more exactly where we are in the sequence. What we know is that the most effective intervention is fluids to prevent hypotension if the hypotension is prevented then you do not get shock gut, that’s something you should avoid. I want you to remember avoid.
If they already have severe injury, the only way you can stop this cycle is to feed the gut with enteral nutrition and that shortens their duration in intensive care unit, it shortens the duration of SIRS, it decreases bacterial infection, it decreases hospital stay, it decreases death, it’s 80 percent cheaper.

Let me just back up a second and just point out two things. The first one is that we’re now learning why some people spill over to get a stomach inflammatory response and we’re figuring out who gets vascular leak syndrome and who doesn’t. Okay. So I’m going to talk about that for just a minute. So obesity turns out to be a huge risk factor and what we see is that if you have a BMI over 30 shown in black your risk of organ failure is doubled. Your risk of necrosis which is the gut shock is doubled and your risk of death is markedly increased. It turns out that fat is an organ that releases adipokines and adipokines or cytokines come from adipose tissue. That’s what worsens the inflammation, at least much of the inflammation and it releases a number of the factors that drive the sepsis physiology.

So obesity is a pro-inflammatory condition, adipokines seem to drive that and there’s a whole list of adipokines that are listed here. They increase with BMI, so the bigger the BMI is, the more adipokines are released with an injury with the exception of adiponectin in red. We’ve actually gone through and looked at all these in our laboratory and what we found is resistin seems to be the key molecule that causes that causes all the problem.
Now look at this. If there’s a person that comes in and you look at the resistin levels on admission, it turns out that they’re markedly increased compared to mild and severe. So mild and severe isn’t how much pain they have, it isn’t, you know, what the APACHE score is, it tells you they have systemic inflammation, it’s being driven by resistin because the other adipokines don’t correlate. It’s also highly significantly increased compared to controls. So here’s an adipokine that seems to tell you immediately that a process is beginning in this patient that’s very, very bad.

Now we looked at the genetics as well. I can’t help it, I have to keep looking at the genetics because that’s what I’m funded to do. But this, this is really interesting because there’s a very common polymorphism in about a third of the people that has an effect just like fat does. It’s so interesting because we know as fat increases adipokines increase. But with genetics, they’re some people who are fat that have low levels and some people that are lean have high levels and if you look at the balance between the fat and lean and you can tell whether or not the resistin is really doing it. And it turns out that if you have this polymorphism then the susceptibility is markedly increased. However, if we just look at people who are lean, the effect is even larger. So we know that this resistin gene is critical in transitioning from local inflammation to systemic inflammation.

Now the second thing I wanted to tell you about is this vascular leak syndrome. Now we know that if you do have systemic inflammation, if you’re older, you don’t have as much physiologic reserve, if you already have 3 organ failing then you’re going to have multiorgan failure before you start and you’re not going to do as well. But the vascular leak syndrome turns out to be very important.
And we found the molecule that seems to be linked to this. Now if you injure yourself locally, if you hit your hand with a hammer you see a local swelling and that’s because the inflammatory response releases the angiopoietin from the blood vessels and it causes all the plasma to leak out of the blood vessels.

Systemic inflammation in the people that are susceptible causes release of angiopoietin2 and the entire body leaks. The first sign of that is pulmonary edema because the blood vessels are leaking plasma into the interstitial space and what we see here is that the thing that differentiates between if you’re going to do well or not is whether or not you have a vascular leak syndrome and especially if you don’t treat it.

Now what we’ve seen is our ____ , I keep asking this and I keep getting the wrong question. If you have somebody with acute pancreatitis and you do an exam which is the first step and you find that they have signs of pulmonary edema should you give more fluids or should you give diuretics. They all say to give diuretics. That’s the wrong answer, you can kill people by doing this. That means that they’re becoming hypotensive and you need to give them fluids. If they can’t breathe, you put them on oxygen and you put them on a ventilator but you have to keep them from going into shock.

Here’s the AVOID syndrome, it’s the acute visceral organ injury and dysfunction. You end up with pancreatic necrosis, acute renal injury and acute liver injury and acute gut injury and they all go in
parallel. As a matter of fact, we published a paper this year in the American Journal of Gastroenterology that said if you have an increase of creatine suggesting acute renal injury it is highly predictive that you have pancreatic necrosis and you missed it. So we had a competitor from Germany who criticized everything we do, published a paper right after saying that’s ridiculous, we don’t see this, the phenomena is not true.

So my fellows came to me and said, boy, we really, we really got beat down by the Germans. I said that can’t be right. And I looked through their paper and came to the last table and I said, gee, why don’t we just take their data and do a square and see if it’s associated or not. And the answer yes, at P point 0008. Their own data contradicted their conclusions. So we wrote a letter to the editor and we said, gee, that’s very funny that they would say it’s not associated when their own data says it is and here’s all the other reasons as well. It is associated. It’s the same as SIRS and trauma and the only way to reduce it is to give enteral feeding. So hypervolemia and abdominal pain equals visceral ischemia and AVOID.

So what do you know about acute pancreatitis, preexisting factors include the severity, we talked about obesity and some genetics but alcohol is also very important for other reasons. The systemic inflammatory response is a physiologic response to cytokine storm, it puts the organs at risk. It starts with the pancreas and shifts to the gut. The vascular leak syndrome causes pulmonary edema and visceral organ hypo-profusion, it causes a variety of these injuries but ischemia likely drives
SIRS after the first 24 to 36 hours. Early treatment, fluid resuscitation, late treatment, enteral feedings.

Here is how we do enteral feedings, we use a nasal endoscopy to place a small feeding tube pass the Ligament of Treitz by 40 cm and then we can feed these individuals and they all do very well, they do amazingly well, they don’t die on us. We just don’t have people dying.

Now we’re doing a big study on severe acute pancreatitis and if you have a patient, send them to us, call, don’t call me, call my fellow 24 hours a day because the study requires that we do a complete assessment and start the enteral feedings with 96 hours of the onset of pain and we really need to recruit these patients so please – I heard somebody is from Portland, Oregon, send them quickly.

Alright, I want to talk about this issue which is really quite interesting as well. Now I’m running a study called the North American Pancreatitis Study II, I’ve been running it for a decade. I got 20 of my closest friends who now are my enemies but now they’re my friends again because after torturing them for 10 years it’s payoff.

Recurring acute pancreatitis, chronic pancreatitis and controls, we did detailed phenotyping, we had broad entry criteria and extremely deep phenotyping, DNA and serum and we got a 1000 subjects and now we’re doing an additional 500 subjects in order to sort out exactly what causes pancreatitis.
It turns out that our paper, our first major paper was published in 2009, at the same time two other papers came out with the identical same results and they were results that were shockingly different than what we were taught. The first one was an epidemiology study from Copenhagen and the other one was an Italian study by Frulloni called the PanCrolnAISP study and it’s results were almost identical to the NAPS study so I’m not going to say that again. We’re going to talk about the NAPS study.

Well the first thing we saw is that women tend to be abstainers and men tend to be a little bit heavy drinkers but the ratio men to women were 50-50. I was taught that it was 80 percent men and it’s not true. Our ability to detect chronic pancreatitis without looking for the – does anybody remember the diagnostic triad for chronic pancreatitis, diabetes, calcifications and exocrine insufficiency. Well that’s extremely end stage, we don’t hardly see that anymore. Now we have a CAT scan on everybody and we can make the diagnosis early.

The ones that do drink, drink heavily. So the number of drinks per day is on the y axis and on the x axis we see patients with light drinking, moderate drinking, heavy drinking and very heavy drinking and this is the National Institutes of Alcohol that has put this together. And heavy drinking is drinking more than 5 drinks a day, more than 60 grams a day is heavy drinking. If you drink less than 5 drinks 7 days a week than you’re not in this other group. But what you’ll notice is that the amount of alcohol they drink is huge. They’re drinking a lot larger amounts than the controls in white and recurring acute pancreatitis in grey.
Now here’s a breakdown of our study and boy were we surprised. We’re expecting 80 percent alcohol and what we found is alcohol was 15 percent. They just don’t drink. So the alcohol categories, it turns out that the heavy drinkers were also heavy smokers. Now this is a multivariable regression, logistic regression analysis that was done by ______ in my group and _____ because he spent 3 years sorting through everything and helping to figure it out and it’s all on this actually simple table. What this shows is male versus female, ever drinkers versus never drinkers, ever smokers versus never smokers and how much alcohol and how much smoking.

The first thing that’s amazing is, if you look at the heavy alcohol they’re the only ones that have any risk compared to abstainers, of pancreatitis. If you’re a heavy drinker, you’re slightly protected. It’s only the very heavy drinkers, more than 5 drinks a day. Smoking on the other hand, there is a linear relationship. The more you smoke the higher your risk is. So there’s a threshold for alcohol. And you know what, I suspected this. Because I did ten years of animal studies and what we found is that if you raised the alcohol above 6 drinks a day you get a sustained alcohol in the blood and the entire physiology of the pancreas changes. And that’s necessary to put you at risk. So I wasn’t surprised but everybody else, they said I couldn’t believe it. The problem is that if you have alcohol at that high levels then your body changes, your pancreas changes but smoking has a direct effect.

Now if you look at ever drinkers versus never drinkers, the question is – is there an interaction? Look at this. If you look at people, in the top right where it says never smoked and heavy drinkers,
it’s not even a significant increase risk. You can be a massive drinker, if you don’t smoke, you barely have a trend toward an increased risk. If you smoke and don’t drink, you do have a significant risk.

Now here’s the Copenhagen heart study and amazingly what you see is that the patients who have any form of pancreatitis, most of them do not drink more than 35 drinks a week and the only people at risk are the ones who drink more than 35 drinks a week which is 7 drinks a day. Copenhagen is the same thing, In their study they also found there’s an increased risk with smoking.

In the million women heart study what we see is that – a million women were studied for alcohol and smoking and they liked at liver cirrhosis and gallbladder disease. Now liver cirrhosis is important because the same cell that causes liver cirrhosis causes pancreatic fibrosis. It is the stellate cell. Alcohol increased the risk of cirrhosis and smoking increased the risk of cirrhosis in gallbladder disease. And what we see on the left is that if you have increasing amounts of alcohol that risk is increased by smoking and if you’re a smoker and the number of cigarettes shown on the x axis and if you had alcohol the risk is increased.

Now I want to bring your attention to this which is even more interesting. If you don’t smoke and don’t drink, you have a relative risk of 1, if you smoke but don’t drink you’re risk is between 2 and 3, if you drink but don’t smoke risk is about 2. Now that’s almost exactly what we saw as well in the pancreas except the combination gave you risk factor of 8. In this study, it’s the same thing. The
The effect of alcohol and smoking is not on the pancreas itself as much as it is on the process of fibrosing after you have injury, after the stellate is over activated and after you have macrophage infiltration.

So the key is that if you have your first episode of acute pancreatitis which activates the stellate cells and macrophages you have to stop drinking and it’s been shown in Finland that your risk is reduced. But the difficult thing is to stop smoking because that’s where all the risk is coming from.

So in summary the risk of alcohol in chronic pancreatitis is the threshold. If you don’t drink more than 5 drinks a day, you’re not of risk of developing it but once you get it alcohol may be driving the process. You have an independent risk from smoking in Caucasians, primarily a disease modifier. The risk of chronic pancreatitis in smoking is linear, the more you smoke the worse your risk is. It has an independent effect and its primarily a disease modifier and the risk of alcohol and smoking is additive.

Take home points, acute pancreatitis becomes severe with systemic inflammation. Obesity and alcohol which we didn’t talk about markedly increases the risk that the inflammation will become systemic so those are the patients you want to watch closely. The vascular leak syndrome is the link between systemic inflammation and organ failure and you treat them with fluids, probably Ringer lactate would be recommended. AVOID syndrome causes gut leak and then you’ve got to use enteral feeding. Chronic pancreatitis is not a disease of alcoholics and smoking is an independent
risk factor. Thank you for your attention and I bet you wish you heard this in medical school so you would have done right this whole time.

Q: (inaudible)

Okay, the question is whether or not we see pancreatitis with oral contraceptives and – not enough to be a blip on the radar screen. Other questions, yes sir.

Q: (inaudible)

Is there any role for steroid or immune suppression and is that in acute or chronic?

Q: (inaudible)

In acute, no. Doesn’t seem to help at all. The only things that helps is, I mean if we can stabilize endothelial cells and prevent the vascular leak syndrome, that would help but we don’t know how to do that yet.

Q: (inaudible)
Okay, the question about antibiotics was raised and I think that’s going to be our last question. It’s been a controversial and the need originally was very high and now it’s very low and probably non-existent. And the reason why is that we’ve also begun feeding the gut and by doing that it prevents translocation and you’re like everybody else who normally doesn’t have to be on antibiotics in their everyday life because their gut is working and your bloodstream isn’t being contaminated by huge amounts of bacteria that are translocating out of the gut into the bloodstream. So it’s probably the use of enteral feedings that have been most effective in reducing the risk of infections and antibiotics become irrelevant.