

History of Heart Failure



Tuesday, September 18, 2007
Washington, DC

Agenda

- 7:00 PM Welcome. Appetizers and Wine Bar.
- 7:05 PM The First Writings of Heart Failure
Hector O. Ventura, MD
- 7:25 PM Adaptive and Maladaptive Hypertrophy:
18th & 19th Century Views
Arnold M. Katz, MD
- 7:45 PM New Discoveries in Heart Failure
Kirkwood F. Adams Jr., MD
- 8:05 PM Modern Therapies & Interventions
James B. Young, MD
- 8:25 PM Presentation of Materials.
- 8:35 PM Adjourn.

The First Writings of Heart Failure

Hector O. Ventura, MD

Welcome, everybody, to this History of Heart Failure meeting. I want to thank all the support of the people that are here for this project. This project – we have been doing it for a long time and finally it became a reality. I remember talking to Dr. Katz last year about this. We got him into the mix with Jim and Mitch and Kirk and finally here we are. And let me thank Laura and Elizabeth for the work they've done. It's wonderful. We think it's wonderful – we'll see what you think! I guess we're biased. We like it as it is. Dr. Braunwald, the fact that you're here makes it more important, let me tell you. I've known you for a long time, although you don't know me at all. But I have! I've had the joy to look at your books several times, anyway!

This is going to be – we're going to go from antiquity to today in a very short time. Now, as I said this afternoon in the hyper-session, I'm from Argentina and to give a Hispanic person ten or fifteen minutes is an oxymoron. I talk and it comes from my Mother, by the way.

Now, I showed this slide when I was at the breakout and I think it's important to look at history in some ways. And I love this quote from T.S. Elliot because it says that historical sense involves a perception not only of the pastness of the past but the presence. I think today we see it in many ways in the sessions, how we knew things in the past that today we apply again. That's all there is to it.

In addition, I think personally – and I learned this from Dr. Katz – history is fun. And this is a guy who teaches history, and don't ask me who it is because I don't have any idea. But I found this on the Internet. And it's fun. I agree with the quote. It's a very good quote: "History combines the excitement of exploration and discovery with a sense reward born

of successfully confronting and making sense of conflicts and challenging problems.” It's a wonderful quote, but I think it's fun.

I remember the first time I met Dr. Katz. He came to the Ochsner clinic and I was talking to him and he said so many things. And I thought it was very fun!

Dr. Arnold Katz: Don't repeat them!

No, you were very kind, by the way – because he took a quote from me that he said he uses all the time. I don't know – maybe he lied about that. But he's using it. And here I am – I was second class. Here you had Dr. Katz, the historian, you know.

We're going to talk about this syndrome and I talked a little bit about it today but I think hydropsy or dropsy still in place today. If you think about it, sometimes we see these types of patients. And the definition as you see there – most of you know it, obviously – is a generalized swelling and accumulation of water. I mean, you see these two patients in here. But it is important to talk about the concept. We're talking from antiquity. And again, I learned this from Arnie Katz – he asked me to call him Arnie so I will say Arnie. It's difficult for me to say that, but I will. And he, as you are quite well aware, published this in the *Journal of Cardiac Failure*. And the reason I'm showing it is, it's his work, but I have to say it because I'm the first speaker. And I think Jim has something in his presentation but this is the world of the paradigms where people have looked at the evolution of heart failure. And it's obviously clinical observation, the correlation between autopsy findings and clinical findings, the so-called circulatory physiology – Dr. Braunwald is one of them; cardiohemodynamics – here he goes; and we have the new paradigms – the biochemistry as we're seeing here, the biophysics, molecular biology. And each of these paradigms move throughout history.

So my job is to talk about antiquity, which is great because many people don't know anything about it and everybody thinks that I'm right! Now, I mentioned this today but it's

a theme in the history of heart failure, which is use in bloodletting. I would like to point out to you one piece of this particular quote, which I think is a very important one. Unfortunately, bloodletting was used for everything – headaches, inflammation, chest pain, whatever. But if you judiciously employ it – this is the first part of the quote, and this is a paper that we published in the *Journal of Cardiac Failure* – it's hardly possible to estimate too highly.

Now, again, I'm a reader of history but when I review the research for this particular paper many times the reason why bloodletting stays is because it works for heart failure. And it becomes very clear – it was done by the surgeons, by the way. I mean, this is the barbers that were used to the surgery. And by leeches – leeches exist in New Orleans today and we have leeches in the pharmacy so if you need some...they do other things, by the way. It might be a nice paper to have ultrafiltration and leeches at the same time, thrombolytics and bloodletting.

Well, I've bored you enough with my accent and with my talk. This is a great quote: "Explanations take a long time." This is from Alice in Wonderland.

So even if you know the historian, you have to go to antiquity. And the first thing you want to talk about are the Egyptians. Now, there is a lot of controversy about these guys, especially when you talk about medicine. But they talk about the heart. And I think perhaps this is the first book in cardiology because actually this is the way they learned cardiology back then. And you can see the quote. Again, there's a lot of controversy about: do they know about circulation? Well, probably they didn't the way we know it today but you can see that the heart was the center and the vessels lead to the members. And when you put the hands on the pulse you're talking about the – you're basically examining the heart, which is what we do taking the pulse, right?

Now, there is a problem with Egyptian medicine. Again, I'm not a scholar in Egyptian history but this is a translation of a translation of a translation. And I've discussed this with

Dr. Katz before – when you say this is the heart how do you know that they're right? You cannot go back and ask them. It was translated from the hieroglyphics to Coptic to German to English so you can imagine that you can find...and it's interesting because in Egyptian medicine I guess IB is the heart. RIB is the stomach. So if the papyrus has a mistake when you think it was the heart it was the stomach. So there is a lot of controversy in that particular piece. Well, there are many, many studies, many books, many people that have shown that they can count the pulse and especially in Alexandria back then. And they're talking about this. Although they didn't apply bleeding as much – and I'm going to show you some quotes in a minute from the papyrus. Now, this is the most controversial quote and we published it in a paper in the *Journal of Cardiac Failure* on Egyptian medicine and the concept of heart failure. The papyrus says when you examine the heart you factor in the abdomen and you find that it's not in a condition to leap the Nile -- that will be exercising tolerance. His stomach is swollen and the chest is asthmatic -- so you have pulmonary edema. And you say to him with the mechanism the blood is fixed and that's not circulating.

Now, whether this is correct I don't know. But I think it's a very nice quote about heart failure. And this is the way they treated it. So people say, "Well, it's emptying the system." Look at this. So we're bloodletting, ultrafiltration, diuretics...now they said that they used this thing called wormwood, elderberry – some of this is actually good for congestion, by the way. And they used perhaps the first diuretic – beer. Now, again, as I said, you can agree or disagree but it sounds like heart failure to me.

And this is the word – one of the co-authors of the paper is the curator of the Egyptian Museum in Cairo and I don't know how to pronounce it too well, but wegeg is the heart, the weakness of the heart. Now, you have to be creative with this. The scholarly Egyptians think this is completely incorrect but you've got to be creative. So you have weakness of old age. It seems that the pain-matters have fallen into the heart. That might be heart failure – I don't know. The heart is bored, so he's not doing anything. That

might be heart failure. The heart is weak. And I don't know about the other part! That's where it gets too confusing sometimes!

And the heart of the man tires, exhausted by the road – this means that the flesh is tired as a result, like the flesh of a man because he has gone very far. Exercising tolerance, heart failure – again, the paper had several reviews before it was accepted and all the people that read it, I agree with all the comments if I would have been the reviewer too. Is this true? I don't know but it sounds good to me.

There's more – look at this. The heart becomes small inside of his belly, pain matters have fallen into the heart and it becomes – and kneels down. Maybe the heart is kind of dilated. I don't know. The heart weakens. He doesn't speak of that. The vessels of the heart are dumb so there's no circulation. The information under your hands which normally appears because of the air -- now here is the concept of air in the arteries, if you will. The air is missing.

Well, we look at all these clauses in the papyrus and we really had the translation in front of us and the curator of the Museum of Cairo was talking to us and it was a very wonderful exercise. And fortunately it was published in the *Journal of Cardiac Failure*. I'm not sure how many people read the paper but it doesn't matter – we loved it. It was a great exercise.

Some more – heart is weak. Again, one more time the receiver is the one who causes it. The receiver is the aorta actually, I think. It's the vessel that gives water to the heart, blood to the heart. It might be the vena cava – I don't know. Something. Debility has arisen to the heart. It's arching as far as the borders of the lung and the liver. Is it dilating? Is it becoming big? Again, you have to be creative. That's what I thought; we were creative, until we had the reviews. The reviews said, "Well, you're too creative. You don't know what you're talking about!" But they're right, whoever they were.

Now, we go a little bit closer and I think Mrs. Katz is here and she's an expert in Greek medicine and Greek philosophy. I don't want to say too much, Mrs. Katz. You have your time if you want to say it and I promise you can stop me any time. This is a little bit easier because these are translated and you can read a little bit more. I know that Arnie published a paper about this. I think the major contribution of the Greeks – separation from philosophy and theology. They made medicine a little bit. And they developed for us a new craft, if you will, Hippocrates and other people. And they observed, which is very interesting.

This is Hippocrates. This is Kos. I've never been there but that's what it looks like. And he has the first ethical code that some of the young people don't know, unfortunately, and some rational scientific and clinical observation, as you know quite well.

Now, these are some of the quotes Arnie wrote in his paper but the ear is held to the chest and one listens for some time. They maybe heard seething inside like a boiling in vinegar, the rales, crackles. And then you have the flame coming from the brain. It can go to the heart. Palpitations and difficulty breathing supervene – the phlegm descends to the lungs and the heart. The blood is chilled. The veins beat forcefully against the lungs and the heart and the heart palpates so that under his compulsion difficulty of breathing and orthopnea. It's a pretty interesting quote. Whether they knew or he knew or whoever, I don't know.

And here you have dropsy. Impurities in the body – that would be TNF or cytokines. The flesh is consumed, becomes water. The abdomen fills with water. The feet and legs swell. The shoulders and clavicles melt away. The so-called consumption, if you will – something that we see not too often but we still see. And whether this is heart failure or not, we don't know. And I think Dr. Katz pointed that out in his book.

Moving on to the Romans – my favorite people, since my parents and my grandparents came from Italy – they didn't do much. We love to talk but we don't do anything. Public

health, sanitation, and they founded the first hospitals. There are some people in Rome, in the Empire, and this is one of them, who we'll say scholar, not a physician. I like this – this also comes from Arnie's paper. We published it here in a chapter that I wrote. You can put this in a book today and it looks the same. Moderate without any choking is called dyspnea. More severe, he cannot breathe without making a noise and gasping – asthma he calls it. Then in addition the patient can hardly draw a breath – it's called orthopnea now. Of these the first can last a long while. The two following are acute. And guess what? Bloodletting is the remedy unless anything prohibits. It's a wonderful observation, in my opinion. And in addition, he says you've got to put the bed up. What do we do today? Same thing – oxygen, bed up, bloodletting. You call it whatever you want to call bloodletting today.

And then we have the other famous Roman, Galen, an authority in medicine. They've been authorities throughout the world on this. And Galen – people say he was wrong. He was doing it in animals. He didn't know. Well, he knew what he was talking about, in my opinion. He was dogmatic but there are a lot of people who are dogmatic in medicine. And he described the circulation. Now his problem is his circulation is very interesting. The heart wasn't pumping too much and I think Arnie makes the point that the heart was a furnace to heat the blood, which is very interesting. The heart can be a furnace – there's metabolism in the heart anyway – but the blood was circulating but it was not because of the heart. The heart was there to heat the blood. And the veins were very important and the liver was very important. As a matter of fact, the liver had a so-called natural spirits and he thought it was the center of the circulation because he saw a lot of blood in the liver. So he knew that, and I'll show you some quotes. Here is warmth in plenty, mostly moves the other parts at the same time, as the pulse, which is very interesting, which also warms them. They consider, again, here in the blood the heart must always be in the boil, the heat flows from the heart to the members not only through the arteries but also with the veins.

It's interesting. One of my patients told me the other day, "When my husband was at home I was touching him and he was cold, like the heart wasn't getting there, the blood to the..." And I said, well, Galen has been talking about cold and wet forever. What about that? The heart also heats the blood a little bit. At least it gets it to the members and to the vessels. We breathe for the regulation of the heat. Heat is the constant, as I said before. This is the principle used for breathing. It's brought about by parts of the breathing, both breathing in and out. The one belongs in cooling and fanning, the other to the evacuation of smoky vapor, which is again the idea about the heart doing these things.

I'm almost done. I'll go into the Middle Ages. People say this is a bad time of the world. People didn't care too much. It's pretty interesting, though. I read once that in the Middle Ages people constructed buildings that were very, very tall to look at God. In the Renaissance people are starting to go this way, traveling to find new things. It was horizontal instead of vertical, which is very interesting. I think it's true. The Middle Ages were not a period of darkness – I don't think so. Again, I'm not a scholar on that, but one of the things that happened is the Roman Empire declined, which some people believe was a good idea, by the way. There were wars – there are still wars -- epidemics, social upheaval – still are – which greatly inhibit the progress of medicine. But what happens is they went somewhere else – not surprising.

So the Galen theories – the Christian Church controlled Europe -- we can disagree about that – preventing further advances in scientific knowledge. So where did they go? They go to the place that now is not a nice place, the Middle East. So these two guys, Avicenna and Rhazes, I guess it would be in the language – these are the guys that do Galen. And they say, "Well, we're going to keep talking about medicine." And it's known a little more about Avicenna. In Iraq actually there are a lot of monuments and things on Avicenna. I've never been there either but I have fellows from Iraq and they have shown me the pictures. He wrote a book. I had the opportunity to have the book in my hands when I went to the Kansas City Library. It's a very interesting book, the

Canon of Medicine. And he compiled all the knowledge that was in medicine. You can see Galen and Hippocrates theories. And it was used in medical schools in Europe because, again, all went that way. And there's a wonderful book that Dr. Katz mentions all the time from Dr. Jarcho, *From Avicenna to Albertini*, which is a classic, in my opinion, on the history of heart failure. And this is one of the quotes that Dr. Katz and I use for other things: Pernicious suffocation – that would be dyspnea. Hastening stopping of breathing – where the patient lies down, the breathing is hindered. Same concept. When his breathing is difficult also. He can keep extending his neck and continues to breathe. You've seen this before. He is restless and wants to stay erect.

Look – again, I don't want to prove history but this is it in heart failure, here. Although I don't have a slide to show you, he also used bleeding and bloodletting. People got that. And he has exactly what patients you're going to use it for. In addition, this is a quote about diastole, which is a very interesting one. Fluids are very often found between the bulk of the heart and the membrane, pericardial effusion, and it's known when they are abundant restrain the heart from diastole. Okay, diastole or whatever he talked about. Diastole is a very hot topic today. Let's go look at the *Canon of Medicine*. Here you go – it's a long one.

I'd like to finish talking about a particular patient and a case, since I like cases very much. It entails a person that was famous during the Middle Ages, Alexius I, his wife Irene, and his daughter, Anna Comnena if I'm saying it correctly – I think I am. This lady, the daughter – this is a very interesting story because she's one of the first women to write a book. She was very scholarly, tremendous at the time, and her father tried to help her out. It's a book called *Alexiad*. It's about her father and his kingdom.

This is a paper published by Dr. Lutz in the *American Journal of Cardiology*, a journal that still publishes history papers – and I think Dr. Roberts is wonderful in doing this. This guy Alexius I was the ruler of the Byzantine Empire. Now, I'll remind you one more time that Anna Comnena was a layperson. She was not a physician. However, she observed her

father's disease. I'd like to show you the disease. Most of the doctors had no idea of all the danger with which you were threatened, but Nicholas Kallicles – this was not a doctor either. He was one of those seers. They said the hell with the doctors so they got somebody that knows what he's talking about. It's no different sometimes than today when people go and look at somebody else. If you watch TV you see Kevin Trudeau and all these guys that are going to save the world in several ways, including the King of England, Prince Charles, talking about traditional medicine. He predicted fearful travels. He told us he was "Afraid of the humours having abandoned the extremities, might move to other directions and so endanger the patient's life." By the way, he was the only one who was right. So they like him – or maybe not, because he died. He foresaw that and we have been told emphatically, "For the time being the matter has left the extremities and attacked the shoulder and neck, but if we do not get rid by purging it will move again to some vital organ or even the heart itself. And if it happens, the damage will be irremediable." And again, she's not a physician – she's just observant.

Now here is a clinical history. Affected by the pressure of daily business there will be stress and many cares of the government, many – at the time there were a lot of wars and things going on. He was telling his wife, the Empress Irene, about it. In a way, he was accusing the disease, accusing that there was so much pressure that he had disease. We had a symposium about stress on the heart today. "I want to take a deep breath and be rid of this anxiety that troubles me. However, often I try. I can't lift even one small fraction of a load that oppresses me. For the rest, it's like a dead weight of stone lying on my heart" -- chest pain -- "and cutting short my breathing. I can't understand the reason for it, nor why such pain afflicts me." Pretty good incident, I mean, really good.

So then the doctors show up. They feel the pulse and they find a lot of irregularities. You might think about atrial fibrillation or arrhythmias of some sort. But they were altogether unable to give a reason for it so then you have a mechanism – they knew that the Emperor's diet was not rich. It was indeed the sort of food athletes and soldiers have so that the question of an accumulation of humours from too rich a diet was ruled out. They

attribute the difficulty in breathing to some other cause and say that the main reason for the illness was the over-work and the constant pressure of his worries. Interesting, I think, in some ways. The heart, they said, was inflamed. How about inflammation on the heart? Here you go. And all superfluous matter from the rest of the body was attracted into the heart – might be cytokines again. I don't know. We cannot ask Alexius I or his family. Every day new wars. Here is the history again. He was unable to lie down on either side, so weak that every breath involved a great effort. He was forced to sit up upright when the stomach was visibly enlarged and the feet were swelled and fever – fever – lay him down. Now, here, a concept of heart failure and fever and cytokines again, some doctors with scant regard for the fever said, “We have to cauterize.” Now, that was another way people took the fluid away at the time in the Middle Ages. They just used iron with fire – not a good thing, but that was the desperate measure.

He was forced to sit upright. If by chance he did lie on his back suffocation was awful. When sleep, in pity, overcame him – there was a danger of asphyxia so that at all times asleep or awake he was menaced by suffocation. Purgatives were not allowed. The doctor said to go try phlebotomy: “The doctors made an incision in the elbow but it also was fruitless. He was just as breathless as before. There was a constant danger he might expire in our arms.” That will be called refractory advanced heart failure. “She kept” -- the Empress, Miss Irene -- “urging me to tell her about the pulse, about the pulse.” So the daughter is taking the pulse now. “I touch it again and recognize that the strength was going and the circulation of the blood in the arteries had finally stopped. Then I turned away, exhausted and cold, my head and both hands covering my eyes.”

I don't know about you – and, again, I don't know Dr. Lutz; I never met him – but this is a wonderful paper and a wonderful creation of – this is the second edition of the book, the one that was in Greek. And you can see from a layperson – I think you can see the stages of heart failure, A, B, C and D. Each one of them is here.

Now, I'll finish with this. The University of Salerno became the Center for Medical Vocation. Transfer of the practice of medicine came out of the church, the laity, and first introduced the system of licensing physicians and autopsies were done and dissection of human cadavers were performed. And it changed a little bit the paradigm, if you will.

So I'll leave you with this, which will take it to the next step. I think Dr. Katz says about this particular paradigm shift – William Harvey, an English physician. I went to the library and I had a book in my hand. I had the two books that William Harvey published, *De Motu Cordis*, DMC for short, and his second book about generation in animals. I had it in my hand. It was a wonderful day when I had that in my hand. My children won't understand that because there is no history for my children – they think that history started when they were born. So I thank William Harvey – and it's a really small book. It's very small. It's a very interesting thing because it's very small. It was published in Germany because he was concerned about what he was going to say was different. Again, the *De Motu Cordis* – he finally put it together, the so-called circulation of the blood. And what he said, which is interesting, is that the passage of the blood goes from the arteries to the veins and then that follows that the movement of the blood is in a circle and that the heart became a pump – not a furnace, but a pump. Now, this seems like a mundane concept today. However, it changed the world in many ways in medicine and physiology.

The other thing I want to say – and I discussed this with Kirk several times – is this is a hypothesis in a way because he didn't know how the blood went from one side to the other. No capillaries, no microscope – like he said, that's the way it should be, which is a hypothesis very similar to Copernicus's hypothesis of the sun being the center of the universe. You know, we live in the world of randomized clinical trials where you have some particular number and so on. I mean, it's a hypothesis and it's a very interesting hypothesis.

And the last thing I want to say about him – I think not only the hypothesis but the fact that he did this in the animal, not just in humans, I think he lived long enough to know that his ideas were correct. As you can imagine people said, “What are you talking about? This is nonsense.” Well, yeah, he made a lot of sense and if you want to call them paradigm shifts this is the one that you're going to hear going forward how heart failure has changed throughout the centuries.

So I'll leave you with Harvey, and I think Harvey makes the paradigm shift. And by the way, the other thing I want to say is that he didn't decide to practice this and say, “Well, I'm going to talk about circulation.” There is a reason why he did that and it goes to mentorship. His mentor was Fabrizio, famous physician, who, although he didn't go this way, discovered the valves in the veins. He knew that the blood was going backwards and there were valves. And Harvey was his student. So he picked it up and he said, “Yeah, okay. We take the valves. It has to go this way.” And he created the next step, which is something that is important in medicine today and it will be important forever in medicine.

Thank you for your attention, and we'll give it to the historian, Dr. Katz, to talk about the new concepts of heart failure. Thank you very much.

Now I am sure that you don't have any questions or comments or if you want, I'll be glad to answer them later.

Adaptive and Maladaptive Hypertrophy: 18th and 19th Century Views

Arnold M. Katz

I'm going to cover just three topics in the 18th and 19th Century. Actually, I'm going to cover one topic in some detail, which is adaptive and maladaptive hypertrophy, and just mention a couple of other things.

The three things I'm going to talk about are the clinical picture of heart failure -- by the 18th Century the syndrome was identified as due to disease of the heart -- just a word about the discovery of digitalis to show the impact of basic science in clinical medicine, and I'm going to spend most of my time talking about the architecture of the failing heart, which is where we are today at the beginning of the 21st Century. And I'm going to demonstrate this by showing by what I'm going to call modern echoes. I'm going to toss in a couple of slides from current literature that will show where some of this work has emerged today.

Clinical picture – just three slides, all from a single description by James Hope, 1832. This is the syndrome of heart failure. I think Gene and I are probably the only people who saw the end of this in this audience, but this is what heart failure looked like all the time before the advent really of modern diuretics. So I'm just going to read this, and you can close your eyes and listen to me or read with me or close your ears and read. This is James Hope describing end-stage heart failure:

“The respiration, always short, becomes hurried and laborious on the slightest exertion or mental emotion. The effort of ascending a staircase is particularly distressing. The patient stops abruptly, grasps at the first object that presents itself and fixing the upper extremities in order to afford a fulcrum for the muscles of respiration, gasps with an aspect of extreme distress.” This reflects the difficulty of breathing, the stiff lungs. “Incapable of

lying down, he is seen for weeks, and even for months together, either reclining in the semi-erect posture supported by pillows, or sitting with the trunk bent forward and the elbows or forearms resting on the drawn-up knees. The latter position he assumes when attacked by a paroxysms of dyspnea - sometimes however extending the arms against the bed on either side to afford a firmer fulcrum for the muscles of respiration. With eyes widely expanding and starting, eyebrows raised, nostrils dilated, a ghastly and haggard countenance, and the head thrown back at every inspiration, he casts around a hurried distracted look of horror, of anguish, of supplication, now imploring in plaintive moans or quick broken accents and half-stifled voice, the assistance often already lavished in vain, now upbraiding the impotency of medicine and now in an agony of despair, drooping his head on his chest and muttering a fervent invitation for death to put a period to his sufferings. A few hours - perhaps only for a few minutes, he takes an interval of delicious respite which cheers him with the hope that the worst is over and that his recovery is at hand. Soon that hope vanishes. From a slumber fraught with the horrors of a hideous dream he starts up with the wild exclamation that "it is returning." At length, after reiterated recurrences of the same attacks, the muscles of respiration subdued by the efforts of which the instinct of self-preservation alone renders them capable, participate in the general exhaustion and refuse to perform their functions. The patient gasps, sinks, and expires."

This is over and over and over again in the descriptions of the 17th, 18th and 19 Century. A word about digitalis, again showing the impact of basic science. This is William Withering. In 1785 he writes: "In the year 1775 my opinion was asked concerning a family recipe for the cure of the dropsy. I was told it had long been kept a secret by an old woman of Shropshire who would sometimes make cures after the more regular practitioners had failed. The medicine was composed of some twenty or more herbs but it was not very difficult for one conversant with these subjects..." -- and, of course, botany was a major part of the medical curriculum in the 18th Century. "It was not very difficult for one conversation with these subjects to perceive that the active herb could be none other than foxglove." *Digitalis purpurea*.

And he goes on in this little book: "Digitals has a power over the motion of the heart to the degree yet unobserved in any other medicine that may be converted to salutary ends." Well, of course, in those days most heart failure was caused by rheumatic fever, rheumatic heart disease. And most rheumatic heart disease was microstenosis and most microstenotic patients had atrial fibrillation. And we now know that digitalis is quite wonderful in these patients in slowing the ventricular rate.

The question came up, of course, when rheumatic heart disease disappeared as the major cause of heart failure in the middle of the 20th Century: what about digitalis in patients with sinus rhythm? And I'm not sure we know that, but here's the modern echo in 1987: "Does Dig. improve prognosis in heart failure patients who are in sinus rhythm?" And there's the answer. Of course, there's sub-group analyses, but the question is still knocked around. And I'm going to stop here – I could go on and tell you a little bit more about Dig. but that would be for another topic.

Let's go now to what I really want to talk about, which is the architecture of the failing heart because this gets into the modern paradigm of molecular biology, genetics, and now we're moving into the field of epigenetics, which I actually heard some discussion of today. It's just how fast science is now moving. Different architectural patterns of cardiac enlargement – cardiac enlargement, of course, was noted when autopsies began, which is in the 15th and 16th Century. And after Harvey, it became possible to link the autopsy abnormalities with the clinical picture. It was Joannis Lancisi in a book published posthumously in 1728 – Joannis Lancisi was the first to distinguish what came to be known as the two types of enlargement. He distinguished between hearts with increased cavity size – today we call this eccentric hypertrophy; in the 19th Century this was referred to a dilatation – and enlarged hearts where the pathology was increased wall thickness. Today we would call it concentric hypertrophy and in the 19th Century that was simply called hypertrophy.

And the words that are from the translation I have of Joannis Lancisi's book, "So varied and so serious are the maladies of the heart that we often discovered that it has suffered from an increase in its own bulk, combined with enlargement." That's aneurysms and that's the term aneurysm was used to describe cardiac enlargement. "Nor do I mean here by increase of bulk dilatation of the cavities only but thickening of the fibers and an increase of density that makes the base of the heart heavier than is normal." You have to read a little bit into it to see the distinction but this became clear with Corvisart's marvelous book. Corvisart published his book in 1812. I see this is actually the English translation. I think his book was published in 1801. Corvisart was the physician to the first Napoleon and really to him goes the credit for the first really clear distinction between the two types of hypertrophy dilatation, eccentric hypertrophy and concentric hypertrophy, and the fact that they had different prognoses.

Corvisart wrote, "It is necessary to distinguish two types of cardiac enlargement." The word he uses is aneurysm. "In the first, the heart is enlarged, its walls are thickened, the energy of its action increased." Today we would say that's concentric hypertrophy, or 19th Century hypertrophy. "In the second, there is likewise enlargement but also thinning of the walls and a diminution of energy in the action of the organ" -- eccentric hypertrophy today and in the 19th Century dilatation.

And here's just a cartoon. I'm going to show this a couple of times in some other contexts – normal heart, concentric hypertrophy, increased wall thickness, and the heart is enlarged, it's heavier, and eccentric hypertrophy where the walls are somewhat thickened or perhaps look thinner because of the huge cavity. And this is dilatation.

Now, the meaning of these two types of cardiac enlargement – as I said, we're still talking about these today but the meaning became clearer through the 19th Century. And I'm just going to walk you through several of the books that were published. John Bell, who was a contemporary of Corvisart, wrote that dilatation weakens the heart. He said that,

"That the heart may be too big for its system is a melancholy fact. For when it becomes relaxed it enlarges, and as it grows in bulk loses its power."

I don't have a picture of Bertin but here's the physician looking out of the hospital window and here's the coffin carrying away one of his patients. Bertin was part of the great Paris school of the 1820s and 1830s that went under very quickly in the middle of the 19th Century because of lack of funding. Bertin wrote, "Considered in the abstract, dilatation of the heart has the effect to weaken the contractile power of the muscular substance. The muscular fibers lose in strength what they acquire in extent." That's dilatation. "The progress of hypertrophy is, in general, slow, tardy, and chronic...frequently, hypertrophy does not merit of its own account anything more than a secondary consideration." Prognosis is worse in dilatation than hypertrophy.

Fothergill, whose book is on my shelf – my dad bought this when he was in London in the 1920s – had a great deal of pathophysiology in this book, *The Heart and Its Diseases*. He was aware that the prognosis is worse in dilatation than hypertrophy. This of course is an echo of Corvisart. Fothergill writes, "Hypertrophy, by adding to the heart's power, tends to maintain itself, while dilatation tends downwards." Other people writing in the middle of the 19th Century – James Hope, whose long description of heart disease I read at the beginning – noted the progressive nature of dilatation. Hope writes, "When dilatation has progressed so far as to occasion morbid dyspnea, it has a constant tendency to increase unless the circulation be kept tranquil by a very quiet life and judicious medical treatment" -- such as it was in the 19th Century, mainly digitalis. Aran, writing in 1843: "If the dilatation has reached a certain degree, and so far as to induce a morbid dyspnea, the disease has a marked tendency to increase, unless the circulation be maintained in a state of complete repose." The bad prognosis in dilatation, the modern echo, and really the remarkable clinical relevance of all of this was pointed out in the classical paper by the Pfeffers and Gene Braunwald showing pressure volume relationships – left ventricular volume, left ventricular pressure. These are the control hearts. These are patients after

myocardial infarction who were treated with placebo. This is the natural history. This again is dilatation. Volume is increasing, dilatation is progressive.

And the modern wrinkle, which has completely revolutionized the treatment of heart failure, was the recognition that ACE inhibitors could stop and reverse this progressive dilatation, which Pfeffer and Braunwald called remodeling – a very interesting term they used, which Gene and I can argue about sometime.

Hypertrophy at this time, going back to the 19th Century, was initially viewed as compensatory – not a bad thing at all. Valvular heart disease, writes Corrigan in 1832 -- “In valvular heart disease, nature, to enable the heart to perform the additional labor thrown upon it, increases its strength by the addition of muscular fiber, and the heart thus becomes hypertrophied in accordance with the general law that muscular fibers become thickened and strengthened when there is additional power required from it.”

Francois Aran, 1843: “What is seen in the arm of blacksmiths and the legs of dancers is also seen in the heart. In proportion as the walls are increased, are thickened, its contractile power augments.” So hypertrophy is compensatory.

The modern echo – this is one of the three papers. This is from Hood, Rackley and Rolett. This is also done by Sandler and Dodge and a paper a few years later by Bill Grossman. They showed exactly the same thing. This is the compensatory response to hypertrophy. What you see on the left is the normal heart. Left ventricular pressure is in blue, left ventricular wall thickness is in red, and left ventricular wall stress calculated by the law of LaPlace, which is rediscovered in the 1950s, is shown here. And this is the normal heart. In compensated aortic stenosis, which is [audio cuts out for about ten seconds] – normalizes wall stress: adaptive hypertrophy.

Austin Flint, the American cardiologist physiologist, wrote in 1870 about hypertrophy as protecting against the deleterious effects of dilatation. He wrote, “Overload excites a

more forcible ventricular action and hypertrophy is produced. The increased muscular growth for a certain period protects against the occurrence of dilatation" -- which of course is bad. "At length, hypertrophy reaches a point beyond which it cannot advance. The causes, however, persist and can produce only dilatation so that from this period the progressive enlargement is due to augmentation of the cavities" -- now called remodeling. Austin Flint goes on: "According to this view, hypertrophy becomes an important conservative provision, first, against the over-accumulation of blood, and second, against the more serious form of enlargement, that is, dilatation."

Interesting wrinkle – dilatation is not always bad. Byrom Bramwell in 1884 wrote, "Hypertrophy is a compensatory and beneficial condition, in fact nature's effort to meet a difficulty. Dilatation is the direct opposite of hypertrophy, inasmuch as it impairs the efficiency of the cardiac pump." But he noted that dilatation is sometimes necessary. "Although dilatation is usually bad, in regurgitant valvular lesions dilatation of the cavity behind the affected orifice is beneficial, provided that it is just sufficient to accommodate the blood which is regurgitated at each systole." So dilatation is actually beneficial, or at least it's essential, to accommodate regurgitated blood.

We're getting now toward the end of the 19th Century and actually toward the end of the talk I'm going to give. And gradually it became clear that hypertrophy is also deleterious and not just compensatory. Schroetter in Ziemssen's *Practice of Medicine*, 1876, writes, "Hypertrophy, which always occurs when a portion of the heart has been called upon to perform work beyond its normal capacity, may exist for many years and the individual still continue to have relatively good health. But in the end it certainly leads to a so-called catastrophe through some of its sequels, which are of themselves full of danger to the patient." And Constantin Paul, now 1884: "It has frequently been said that the heart hypertrophies in order to establish a sort of compensation. This view would be correct if hypertrophy remained stationary but experience has shown that the excess of work imposed upon the heart finally deteriorates its fibers" -- the modern question that we're still asking: what's going wrong?

Well, one of the modern echoes are these papers Izumo published, showing one of the interesting consequences of the response to overload. Hypertrophy is accompanied by a reversion to the fetal phenotype. And what you see here are blots of three different proteins, beta and myosin heavy chain, and on each of these the normal heart is in the center – normal adult heart. And the fetal heart, fetal ventricle – this is all ventricle – is on the left and pressure overload is on the right. And you see that the adult ventricle expresses alpha fast myosin, the fetal heart expresses a slow beta myosin heavy chain, and pressure overload goes back to the fetal isoform.

The same thing is true of beta tropomyosin – you don't find much of this. This is a fetal isoform in the adult heart. Here it is in the fetal heart and here it is in the pressure-overloaded heart. And here is skeletal alpha-actin, which is the fetal isoform in the human ventricle. This is rat ventricle – sorry. This is the normal adult, this is the fetal, and here we see the re-expression of the fetal phenotype. There's a lot more to the re-expression of the fetal phenotype, most of which is bad and some of which is responsible for a lot of the problems in heart failure, including arrhythmias and sudden death.

But enough – just to show you that we have returned to these questions of if hypertrophy is good or bad, but now using the modern paradigm of molecular biology. This is all put together by William Osler in the first edition of his textbook of medicine, published in 1892. And this is Osler writing the text, with the picture taken in 1891. Osler clearly describes adaptive and maladaptive hypertrophy in what he considered to be the three stages in the heart's response to overload.

The first stage in the response to overload is development and how fast and how much it develops, the hypertrophic response develops, depends on the nature of the underlying abnormality. That leads to the second stage, full compensation, in which the heart's vigor is increased by the hypertrophy, enough to meet the increased hemodynamic

demand. And this is the adaptive hypertrophy and I show one way in which hypertrophy is adaptive in the normalization of wall stress.

But then the process doesn't stop, and goes on to what Osler called broken compensation, which can result in acute dilatation, which was the term that was then used for what was pulmonary edema. So broken compensation can lead to pulmonary edema, but more commonly evolves slowly as the result of degeneration and weakening of the heart muscle. And again, heart failure – we are now worried about trying to understand what is degeneration and weakening of heart muscle. And this is maladaptive hypertrophy. Part of this is the reversion of the fetal phenotype but there's much more to that story. But that's the modern story.

To go back to these three architectural patterns – and I'm almost done – I just want to show one other insight that was available in the middle of the 19th Century, these different types of hypertrophy, dilatation and hypertrophy. And we're back to Fothergill, who is talking about the fact that hypertrophy and dilatation result from different mechanical stresses. And Fothergill is looking again at mostly rheumatic heart disease – aortic stenosis, aortic insufficiency – and Fothergill wrote, “In obstruction without any increase in the distending forces in aortic stenosis, there is pure hypertrophy, usually without dilatation.” Obstruction – increased systolic stress. “With increase in the distending force as in aortic insufficiency, hypertrophy is always combined with dilatation of the cardiac chambers.” Increased diastolic stress... And that's shown in this slide. Here's aortic stenosis, where the stress is during systole. During ejection the ventricle is contracting against a narrowed aortic valve.

That's increased systolic stress. In aortic insufficiency, the stress is during diastole. The heart relaxes, blood comes pouring through the aortic valve, and you have increased diastolic stress.

The modern echo – this is a remarkable paper, published now six years ago in *Circulation*, Yamamoto et al. And what these investigators did was to take cardiac myocytes and place them on an elastic framework. This is some sort of an elastic matrix. And the investigators stretched – this is externally applied stretch of the myocytes as the hearts were paced. The up and down doesn't make any difference. This is a pacing, that's a pacing, that's a pacing. When they stretch the heart during systole – this is immediately after the pacing, the electrical stimulus – they got one pattern. You'll see that in a minute. And they compared strain imposed during systole and here strain is imposed during diastole. And what you're seeing in the bottom – and the details are unimportant for this talk. What's important is the distinction between two signaling pathways that activate growth. These are MAP kinase pathways and these funny letters are what molecular biologists love to torture us with when they are naming different pathways.

The point is that when the strain is imposed during systole and when the strain is imposed during diastole you get different responses. Here is the strain imposed during systole. Here is the strain imposed during diastole. What this shows simply is what I guess Fothergill was trying to say but didn't know how to phrase it, because molecular biology didn't exist in the middle of the 19th Century, is that different signaling pathways are activated almost certainly by different cytoskeletal signals. The different signaling pathways are activated when the heart is stressing during ejection – aortic stenosis – and during filling aortic insufficiency. The translation of this information into clinically useful products has not yet occurred, but just stay with it because clearly this is important.

So what I've tried to do in this brief talk is to give you one example of the clinical picture of heart failure in the 18th and 19th Century, a little bit about digitalis and the basic science of the time – which was botany – and to show you some of the concepts, some of the observations on the architecture of the failing heart which today are having modern echoes, which is really what you are hearing so much of in this meeting. Thank you very much.

[NOTE: For the next ten minutes everything is completely off-microphone and often unintelligible.]

Female Voice: I have a question. I was thinking about how remarkable it is that they figured this out by seeing each patient at only one point in time.

Dr. Katz: They didn't. They followed the patient.

Female Voice: No, but they'd only see their hearts at one point in time.

Dr. Katz: Yeah.

Female Voice: So I'm wondering if in fact --

Dr. Katz: Ah, but they didn't. You see, this acute dilatation -- how was it that they were able to recognize that there was hypertrophy and dilatation? This is [unintelligible] and the cardiac impulse. Physical diagnosis was very [unintelligible].

Female Voice: Let me just propose something to just think about here. Because they could only actually see the heart once and almost all the stresses at that time were [unintelligible], is it possible that in fact they made the right conclusions for the wrong reasons? Which means that they had the hypertrophy of the stenotic [unintelligible] and then as they got close to the end in general there's an [unintelligible] leading to a volume overload without actually having the pressure overload [unintelligible] itself. And we know now that that happens but I'm wondering in their case if that was really what they were seeing.

Dr. Katz: It's possible but having seen a few patients die of aortic stenosis, the heart does not [unintelligible]. The heart can remain very tight and very [unintelligible]. [Unintelligible] sudden death [unintelligible]. This is clinical investigation in the 19th

Century with physicians taking care of [things], observing the signs and symptoms with physical examinations. And they were trying to figure out what happened when the patient died and they did an autopsy. This was my father's experience. My dad graduated from medical school in 1918. In 1920 he went as an intern to Cleveland General Hospital and he said that --

Male Voice: Which is my hospital, by the way!

Dr. Katz: I will not insult it! [Unintelligible – laughter] What they would do is that the doctors would sit around and watch these patients dying of heart disease and try to figure out what they would find at autopsy. And then they'd do an autopsy and they were either right or wrong. And my dad said, "This is no life for me" so he went back [unintelligible].

So this was really clinical investigation. [Unintelligible] When you read the descriptions of the natural history – I just gave you one snapshot in the James Hope description but there are other descriptions [unintelligible], descriptions of the patients at various stages of the disease. How they distinguished between dilatation and hypertrophy before death I'm really not sure. But I think they did and they confirmed it at autopsy.

Female Voice: [Unintelligible] because we were talking in the hypertrophy session and [unintelligible] have you actually seen somebody with very [unintelligible] with hypertension go on to develop [unintelligible] heart failure? And the consensus of [unintelligible] – although we think of that happening, in fact it is curious how often we have actually seen that happen in a human model. We certainly see it in animal models, but in human models. So it's just interesting to speculate what we're actually seeing by looking at one point in time and then trying to piece this together.

Dr. Katz: Gene, help me out. You're the only one here who's long enough in the tooth to have watched people die of [unintelligible – laughter].

Female Voice: I'm not saying they don't die but do they die really dilated? And once they have been hypertrophied – there's no question they can die either way.

Male Voice: It's very interesting that you mention this because in our practice in the African-American population you see that. And I've either been fortunate or unfortunate to be at the same place for so many years and we would see these patients come in well-treated and then they would go out, get off their medication, and get hypertension and they'd get worse and eventually they'd start to dilate. Then, of course, their blood pressure would go down. So the worst thing that could happen is they'd come back from 160/100 with a pressure of 115/70, and they were in big trouble.

Now, I would agree that in Caucasians in the [unintelligible] in the last twenty years, it's much less common. But I think in the African-American I'm sad to say we can see that [unintelligible]. And I have seen it in some Caucasians. I have a particular guy from Raleigh in mind and he would do this. He would come in with very high pressure, 201/140. And we would treat him and get him down. His pressure would come back down, he'd go out and he would try and comply and he'd come back in again. And he went through about four of those cycles and after the fourth one he was dead. He never would come back. And you can just imagine every time [unintelligible].

Male Voice: In 1951 [unintelligible] hypertensive heart failure was [unintelligible]. [Unintelligible] and there was no treatment at the time, period. [Unintelligible sentences] So I think it's very similar to [unintelligible].

Male Voice: [Unintelligible] to your question. You have made the point, I think, [unintelligible] and that is that there is much to learn [unintelligible]. But they were every bit as smart as [unintelligible] and in some ways they were not as cluttered, and certainly not all the damn technology [unintelligible].

Male Voice: I have a question for Arnie. I'm looking for the [unintelligible] also and I realize after looking at the first four pages that it probably was [unintelligible].

[Unintelligible crosstalk]

Male Voice: But I wonder about – she probably would have been considered a witch at the time. Do we know anything about where she inherited this knowledge?

Male Voice: [She should have been a co-author!]

Male Voice: Well, authorship --

[Unintelligible crosstalk]

Male Voice: Presumably, it's passed down from somewhere but it didn't just arrive [unintelligible]. So where did that information come from?

Male Voice: [Unintelligible] But what he did was to realize that the main principle of this potion that she used was [unintelligible]. So he said he went to see her personally supposedly to get trained, so the story goes. And when [unintelligible] he looked at it and he found that she was using a potion that came from the [unintelligible]. [Unintelligible] and he said [unintelligible]. There were many things in that potion and one was foxglove. And he said the only reason that he was involved in it – he wrote a book about that [unintelligible]. He knew about the times more than anybody else in England. And I think that's because [unintelligible crosstalk].

Male Voice: And he published [unintelligible crosstalk].

Male Voice: But it's a really interesting point that people were in fact taking things and giving them to people to [achieve] effects. And that's a very, very fundamental idea and I think what he did magically was figure it out. He did a lot more than that. [Unintelligible crosstalk]

There's a great story behind that [unintelligible] story which we could do later on but that's a fundamental principle [unintelligible].

New Discoveries in Heart Failure

Kirkwood F. Adams Jr.

I have to just say a couple of words here before I start. I know we've been here an awfully long time but it is really exciting for me to see this happen. And I know Jim Young and I were talking about this four or five years ago and we kind of picked out the Heart Failure Society as the place to do it. And we got started, and of course Hector has been a champion of all this and of course Arnie Katz. So we're just really glad, and it's kind of a magical thing for me, to be perfectly honest. I just had to do my lectures the way that I love to do them, which is that I was working on it right up until almost the absolute last minute! And I really want you to know that I have got the PowerPoint disease and I have got the CME disease and everything is prepackaged now and many of my lectures go up two or three weeks ahead of time and they're always crap. Now, the thing is I don't really know whether this will be crap or not because I wasn't thinking about it as much. But anyway, I just want to thank Laura for working so hard and Elizabeth and all of our sponsors, obviously, for trying to make this happen.

So of course if you talk about this with the house staff now they'll say, "Why are you bothering with this?" And there are so many reasons why we should. And you have to think about, which is what Arnie was talking about, Lynne's comment. So you think about really how these people approached problems and that's going to be a theme of mine. But I think tonight the get-together and the camaraderie is probably reason enough, because I guess you could study history by yourself but it's fun to talk about it because of course it's a series of stories. It's tales of individuals.

I really like to focus on the lives of ideas. We were getting into that – giving somebody something to make a physiologic action, thinking about patterns of anatomy and the ideas that Hector was tracing. And I think if you go back to this, I guess the Greeks do get a lot of credit for almost everything. But I think this concept of an image – when we think about this maybe it starts as an image, something visual, many times. But then the terminology or the definition evolved to a concept and then abstraction, which is clearly what we think about. But I don't always get it as an image, you know. So I'm also talking about how we think. It's funny – we don't want to teach people how to think anymore but if you look at Dr. Braunwald's work or Dr. Katz's work, how did they think? How were they thinking when they did these experiments, when they had these things? And I think doing it in images obviously can be helpful.

I've had this book in my study at home. And I am going to say this – I don't know that this is actually the truth but I think I've had this book for thirty-five years! And maybe I always knew one day it would come in handy! But this guy, Arthur Lovejoy, wrote this thing. This is about life as a hierarchy or existence as a hierarchy and there have got to be lower forms and higher forms. And this is what the great chain of being, in a very simplified manner, refers to. But he talks about these unit ideas. And I'm not going to spend much time with this because I'm still learning about it, but I think it's like what I was saying about giving a potion to somebody, giving something to somebody to make them better. Or something can't come from nothing – when I was a sophomore at Duke I took this marvelous philosophical course with this guy and this is really what Western philosophy is about. You

have to have a creator, because something can't come from nothing. And that's one way to think about this unit idea, so maybe I'll get a couple of these across as I go forward.

Now, I'm actually in the very enviable position of showing a slide that Dr. Lefkowitz showed already! And I did put this in before his lecture because it's burned on the CD. So part of what it is that we need to let young people know is that we make a lot of mistakes, and oftentimes we're stupid. And he showed this because basically he was talking about how skeptical people were about the receptors. And of course, it was Ahlquist who proposed the receptor sort of concept but then of course he went on to utter this statement that nobody really possibly could believe that these receptors actually existed: "And I really didn't mean it, guys." And you could see it was an abstract concept conceived to explain responses. So I'm obviously talking about beta blockers here and I should have put that in the title but you're getting that, I'm sure.

So what Lefkowitz did was to go on and to demonstrate the realities of these. And he makes this point. I know that sometimes I hate technology too but technology allows you many times to make these advances because you really do have to advance the technique. And of course, Harvey was an advancement over earlier techniques of exploring the body and it was this radioligand bonding that allowed him to make this progress and then really characterizing these receptors and proving their existence.

Now, we would all like to win the Nobel Prize. And this character, James Black, is one of the people who actually did it. And I love this quote about how he started out to study medicine. I kind of imagine that maybe Hector would have a similar quote if he ever wrote it up. Basically, it's "the joys of substituting hard disciplined study for the indulgence of daydreaming." And of course, I can just feel every cardiology chief in America shuddering! And of course, this is me! But I think you can carefully disguise yourself as long as you – see, they keep changing the damn computer system! And I think they're sitting over there and they say, "Adams has got it so we've got to change it! We've got

to change it and now it's this way!" So indulgence of daydreaming...and these characters of life are so amazing.

All right. So then you say, "How did he win the Nobel Prize?" And actually, I was trying to get a picture of the Schrodinger Equation, which really is fairly complicated and apparently he did dream it, actually, one night. But look at this. This is what he did. He just said basically the sympathetic drive is creating this excess need for oxygen and the arteries are narrow. And, see, this is the great thing if you get it right. And you see people don't see it but then once you tell them everybody can see it because it's elemental. It's fundamental. It's right at the core. We would have these debates about: with nesiritide, does blood pressure matter? Well, probably. I mean, if you give it to somebody and their pressure goes to 70 systolic that probably matters, you know! It's just so important.

So anyway, this is how he won the Nobel Prize. Now, this is the thinking. This is what you could call linear conceptualization of drug effects. So basically you increase the beta blocker dose. And actually, I've got this inverted because the high doses would be down here. I just did this fifteen minutes ago. But basically, this is a very simple model. You've got this high heart rate and then you lower the heart rate and you decrease the heart rate and you decrease the MVO₂. And this is something that would be pretty easy to recognize, right? Because you're taking the patient – the patient comes to you, they're having angina, and you give them some beta blocker. You measure the pulse, it goes down, the angina gets somewhat better, you increase the dose, the heart rate comes down – the whole thing is this nice little linear thing. And it really is probably pretty straightforward once you have the idea.

Now, this is also academics working with industry. Now this has really become such an awful thing that we do and how evil all these things are. You know, they have these relationships. And this is from his autobiography too so it's easy to get to on the Web. It's on a page I go to often because I'm thinking maybe, you know – it's called

nobelprize.org! They haven't asked me for my contribution yet. They haven't asked me to submit my autobiography yet but I keep hoping maybe one day, you know!

So he just has this wonderful description. I mean, I can just imagine if I put this slide up that UNC and I would immediately have eighteen conflicts of interest and I'd have to resign immediately. And here's the guy – we all know these people. I have no idea who Garnet Davey is, you know, but he was the person who fought these battles. And we've all worked with wonderful people like this in the industry, who fight these battles. And of course, this is really how he was able to do his work.

Now, when you go to heart failure we have a little bit different history here where maybe we thought that sympathetic activation was good. And I think there were a lot of reasons why we were so stupid, because when you look at it you get more heart rate, you get more contractility. If it happens for a while now we know it causes hypertrophy. And you maybe even get some improved relaxation. So this is sort of non-intuitive. Decreasing the oxygen and all that was kind of intuitive and this is a little bit less intuitive. But again, Dr. Katz rescued me with this wonderful slide which was in some of his earlier slide sets he sent out. But this is basically giving the sympathetic stimulation to somebody in cardiogenic shock and of course this is beneficial.

So you have to ask this paradox – why should giving a beta blocker...how could this be of benefit? And when you really look at Waagstein, I've really never met him to talk to him. It would be very interesting to do that and we should have him come and talk. And this is kind of a wordy thing but he's talking about why he gave the beta blocker to these heart patients with heart failure. And I believe there were about – I had more slides on this but I didn't put them in for time, but his concept here is that maybe in the failing heart if you reduce the workload that maybe that would be beneficial. So he's still sort of thinking...

But this is another way to conceptualize this. You start thinking about: what are these receptors doing? So we're going back now maybe to these unit ideas: what are these

receptors doing? They're really acute regulators. They're really not made to be chronic regulators. So when you think about Dr. Katz's slide, the cardiogenic shock, it's all over in a couple of days. It's going to be stopped and you're either going to make it or not, but this sort of sustained activation. This is from Ovid: time kills off everything. But maybe it's this idea of over and over and the repeated response – maybe that's bad.

This would be a non-linear conceptualization of drug effect, which is what I think we all believe about beta blockers. When you're treating that angina patient and the heart rate is going down and the person is feeling better this is good and we can all see that. But when you're giving these beta blockers and you're seeing the patient get sicker and not improve or not improve for a period of time this is non-intuitive. This is not something that you're going to immediately hit on. But this is kind of that response curve so it's that non-linear – and this is much harder, I think, for us to concede that this might be possible and it might work. And of course, it took us a long time really to figure it out.

This is the Barrett data of course and you see this period where it looks like nothing is happening. And there was a time in heart failure where we really only did trials for three months. So there we would be with no effect.

This is one of our small contributions. This is in asymptomatic individual, just showing that the same phenomenon applies – dose-related response in ejection fraction. Actually, my Mac rebelled and I guess I was too excited there to realize that there were a couple of slides missing. But it's a good thing! But the point that I want to make here is: what's going on? Why is the ejection fraction going up? And I think this also could be approached as an intuitive idea. And Lefkowitz already covered it anyway, but the point is when you get receptor desensitization you lose contractility because the receptor carries a benefit of contractility and when you give the beta blocker you decrease BARK and you reverse some of that contractility. And my point about this is really that you're not rebuilding the heart. That would be a marvelous thing and if we could give these beta blockers and really produce some new architecture or create some new calcium

process...but we're not probably not doing that, so what we're doing is probably bringing something back that that chronic stimulation has taken away. So it's thinking about these ideas and thinking about these unit concepts.

And then just two more slides, my art slides – this is called “The truth will out.” And I think one of the great things about science is it does seem to do that and I think it's one of the best parts about it. This is one of these totally incomprehensible pictures but fortunately when you're walking in the museum you have a box on your belt and somebody's talking to you and they give you some insight. But the fun part is once you start to see it. So there is a vanquished person. And, see, we've lost all this stuff because we're looking at the Simpsons and the Sopranos. So these visual things that used to be – if you are reclined and somebody is standing on your chest you are vanquished! Somebody is losing here. Somebody is losing.

Male Voice: It looks like the Chairman of Medicine!

Yeah, it could be Dr. Young! And then somebody is looking in a mirror. Now, I admit that the mirror part might – but a mirror is truth, right? It's not exactly underlying what somebody is really like but it's going to show your true reflection. In the symbolism of the time the mirror was the truth, so we have truth vanquishing something here. And I admit this is really hard to see but if you look very closely this woman has two faces. So what am I getting at? And this is why I think we need to study history because when we look at the history of beta blockade it's the history of persistent people who kept at this and kept trying to understand it. And that initial perception that these drugs were poison and harmful. I think is such a phenomenal lesson.

And I think what we've got to do with groups is – if you don't preserve the history you don't know how these things happen. You don't know what it takes to have an academic medical center. You don't know what it takes to have science and a scientific method. It's not a straight line. It's not something where you come in in the

morning and you punch your clock and sit down at your desk and write out this great idea and then you go home for the day and it's some regular thing that happens, and it's automatic and we don't need to nurture it or pay attention to it. I think we live, in many ways, in a great culture and we are really everlastingly – we should be everlastingly thankful for that. We have many problems and many things wrong with our country but what we don't want to do is lose sight of what's right. And I think groups like this can help us and I think with time maybe the truth will still out. Thank you.

Female Voice: Can I ask a question? Just to play devil's advocate in this, the [unintelligible] hypothesis [unintelligible]. Would it be possible that because that's what we adopted that that's what we see in beta blockers? [Unintelligible]

Male Voice: There is another issue that has never come out or never been talked about that I learned from Karl Swedberg and talking to Karl about his knowledge of all of this. These folks had given Inderal, although the heart failure studies were done with Practolol. But they had given Inderal to thyrotoxicosis patients that had high-output cardiac failure and had anecdotally demonstrated this pulse reduction and this improvement. And the reason they were giving it was to reduce the pulse. And this was before the publications – a lot of the focus in publications had come out with thryotoxycosis and high-output cardiac failure. So I think that link then to this heart rate issue was huge.

But that's never been referred to. If you look at the references in some of these early papers it's never talked about.

Male Voice: And I think it's a very good [unintelligible]. I think it's also a point about how you may have different mechanisms in different people. And I didn't get a chance to go into all that but if you look at that first table with the sixty-seven people, those people have heart rates of +400. What we got interested in was the merit findings so we were in the midst of these culture wars and what do we do about [unintelligible] and dose response and all that. So we proposed this experiment [unintelligible], which was to go

back and look at the dose response in [unintelligible]. And of course what we found was that the mortality rate at low dose was the same as high dose. But then when they looked at the heart rate the change in heart rate was the same in the two groups. So it didn't matter what the dose was as long as you reduced the heart rate.

Now, we just got through doing a study with a little group here. We got some money from them. And the confounding factor is that when you decrease the heart rate like that you have better receptivity occupancy, as we all know. And the peak treadmill is a good indicator of that. It's confounded, so you could be decreasing the heart rate but it could be some other effect of the beta blocker because you're getting high levels of receptor occupancy so clinical experiments can be very difficult to dissect that out because the occupancy may --

But then we also wanted to even say: does the occupancy have anything to do with the efficacy? And the truth is nobody's ever shown that. So I think you're right – whenever we think we understand something we're halfway usually wrong.

Modern Therapies and Interventions

James B. Young

Mike DeBakey's younger sister wrote a book called *Preserving the Passion*. It's in the second edition of it, and it talks a lot about how physicians learn things, continue their medical education, and keep engaged in this progress, whether it be how to treat patients or whether it be new knowledge. And so one of the things that I'm particularly

interested in, is using history as a springboard to teach people about concepts like beta blockers, like we were just talking about, or other sorts of things. And so I was asked to throw in my thoughts about modern therapies and interventions and it is related to the evolution of Arnie's philosophies regarding how we move forward to the understanding of the pathophysiology of heart failure – which arguably, though terribly incomplete, has an extraordinary nuanced description right now. And in each one of these areas, we're learning an extraordinary amount about heart failure.

Now, it's interesting that the discussion focused on hypertension, LV hypertrophy, utilization of Dig. for LVH and diastolic dysfunction and hypertrophy due to hypertension. The other thing that we need to remember is that the public drives many of things that we do. It's the public that drives Congress. It's the public that drives research allocations. And so it's public knowledge that we have to pursue. And in heart failure FDR is a fascinating example of a terribly difficult heart failure patient and in fact I like to argue that the Cold War was caused by congestive heart failure. If you look at a lot of work that's been written and published recently – and there's a wonderful review article in the *Journal of the History of Medicine* that just came out last month about people writing about FDR's illness and public awareness of FDR's illness – he was extraordinarily hypertensive. And if you look at Howard Bruenn, who was a “cardiologist” at Bethesda in the '40s, the Surgeon General sent him to Bruenn for a consultation because of FDR's weakness, fatigue, and breathlessness while he was in office in 1944 during the peak of World War II and during all of the stress of World War II. And Bruenn noted him to be cyanotic, breathless, with an enlarged left ventricle and a blood pressure of 186/188. He diagnosed hypertensive heart disease and wanted to digitalize the patient, apropos to what was talked about earlier, but the the Surgeon General – who was an ENT doctor – wouldn't allow it. And so Roosevelt was never treated for his hypertension and then in a great article that Franz Messerli published about a decade or so ago it was pointed out that FDR had a stroke. It just came out of the clear sky. Nobody anticipated it. Nobody expected it and the public was just absolutely, totally clueless – and yet his blood

pressure at the time of his stroke was diastolics of 120 and systolics of 220, 230, well documented in Bruenn's notes.

Interestingly enough, FDR's medical records have disappeared and have apparently been destroyed, purloined, or whatever. The argument about Yalta is if you look at the pictures of FDR, he had sleep apnea. He had sleep-disorder breathing. And the descriptions of him smoking a cigar and nodding off and burning the tips of his fingers as the cigar burned down during the talks and during the negotiations is extraordinary and tells you about how heart failure, sleep-disorder breathing and whatnot in fact impacted probably the negotiations at Yalta, which set the stage for post-World War II division of Europe and in fact others have argued has created the Cold War.

The other thing about heart failure that from a public awareness standpoint is interesting is looking at ischemic heart disease. And if you look at Eisenhower serving from '53 to '61, Eisenhower, again as Franz Messerli nicely described, had a billion-dollar heart attack when he was in office. And the story is well-known about how he had indigestion, lots of indigestion, was out on the golf course golfing when he probably had his acute event. And when this became public it triggered a tremendous crash of the stock market because people were told that he was going to be confined to bed rest for three weeks and that his chance of surviving was very poor and was very miserable. He did survive, he did get through, he did get through office. And his medical history, interestingly enough, if you look in all the history books, has been totally ignored. And yet what Eisenhower had was a profound ischemic cardiomyopathy. At the end of his life he had horrible heart failure, multiple subsequent heart attacks, multiple cardiac arrests, was resuscitated frequently, and really in April of 1968 died a miserable death, it sounds like, in kind of obscure surroundings of an ischemic cardiomyopathy. That is not known, but his heart attack triggering public awareness I think did a great deal for setting the stage for moving things forward.

Now, the other thing I think that is interesting from a historic standpoint and segues with a lot of comments that the other speakers have given is that there's an incredible amount of serendipity if we look at the history of the development of products, the development of medications, and just what we do. And one of the ones that I find particularly interesting is the development of ACE inhibitors and ARBs that is in fact linked to *Bothrops jararaca*, the Amazon pit viper, arguably the most poisonous snake in the world, who kills by envenomation with subsequent hypotension and cardiogenic shock, neurologic impairment, and profound white lung syndrome that develops.

And the story is long, but a herpatologist by the name of Clodomiro Picado, who was from Brazil and studied venomous snakes, figured out that the compound that caused the hypotension and was responsible for the white lung syndrome was an 8-amino acid compound that in fact was captopril. And the story of this evolution of the knowledge I think is extraordinarily important because it does in fact emphasize how rooted in history sometimes becomes our understanding of the development of compounds and the development of new therapies.

Now, it was good that the beta blockers were talked about. This is the same paper that was just shown and this is not in the paper but this is an X-ray that Karl Swedberg has, which is reputedly the X-ray of the original patient that was treated, having pulmonary edema, with beta blockers, demonstrating the resolution of the pulmonary edema and the decrement in cardiac size that is present.

Now, one of the things I think that has both helped and hindered our progress – and now it's time to put a historic perspective on clinical trials and the movement forward with clinical trials – is the fact that evidence-based medicine really has been rooted in this. Lloyd Fischer, well-known statistician for the FDA Cardio-renal Advisory Panel back in the '70s, used to have a frequent quote. And every time I showed up in front of that panel I used to hear him say, "There are lies, damn lies, in clinical judgment and I want data!" So what has happened is those historic understandings and perceptions then have been

put into clinical trials, arguably with the multi-center RCT being the most valid and the most precise way to gain knowledge. But we can't gain knowledge with a clinical trial in everything we do in medicine. It's still an art and, again, studying history reminds us of the artful nature of the historians and also the fact that some things we can count, like dead bodies -- or funerals, as Hector pointed out, which is a pretty interesting surrogate end point for death that was counted back by the Romans and whatnot. It's important, but some things that really count can't be counted.

And let me run through a little quick evolution to set the stage for a glimpse into the future. This is kind of how I put together the modern evolution of heart failure. Really, the Netter drawings show the old congestive heart failure patient, dropsy, the rudimentary treatments that are here and then the seminal publications and seminal observations that were sort of made here. And I'm glad Dr. Braunwald is here because when people ask me to mark the day that the modern era of heart failure began I mark it right here in 1967 with the publication of Dr. Braunwald's multi-part paper in the *New England Journal of Medicine*, which was a three-part series. I don't know if you remember, Gene, or not -- it contained fifty figures and was an extraordinary accumulation of all of the concepts, all of the philosophies, and rooted this hemodynamic concept into the therapeutic evolution and set the stage for moving forward. And to me the most interesting thing is that some of those diagrams are the most often-reproduced diagrams that I've ever seen. You see those diagrams everywhere. And a couple of them are even attributed to you, Gene, and the paper is actually quoted with that!

And this marked the stage, along with the publication of the Framingham studies in 1971 showing the unbelievably high morbidity in heart failure. But we segue from those observational types of studies with actually some pretty radical things. Kelley, for example, publishing the first papers with hexamethonium in heart failure from Freedman's Hospital in Washington, D.C. -- an African-American and working in a very challenging environment in what has become Howard University to do some rather radical things with hypertensive congestive heart failure patients admitted to the hospital with

decompensation. And the article is an absolutely fascinating one to read, progressing through where some of my mentors ended up, Rich Miller, back when he was Chief of Cardiology at Baylor, looking at these and then segued into the clinical trials that set the stage really for the future. And I think the '90s and early part of this century really were rooted in clinical trials driving us forward. These green clinical trials are those that were positive clinical trials. These are kind of clinical trials that didn't quite give us the same results, the negative clinical trials. And we have a bunch of equivocal clinical trials down here. But the point is that the potpourri and the alphabet soup of clinical trials here really has given us the evidence to set the stage for heart failure, with today now a tremendous focus on device therapies, mainly because we've perhaps reached a limit to the number of drugs the patient can take and people are kind of tired of the pile-on sort of attitude.

So if you look at the future – I'll delve into this briefly in just a minute – I think the future can be represented by new interventions and new devices, better understanding the pharmacogenomics associated with heart failure that perhaps can lead to more prevention and really a focus on the well patient to try to create an atmosphere where you don't develop heart failure in the first place.

Now, there are a whole lot of things that have gone on in the modern era that fascinate me that I think you're going to see moving forward even more. The discovery of B-type natriuretic peptides has an interesting history. I'm not going to go through that or go through the number of publications in the recent period of time that has developed. But I'll simply point out that one example of the insight into new pathophysiology of heart failure is the issue of natriuretic peptide discovery and how we have utilized them for therapy, albeit it a controversial gene, neseritide, and diagnostic means, knowing that there are probably many, many other hormones that also play a critical role and many, many other hormones that can be tapped into to give us some insight.

And so if you take that, and you take the evolution of the clinical trials and look at the future directions, I think there's going to be additional clarification of pathophysiology.

And for those of you that saw my presentation Sunday morning, I went into great detail about the brain/heart connection, which I've become interested in. And so has Dr. Braunwald, with some of his very, very first work with Nina Braunwald on vagal stimulation for the treatment of angina pectoris. And recently, the relationship of inflammation to activation and deactivation of the sympathetic nervous system has seen a recrudescence.

And so I think we're going to see clarification of pathophysiology that is quite different and in some senses we're like Osler was, sitting back at his time describing the decompensation of a hypertrophied left ventricle and us today noting what drives the fetal phenotype in some of those ventricles as a signal that Arnie focused on.

But I think there's going to be a lot of attention paid to prevention, to pharmacogenomics -- and the controversial story of BiDil is an interesting one. I'm particularly interested in this non-pharmacologic strategy again because my patients are taking enough drugs and I don't want to necessarily pile on top of them. But mechanical circulatory support, volume overload management, removal of fluid with some of the devices that are now available -- self-therapies, I think, is where the future lies. And getting back to the Eisenhower and FDR issue, increasing public awareness is occurring. Arguably, direct-to-consumer advertising is bad according to some people, but I take a different view with respect to the lipid advertisements. I can't tell you how many patients come in asking about their lipids and it is due to direct-to-consumer advertising, no ifs, ands or buts about it. You might not like Dr. Jarvik's commercials but I do think that it gets patients to ask their doctors about them.

This was the one comment about the future research. This is Tracey's article about the heart/brain connection and the relationship to inflammation. And this is just an example of the types of devices that are coming out and moving forward with ultrafiltration and fluid removal.

Another area that I think is fascinating is looking at peripheral problems that then affect heart failure. And the whole arena of sleep apnea is getting huge attention at this meeting, and it's a trick that I don't particularly like to get out because when people refer patients with problematic heart failure to me it's kind of one of the tricks we have – get a sleep study, lots of them are desaturated, and if they can tolerate positive-pressure breathing this desaturation that occurs, as evidenced right down here, can be cured.

And then there are a whole lot of other things I think that are going to be – that's just another sleep apnea test – there are a whole lot of other things that I think are going to move forward and it's an interesting time. It's the 50th anniversary, 1957, of Kolff in Cleveland putting in a total artificial heart in a dog and keeping the dog alive. And it was December, 1982 that Barney Clark received his total artificial heart so it's the 25th anniversary of Barney Clark getting his total artificial heart. So these are pretty remarkable and pretty seminal times. And if you look at the first ventricular assist device that went in in 1966 – here's Mike DeBakey with the first successful patient here – we've told this story a lot. The patient had had rheumatic heart disease, bad AI, bad MR, went to surgery, couldn't be weaned from cardiopulmonary bypass, they put the device in without IRB approval but as life-saving measure. It tided the patient over and they were able to wean the device, the flows, to the patient, and they removed the device at the bedside under local anesthesia because the outlet cannula came out through the chest wall and the inlet cannula came in here through the axillary artery. They did it under local anesthesia and just clamped off the flow lines and let them clot off -- with options, as Lynn well knows, dramatically advancing and moving forward but with the challenge, as Eric Rose often says, being the fact that biology trumps engineering.

But I do think that the future is going to see development of a lot of these other devices and I think that we're close to mechanical circulatory sustenance. I'm not going to go through that here. And then finally, this issue of cell transplantation – I don't know. Norm Shumway used to always say that the total artificial heart was just around the corner and coming down the road and would always be just around the corner and coming down

the road. And some people can say that self-therapies are the same thing, but I think the insight that's being gained into myoblast transformation and the use of intrinsic and extrinsic autologous stem cell formation is in fact going to work.

So juxtaposing the history that we have in common about heart failure with the knowledge that we've gained and with the progress that we've seen, it's remarkable. I think the future is bright and I think for all of us unfortunately the need is going to be there. I think we're just going to see an explosion in the number of patients with this difficulty and problem. And I hope that we can go back to set the navigation points. You know, a good navigator does three things. Number one, he takes accurate sightings and he knows what time it is. That's an interesting essential component, to know what time it is, and it's somewhat of a difficult thing to do. Number two, a good navigator knows where he has been. And so, as Churchill said, the farther back we can look the farther ahead we're going to be able to see. And then the third thing that a good navigator does is plot the way points in a course so that he can chart where he is going and he can make modifications to that course, depending on discoveries, insight, and history as it evolves.

So this is kind of exciting, to see this project begin. We appreciate the support. There are lots of little nuances that we can talk about, lots of lectures, lots of presentations that can help us chart these way points and help us set the course. So I'll stop there and see if there are any questions or comments overall that people would like to make. But this has been fun. Thank you.