The History of Heart Failure
A Journey From Ancient Therapies to Modern Interventions

Monday, March 31st 2008
6:30 to 9:00 pm
The Palmer House Hilton
17 E. Monroe Street
Chicago, Illinois

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Transcript

6:30 pm	Onsite Registration
7:00 pm	Welcome Hector O. Ventura, MD
7:10 pm	The First Writings of Heart Failure Hector O. Ventura, MD
7:35 pm	Good and Bad Adaptation: History of Hypertrophy-Muscle to Matrix Kirkwood F. Adams Jr., MD
8:00 pm	Modern Therapies and Interventions James B. Young, MD
8:25 pm	History of Diversity in Cardiovascular Research Clyde W. Yancy, MD
8:50 pm	Presentation of Materials and Discussion
9:00 pm	Adjourn

"The First Writings of Heart Failure"

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First of all, let me welcome you to the History of Heart Failure Symposium tonight. You see the title, so this talk is going to be from antiquity to today. This is an amazing undertaking and I cannot tell you how excited I am to be doing this. The entire faculty is very excited to participate in this particular meeting. The fact that people are sitting on the tables is very good, because it means people like history and this is a good thing. So please, when you fill out the evaluation, say that it was the best meeting that you have attended in a long time. (Laughter)

Now there is a big problem, because Dr. Young told me that I speak too long. I'm going to try to speak for 25 minutes, which is very difficult for somebody who is a Spanish-speaking person. I am going to try, though.

Now this slide is about me. You don't want to know about me, anyway. There are a few housekeeping items. This is an activity jointly sponsored by Educational Review Systems, Medavera, and the Medical Teaching Foundation. You can see that this will give you two hours of AMA PRA Category 1 credits. Please fill out the evaluation and say that this is the best meeting you attended in your life. (Laughter) We have received educational support from Amgen, Biosite Incorporated, CHF Solutions, Otsuka America Pharmaceuticals and ResMed. I also want to acknowledge the Cleveland Clinic Foundation Division of the Medicine of Humanities. Thank you, James, for that, by the way.

I will tell you the agenda in a few seconds here, but we have dinner being served. Do we have dinner? The first item on the agenda is that you've got to have dinner. Then you are going to have to listen to me, which is a bad idea when you eat.

Now I am going to talk about antiquity. I am going to talk about the first writings of heart failure. So don't ask me any questions, because if I had to answer you, I have no idea what to say. It was done a long time ago. Then we have Kirk Adams speaking, which is a very nice lecture. He is going to talk about good and bad adaptation, the "History of Hypertrophy" and "Muscle to Matrix", which is a very important point today. Then we have my favorite person, Dr. James B. Young, who is my mentor in scholastic medicine. He's going to talk about "Modern Therapies and Interventions". Then, perhaps one of the most wonderful talks -- I've heard the talk and its wonderful. It is by Clyde Yancy, who as you know is a wonderful speaker -- in English. Is that right? (Laughter) He's going to talk about the History of Diversity in Cardiovascular Research. You are going to enjoy this talk very much. Then we have the presentation of materials, and then we all go home or go wherever we go.

Now I don't have too much to disclose. (Shows slide) That's it. Now the other people might have a lot to disclose; I don't have much. But I don't need to disclose anything, because I'm going to talk about antiquity.

Now, before I give my talk, some of you might know this gentleman here called Dr. Charles F. Wooley. He just passed away February 15 or 17, 2008. For people that don't know him, this slide shows what he's done through his life and career. I had the opportunity to know Dr. Wooley in the Ochsner Medical Society and the History of Medicine Society. He was a gentleman. He really liked me, which is unusual. I would like to dedicate this meeting to him. He was invited to come to this meeting. Obviously he is no longer here with us, but he will be here in spirit. He would have agreed to do these things. He wanted to preserve the history of cardiology for a long time.

As you probably know, in the last edition of Hearst, the cardiology book, the first chapter is about history of cardiology. This is the first textbook of cardiology that has a history chapter. Dr. Wooley was one of the authors. So, if you want to read about him, I wrote a paper that is going to be published in the American Journal of Cardiology about my interactions with him. But I would like, as a fellow historian, if you will, to dedicate this meeting to him. I wish he would have been here, but unfortunately he won't be here. (Applause)

The question that you ask yourselves is why are we talking about antiquity? Why do we need to examine these early writings? Well, there is a person that is not here, but is also a part of the Foundation, part of this particular meeting. It is Dr. Arnold Katz, who is in Taiwan visiting his family, so he cannot be here today. He says something that I think is very important and why we need to look at these things.

He said "The clinical practitioners of the past, although they had no understanding, or little understanding of pathophysiology responsible for the signs and symptoms of heart failure were often careful and thoughtful observers." I don't know about you, but nobody observes anything anymore.

You know, Yogi Berra said, "I have to observe --" and there is something about watching and observing. I think it's very important, though. We don't observe anymore. I don't know about you, but I don't hear people telling you symptoms and signs. This is a very important point and one reason why we need to examine these old writings.

I'm going to talk about this disease, called hydropsy, or dropsy for short, which is generalized swelling due to accumulation of excess water. Now, this is a very old picture, however today we are seeing it more because people live longer. We are seeing these patients, maybe not like this, but almost like this.

Now before I move on, I'd like to thank Laura McCaskill and her staff for putting this together. I forgot and I would be remiss if I did not say that. Not that she's going to tell me that I forgot, but I mean, this could not be done unless Laura McCaskill and her staff would do this. So I would like to give applause for her, too. (Applause) Thank you, Laura. Thank you. See, I didn't forget that because it would have been bad.

Okay, so if you don't know anything about history let's talk about ancient Egyptian medicine. People say, "What do you know about heart failure in Egyptian medicine?" I'm going to talk about 3000 BC, so here you go.

One day I was looking at this book and I read this quote. It says, "When you examine the obstruction in the abdomen and you find there is no condition to leap into the Nile" That sentence would describe exercise intolerance. Then the writings say:" And the stomach is swollen, and the chest is asthmatic. You say to him, "The blood got itself fixed and there's no circulate." I don't know about you that sounds like heart failure, right? You have fatigue, you have exercise intolerance, you have asthma in the chest, so rales, and then there is no circulation of the blood. So, as far as I'm concerned, this is the first description of heart failure. Now, you can disagree, but how can we disagree?

But, the important point is that I look at the treatment. You are talking about emptying the system -- you see it here in this slide. They use a medical remedy that has all these ingredients, but also they use beer. Some of you drink beer, right? It is a great diuretic. So here you have the first treatment of this disease called heart failure.

Not only that, if you look at the Ebers papyrus, which is right here -- this is the first book of Cardiology, by the way. They were teaching cardiology to the Egyptian doctors with this book. If you look at some of the quotes in the book -- this is a paper that we wrote in the Journal of Cardiac Failure, by the way -- The next excerpt describes the heart becoming "small inside his belly" and "kneeling down," possibly indicating the failing function of the heart. As a result, the pulse is difficult to detect by the physician.

The next quote says: There's no blood in the circulation, which I think is a very interesting quote. Now the one before was the congestive heart failure, and this is the so-called heart failure with weakening of the heart. The reviewer didn't like it too much, by the way, but we will finally publish it.

This excerpt describes a vessel called "the receiver" (the aorta) as the cause of heart failure since it provides the blood to the heart. The heart then grows in size (hypertrophy) due to the "debility" which then affects blood flow to the rest of the body.

This means there is arcing in between as far as the borders of the lung and the liver, so it's enlarged. Now, you know, we interpret in history. You can imagine these writings were in hieroglyphics, Coptic, German, and English, so I can be completely wrong what I just said. However, I think these perhaps are the first varieties of heart failure, and this is the first book of cardiology.

Now I will move on to the Greeks. We have to talk about Hypocrites. Hypocrites had the first ethical code, which is very important. He also talked about clinical observation, the thing that we don't do anymore today.

Let me show you rales, or crackles. Hippocrates wrote: When the ear is held to the chest and one listens for some time, it may be heard to seethe inside like a boiling of vinegar. This is rales, ladies and gentlemen.

Okay, so dropsy is produced when the patient remains for a long time with impurities -- that would be cytokines (Laughter) and TNF-alpha, interleukin-6, neurohormones, renin angiotensin. Following for a long illness, the flesh is consumed. That's the TNF-alpha, right? Hypocrites then says "And becomes water. The abdomen fills with water. The feet and legs swell, and the shoulders and clavicles melt away. "This is a typical cardiac cachexia, I will say, in heart failure.

Now, this is from my friend Dr. Young, who gave me this slide. But this is the way they treat heart failure, by a surgeon. As you probably know, the surgeons don't have any evidence-based medicine. The slide shows that "…we gather that dropsy was treated in a novel way: Asklepias cuts off the patient's head, holds him up by the heels, lets the water run out, claps on the patient's head again." A typical surgeon, and it was done as an outpatient. (Laughter) It was not charged to the hospital. It was not JCAHO criteria, no HIPPA problems with this. But it was done. People went home with the water that had come out from them.

Now so that's Greek medicine. How about Romans? The Romans didn't do too much. That is my ancestors, the Italians, so. . . They liked to drink, that's for sure. Here are some quotes. This is from Celsus, who was a scholar, but not a physician. Look at these quotes in regards to dyspnea. "When moderate, without any choking, it is called dyspnea. When moderate to severe that the patient cannot breathe without making a noise, it's called asthma. When in addition the patient can hardly draw his breath unless with the neck outstretched, it's called orthopnea. Of these, the first can last a long while. The two following, as a rule, are acute. And bloodletting, emptying, is the best remedy." Now the leach of today is ultra-filtration (Laughter) He goes on to recommend bloodletting. In addition, he writes that you have got to keep the head raised. I mean, this is a very interesting quote. This is heart failure, guys.

Okay, then we have poems about heart failure. I don't want to say this poem, because I don't think I can speak English too well. It is by Horace. "Dire dropsy swells by feeding, and thirst is not quenched until the disease's cause has fled from the veins and watery dullness from the pallid flesh." In heart failure, edema, same thing.

Now, this guy has a big-time name, Aretaeus of Cappadoccia that would be in Italian, or in Latin. Look at this.

"When in an erect position, then (the patients) become swollen in their feet and legs, but when reclining, in the parts they lay upon; and if they change their position, the swelling changes accordingly, and the course of the cold humor (edema) is determined by its weight." Better than any history of physical today, I promise you.

Now, if you talk about Roman medicine, you talk about Galen. Galen was a very interesting guy. He made medicine difficult, although there are many Galen's today, too, I promise. But, you know, he was dogmatic. I mean, I remember my professors, they were all dogmatic. I mean, you know, you say it one way and it was one way.

Now, you can see here the circulation of the blood. The blood was circulating and everybody knew that, Egyptians knew that. On the other hand, you see that the liver was the major point, not the heart, for the circulation itself. The lungs didn't matter either. The blood went from one ventricle to the other without going to the lungs. They believed the liver was the most important part of the circulation.

I'll show you some quotes. "in the heart there must be warmth in plenty, for it both moves itself and the other parts at the same time as with its pulse, and it also warms them . . . The heart must always be on the boil . . . the heat flows from the heart to the members not only through the arteries but also through the veins" and quote "we breathe for regulation of heat. This then is the principal use of breathing which is brought about by both parts of breathing, both in breathing and out; to the one belong cooling and fanning, and to the other evacuation of the smoky vapor."

Now, if you can see here he said "I think the heart was the furnace. It was there to give the vital warmth to the body and it was the heat of the" -- which makes a lot of sense, because when you die, there is no heat. I mean, Galen was correct. Now, Galen did a number of experiments in animals, by the way.

Okay, so I'm doing well. I have five more minutes. Let's talk about the Middle Ages. Now this is a very difficult time in history. It was called the Dark Ages, which I think is ridiculous, if you will, because they were not dark, I promise you. There were a lot of good things going on.

We have the Catholic Church and all the European churches disappear. Everything went to the Iraq/Arabian Sea and this guy we call Avicenna, who was the master of medicine at the time. He wrote a book that if you have the chance to look at, it's very nice. It's called The *Canon of Medicine* and you can see he continued the ideas of Hypocrites and Galen. It was a standard book in many European medical schools in the 17th Century.

He described dyspnea very well. He called it pernicious suffocation. You can see that very similar to Celsus and others he writes "…pernicious suffocation hastens to stop the breathing; when the patient lies down, his breathing is hindered completely, and when is not recumbent his breathing is difficult also. In addition, he himself keeps extending his neck in contriving to breathe. He is restless and wants to stand erect and cannot lie down." So you see this is today, too, right? He's restless and wants to stand erect and cannot lay down."

Now, this is diastolic dysfunction -- no, not really. This is pericardial effusions. He writes "for fluids are very often found between the bulk of the heart and the membrane" (pericardial effusion). He also writes -- and by the way, this is the first description of pericardial effusion causing diastolic dysfunction... "And it is known that when they are abundant they restrain the heart from diastole." So, there is nothing is new under the sun, okay?

Now, I'd like to show you these three people here, that there are no pictures at the time, no photographs, all right? These are paintings. You see Alexius first, then Anna Comnena, and Irene.

This lady, Anna Comnena, wrote a book called The Alexiad. Anna Comnena was the daughter of the king Alexis I, who was the rule of the Byzantine Empire. He had a disease. She wrote this and I will read it to you "He was lately affected by the pressure of daily business and many cares of the government, like in the United States of America. I often heard him telling the Empress about it. In a way, he was accusing the disease. What on Earth is this trouble that affects my breathing?" You hear from a patient that, right? Now mind you that a person writing this is a layperson; it's not a doctor, it's the daughter.

"I want to take a deep, full breath and be rid of this anxiety that troubles me, but however often I try, I can't lift even once a small fraction of the load that oppresses me. For the rest, it's like a dead weight of stone lying on my heart and cutting short my breathing. I can't understand the reason for it, nor why such pain afflicts me."

The doctors now felt the pulse and admitted that they found all kinds of irregularities -- atrial fibrillation -- but they were altogether unable to give a reason for this.

They knew that the Emperor's diet was not rich. It was, indeed, the sort of food athletes and soldiers have. So the question of an accumulation of humours, (again, cytokines) from too rich of a diet were ruled – (I mean, that would be CRP these days --) was ruled out.

They attributed the difficulty in breathing to some other cause and say the main reason for the illness was overwork and constant pressure of worries. His heart, they say, was inflamed and was attracting superfluous matters from the rest of the body -- inflammation. Every day it grew worse, unable to lay down, either side so weak that every breath involved great effort. He was forced to sit upright to breathe at all when his stomach was swollen, enlarged, and his feet, and fever. (Again, cytokines.) "Some doctors with scant regard for the fever, has recourse for cauterization…" which is a form of bloodletting, if you will, at the time.

You can see what she writes here "He was forced to sit upright in order to breathe at all; if by chance he did lie on his back or side, the suffocation was awful: to breathe in or exhale even a tiny stream of air became impossible. 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. As purgatives were not allowed, the doctors tried phlebotomy and made an incision at the elbow, but that also proved fruitless.

He was just as breathless as before and there was a constant danger that he might expire in our arms." Very interesting publication of his – "And then, exhausted and cold, my head bowed, and both hands covering my eyes, when the arteries stopped." This is the first description in the Middle Ages of heart failure, done by a layperson, not a physician, Anna Comnena, about her father.

Okay, I want to leave you with The Renaissance. I'm on time here. The reason I want to say this is because I think it will go along for the next lecture. The Renaissance was a renaissance, obviously, a rebirth of many other theories. But there were two universities, Bologna and Padua that were very important in the rebirth of the understanding of anatomy, heart failure and so on.

The printing press also facilitated the way we knew about these things. And one of the important persons during that time was Andreas Vesalius. Andreas Vesalius is important, because when he did the anatomy in his book called *De Humani Corporis Fabrica*, he showed that there were no holes in the ventricles to get the blood from one side to the other. So he said the pulmonary circulation is the way the blood goes. It goes in the right heart, to the pulmonary artery, and then to the lungs. This is very important. Now, although he was concerned, because, you know, he was going to be destroyed by the Galen theory. But he couldn't find it in his anatomy discoveries. So it's a very important piece of the understanding of the circulation.

And last, but not least, William Harvey. William Harvey was the first one in this book called "*de Motu Cordis* "-- by the way, this was the first book that has the heart in the beginning, on the cover. So Cardiology is as old as 1628. He said that if you apply a ligature, the passage of the blood is from the arteries to the veins.

Then there is a movement of the blood in a circle and it is done by the beat of the heart. The heart, instead of being a furnace, became a pump. This is the beginning of the new understanding of heart failure, because you can put catheters in and measure things.

Harvey was an English physician who married well, by the way, and did all this research. He is the father of the discovery of the circulation of the blood, although people knew that it circulated.

I'd like to show you this to finish up. This is the last slide, I think. But because of Harvey's idea about circulation, Giorgio Baglivi said about heart failure "A dangerous disease…which is called suffocative catarrh…in this kind of catarrh the patient has…pain in the chest, and difficulty in breathing; also interrupted speech, anxiety, cough, stertor, foam at the mouth…the foam at the mouth is caused by impaired circulation of blood about the lungs…" I mean, you know, pulmonary edema -- is caused by impaired circulation about the lungs. You can see the mechanism that is coming up. "This kind of catarrh comes from sudden stagnation of blood in the vicinity of the heart and lungs…an instant remedy of the disease during the paroxysmis repeated bloodletting…the disease is very precipitous; unless that phlebotomy is done immediately the blood coagulates more and stagnates. Thus the opportunity for cure is lost." You know, the mechanisms have changed, obviously, but this is the beginning of the understanding of a new way to talk about heart failure.

The way you treated, and I remember doing that, is phlebotomy. I used to take blood from these people. This is the same thing.

So I think if you don't do this pretty fast, the opportunity for a cure is lost. But you can see, you didn't see this from the Egyptians, now here we have from the mechanisms that Harvey discovered, the new way to treat heart failure. I always say the same -- I mean, the last slide, for the Spanish people, is three more. I don't know. (Laughter) I think I'm going to leave you with this quote from Richard Horton, who is the editor of Lancet. You can read it. "Medicine pays almost exclusive homage to the shock of the new.

We place a constant emphasis on novelty. We trumpet the most recent discoveries and give far too little attention to the concepts underlying our accumulated knowledge. Ours is an era of the instantaneous and immediate fact, a time when traditions are dissolving and the perceived need for a dialogue with the past is all but invisible." I don't have any more time. I thank you for your attention. I think I'm going to move on before Laura tells me to go. So thank you very much for your attention, though. (Applause) So, Kirk will give the second lecture. Thank you very much.

"Good and Bad Adaptation: History of Hypertrophy - Muscle to Matrix"

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I'd like to thank everybody for coming out and I'd like to echo Hector's thanking of Laura. She's shown a tremendous amount of determination to bring this program off. Obviously it would be impossible without the sponsors, and so we really appreciate their contributions as well. Hector and Jim and I have been talking about doing this for several years and it was really quite exciting to me to be able to get a chance to actually share this with you all.

I think we are still a little bit in the stages of developing the best format for this. I think it's very interesting, because you'll really see four very different approaches to the subject. You know, I actually don't have the depth of knowledge of Hector and Jim about medical history, but I definitely have an extreme passion for history. As we all know in our modern world, we lack, I think very frequently, institutional memory. We lack, basically, some of the types of persistence of thought that have helped us so much in our society. I think as we look forward to what we can gain from these sessions, hopefully that is going to be part of it.

I have a lot of disclosures here, but I think I'm not actually going to talk about a single product, which will be a first for me in a lecture for a while.

If you look the definition of history, you can obviously come up with a lot of different ways to define it. I think one of the key aspects that I like to stress is this concept of it really being a story. I think all of us like to tell stories when we lecture, and I think one of the points that I like to emphasize are the ideas.

When we look across the history of any discipline, we find out that we are really talking, in large part, about the history of ideas. So I'm going to focus on kind of adaptation and hypertrophy and changes in the heart and the myocardium. This is a very old story, and I think, hopefully, you will see some of my thoughts about the development of this idea.

Of course, when we think about specific examples in history, they can be used to apply to many concepts. I hope over the course of these lectures that I'm able to explore many different ideas and show you the evolution of those ideas. That obviously has a lot of relevance for thinking about our own research and advancement of knowledge.

I guess we always want to go back to the Greeks and think about their concepts of things. I think when you look at the history of the word "idea," it really started out as an image. I think if you were to think about cognition when people were starting to articulate more and to try to think abstractly, how did that process begin? I think it started with mental images. I am actually short one slide tonight, which is uncharacteristic of me, which is a picture slide, an artistic slide.

I would just really encourage you to think about that concept, that when you look at a painting, it is amazing the different levels of meaning that go on associated with that image in your brain. So really, ideas for the Greeks were images.

You can see now, today, we think of ideas as concepts. So somehow, we form images now of some of our conceptual things that are not necessarily associated with a physical reality, but we form this mental image and we work off these ideas. Obviously there are a great many ideas that drive medicine.

One of the other fun things about giving historical lectures is you can talk about people that used to be very famous when you were significantly younger and, unfortunately, many times are forgotten today. So if I had given this lecture about 20 years ago and I had talked about Thomas Kuhn, I would have basically been almost being trite, because he was so popular at the time. He was a historian of science, and he was very interested in creation of new ideas and transitions in theories. He developed this concept of the paradigm.

Now, again, if we look at the definition of paradigm, we only partially appreciate what he was really trying to get at. What he was really talking about is a collection of ideas, collection of attitudes, generalizations, and experiments that form the basis for a particular theory or position in science. He focused a lot on transitions from one paradigm to the other. Actually, paradigm switch is one of the things that have persisted. He didn't actually use that term, it was actually somebody describing his work.

What we are going to look at, over the course of the next few minutes, are several different paradigms of adaptation in cardiac remodeling and how these changed over time and how they alter our thought.

If we look at paradigms of heart failure, the pathophysiology, we realize that we've been through a number of different concepts of what is important for heart failure. Now, of course we now recognize that all of these aspects are important in the pathophysiology, but if you look over a decade of time, it's usually one that's particularly dominant. We are now thinking about this remodeling, and have been thinking about this for quite a while now, and it's kind of been the dominant paradigm and the way that we've thought, conceptually, about heart failure.

If you look at one of the early kinds of concepts -- and this came out from clinical medicine, as Hector said, from observational medicine -- this transition to hypertrophy and then transitioning from hypertrophy to failure. This was really clinicians observing people, a lot with hypertension, untreated of course at the time, back in the 1700s and 1800s, also people with aortic stenosis who would first develop a hypertrophic response. Then the natural history of this untreated, which fortunately we see pretty rarely today, the natural history is to go from hypertrophy to dilatation. This was really observed, initially, as a clinical phenomenon, and fortunately is not very common today.

One of the people who popularized this notion of hypertrophy leading to failure was Austin Flint. He's famous for the diastolic rumble, the murmur. He also was really one of the major forces in medical education in the late 1800s. He popularized the stethoscope and was really a mentor for many future, important academic positions.

This just gives a little bit about his history. I think one of the things that you'll find characteristic of productive people in scientific research is their tremendous amount of writing. It is really interesting to me because sometimes today, with the computer and the word processor, - I think there's still something about picking up the pencil and jabbing down notes and writing things down. Look at this. We're going to probably not talk about too many of these 16,000 pages.

One of the things that you discover is, most of what famous people write you would have no interest in reading. It is not really very important. What must be important is the process, because they produce -- Newton would stay up at nights and formulate theories about the motions of the moon that were not really very scientific at all. Jim can probably expand on my knowledge on this, but Newton wrote a lot of absolute gibberish about strange religious beliefs. But of course he wrote a lot about physics that turned out to be true. But there's sort of this ceaseless kind of mental activity.

Then I also wonder -- I know there must be a few of these people left around, but I don't think anybody would ever let me put this in my title at UNC, but I love this. He was the first professor of the theory of medicine. (Laughs) So this was back when clinicians were supposed to actually come up with theories about medicine.

Then, of course, you have in the same individual, the linkage between the theory and the practice. So it never would have occurred to them to somehow have one group of people in a really tall building, looking at test tubes but never talking to another group of people who were over in the clinic, taking care of patients. So the concept is that you are a professor, but you are a professor of theory and of practice.

Here's a more modern-day sort of approach to this, where we see these words like hypertrophy come creeping in, and we get muscular growth. He did this from pathology, obviously. Then he talks about dilatation. So we have this hypertrophy and dilatation and this transition where they patient obviously gets in a significant amount of trouble. According to this view, hypertrophy, the more serious form is the dilatation, which we all know generally is more serious than hypertrophy.

This is an example of this hypertrophy as compensation. This is one of Arnie Katz's slides, which I borrowed freely, basically looking at aortic stenosis, and shows you the adaptive changes. We all recognize that frequently people can adapt well to hypertrophy.

One of the first people to study this process experimentally in the lab was actually a Russian. He published a lot of papers in Russian before his work was finally translated into English. Some of his contributions were the creation of an animal model. He did this by banding the aorta to make a chronic model of aortic stenosis. Then he developed this concept of these three stages.

Many of us have seen people in cardiogenic shock, and this is obviously not the same phenomenon that he was observing; he was banding the aorta. But what he observed was that some animals really had very little ability to adapt to this sudden change in hemodynamics, and about 20 percent of them would die without ever leaving, really, the acute stage. Then there was this protracted, and I think he had this concept like we might see aortic stenosis stable for many years, and then finally the protracted stage gives way to this cardiac exhaustion.

I think what he also wanted to do was to try to come up with something about the mechanism of cardiac insufficiency. He did something that I think is still used quite frequently by our basic scientists today. So when they're writing about mechanism, they list every possible thing that they know. You can see here that he has a whole long laundry list of alterations.

What was important about this was that he was taking this to the molecular level. So now we have gone from a physical exam and evidence of hypertrophy. Now we are beginning to actually get into the molecular biology, understanding that DNA, understanding protein production is up, and it is kind of the first real attempt to understand this.

We also made another advance when we were able to distinguish hypertrophy and dilatation. That is dilatation occurring early on in adjustment to the disease. So now we are moving away from hypertrophy, from dilatation only following hypertrophy, to dilatation basically being another adaptation to another type of cardiac load. So now we have the concept of increased diastolic stress leading to ventricular dilatation, versus systolic stress, like an aortic stenosis or hypertension, leading to a hypertrophic response. Now we have the diastolic stress leading to a ventricular dilatation.

This would be the concept of basically looking at aortic stenosis as one form of adaptation, the hypertrophic heart, and now the dilated heart as a second form of adaptation. Hypertrophy coming from increased systolic wall stress and basically the dilated ventricle coming from increase diastolic.

Now we move to these different types of remodeling, one that's predominantly hypertrophic, and one that's predominantly dilatation. Of course we can associate these as different from normal. We can also relate these to cardiomyocyte pathology at the microscopic level. So what we know is that these are basically short, fat myocytes, and these are long, thin myocytes. Now we're able to take it a step further and say that concentric hypertrophy results in a thick LV, which is, in the early stages at least, characterized by myocytes that are broad and short, whereas a dilated aortic insufficiency ventricle dilates and expands, and that is associated with long, thin myocytes. So we are able to move from gross anatomy to microscopic anatomy.

Sometime along the way, somebody comes along and starts looking at things a little bit differently. And I want to just show you some of the writings of Karl Weber and Janicki some years ago, who refocused our attention, basically, on the interstitium.

They are saying -- and they're starting off with a very typical sort of a way that these paradigm shifts occur, where they are saying that, "Look, if you just think about this for a second, you're going to say the heart's a muscle pump." So of course the major element must be the myocyte. And really, this is really where the action is.

Then he goes on to point out that despite the focus, the appropriate focus on the cardiac myocyte and the hypertrophic changes, either dilatation or thickening of the myocyte, that we don't really have -- despite all this good work, we still don't have a complete understanding of the phenomenon.

Then he goes back to say, what you do when you're going to change paradigm, a lot of times you just simply go back, and as Hector was saying, and as Yogi would say, "You can observe a lot by looking." So what you do is you go back and you look at the myocardium again. And low and behold, you find out that myocardium is a much more complicated structure than just cardiac myocytes. So now you have the coronary microcirculation, you have all this interstitial space, which of course is not empty, but it turns out that it is made of protein.

Then it took us, obviously, a long time to understand that the myocardial protein turns over roughly about every 30 days or so. So about every 30 days, you basically create a new heart. So these things are dynamic and this interstitium is dynamic, and the protein in the interstitium is dynamic.

What he is going back to would be an extremely old concept in medicine. So you see he used the word equilibrium. You can see this in Hector's slides about the imbalance and the balance in the body. So he is saying that there has got to be a homeostasis here, there has got to be a normal interaction between these various elements of the myocardium. When we lose that normal interaction with the interstitium, we run the risk of developing problems.

Now, collagen is a lot about this, but of course it turns out that it is very much more complex than just collagen alone. But this is a very key part of the interstitium. Of course, cardiac remodeling involves this kind of reactive fibrosis and reparative fibrosis, and now we are back to the wound. If you want to think about this, when you put stress on the interstitium of the heart, it is like you create a wound, it is like you make a gouge in your foot, and you're going to have reactive changes that occur as a result of that injury. Those reactive changes are a lot like wound healing.

Now we are beginning to get a more complicated picture of remodeling. Eighty-five percent of the myocardium, by weight, is the cardiac myocytes. Obviously, what changes occur in the cardiac myocytes is absolutely of major importance. But also, we have this interstitium, and we have these proteins in the interstitium, and we have cells like monocytes that are outside the cardiac myocyte that are very important.

If you want to get a lot of insight into this, you can read this beautiful review by Frank Spinali, and I am stealing some of his pictures here. Here is the normal -- and now we're going down to the microscopic scale, and we are looking at this beautiful fibular collagen matrix that surrounds. Here we have a pressure-load ventricle, and you can see the grossly abnormal changes that occur in the collagen matrix. So things are not completely well.

This is Chagas chronic cardiomyopathy, and you can see the changes that occur in the interstitial space secondary to this chronic cardiomyopathic state. We have another paradigm shift, of course, in physiology some years ago, when people developed an understanding of receptor coupling. This is from the molecular biology of the cell, from Watson's book. It just makes this very generalized paradigm for how do we get communication between cells and between organ systems in the body? So basically, we've got these myocytes sitting in this stew of collagen and fibroblasts and progenitor cells and endothelial cells and monocytes. We have this stew that these myocytes are sitting in, and these cells get the idea that they can have a role in life, too. So they are pumping out these signaling molecules, which are, of course, bombarding the cardiac myocyte and allowing the interstitium -- interstitial proteins are binding to the surface of the myocytes, so the interstitium is kind of like the barometer, it's like the pressure gauge.

When the pressure goes up, those interstitial proteins start to get stretched, and they start to interact with their fibrocytes, and then they start to make molecules like fibronectin, and then they start pushing these out.

Then that binds to the myocyte and starts changing the inside of the myocyte. This is such a fundamental paradigm of how cells interact and how physiology works, and of course it applies to the heart, as it does to many other organ systems.

We could talk about aldosterone, which was for a long time really the forgotten hormone. I remember some years ago when I was trying to have a career in the basic lab, we would feed rats DOCA, and of course that acts very much aldosterone, and we would produce fibrosis in these normal animals and they would pretty much just sneeze at it. This was part of the problem in the field, because the basic laboratory data didn't really give us that much insight into what aldosterone could be doing in the abnormal heart. Of course, if you unleash aldosterone on a hypertrophic ventricle, you produce a lot of problems. So that was a paradigm shift as well and we finally understood that you can't tell everything from modifying normal animals.

Spinale done a lot of work with metalloproteinases, and these are a group of catalytic enzymes and a system that regulates the interstitium. There is a lot of crosstalk, basically, between the interstitium again and the myocytes. This is an area, obviously, of very active research. This just shows you some of the details of the regulation.

When we go into the molecular biology, we get into these very complicated pathways of these various hormonal systems and these enzymes and proteins. But we are still back to the same fundamental Watson diagram, that these interact with receptors, this triggers activity within the myocyte, and this becomes a very fundamental part of the remodeling process.

I think what we want to recognize is that we start off with observations. As Hector stressed, clinical observations. We take that to gross anatomy, we take that to microscopic anatomy, we develop paradigms of how molecular systems work, and that leads us, obviously, to a better understanding of the process.

When you knock out these regulatory interstitial proteins, you produce a dilated cardiomyopathy. This is in a normal animal, and these are the microscopic changes. But what I really want to focus on here is, notice that you don't change LV mass that much in these animals, despite the fibrosis, because most of the LV mass are myocytes. If we look at the volume here, we don't see nearly as much dilatation in the normal animal, but we have to be very careful, because if these are occurring in an abnormal setting -- and you see the decrease in the ejection fraction is relatively modest.

I think we have to go back to understanding that, clearly a lot of the mileage is going to come from understanding remodeling of cardiac myocytes, but then we want to understand the role that the interstitium plays, and we want to move toward a complete picture of this historical process.

What I would say is that when we study the history of medicine, the history of medical science, and the ideas in medical science, you can see the evolution of this concept of hypertrophy moving into different types -- dilatation, concentric, eccentric -- moving into different concepts of cell types, moving into the interstitium, and clearly the myocytes being a major part. Then if you go back and look at the microscopic anatomy, you can see that the changes invoke the interstitium as well.

Hopefully, if we use these basic lessons of looking at the history, we can have, I hope, a better understanding of discovery by watching how people have worked through questions, worked through the remodeling question, looking first at the gross anatomy, then the myocytes, then thinking about the total picture. That is the evolution of science. I think understanding the history of how these things change can help all of us. Thank you very much. (Applause)

"Modern Therapies and Interventions"

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Kirk, that was nice. I appreciate you setting me up to bring us to the present time. If you haven't managed to note the theme that's in here, it's looking past, really, to set up a soapbox to spring forward. That's what we're trying to do, and that's really where our interests are.

I never really, frankly, enjoyed history very much. I don't know about y'all, but I wasn't that good in school and had to work a little bit. Being on our admissions committee at our medical school today, I sort of give thanks that I went to medical school when I did, because I don't think I'd make it in. But the point about tonight's presentations are, really, how we can break forward with innovative ideas, concepts, and move into the future of health care more than anything.

I am going to talk about the past, stealing from Shakespeare a little bit. I will speak about the past as a prologue to the future, and try to put into a little bit better perspective really what is going on. Of course, when we think of ourselves in the context of clinicians taking care of patients, we always have to root ourselves with what happens between us and the patient.

After all, when we close that door and the patient comes into the room with us and brings a problem and says, "Help me, I don't feel good," or, "Help me. I'm scared because I might die," or, "Help me," because of a certain disease that we want to treat or prevent, we're really there with the knowledge and skills that have been accrued from the entire exposure that we've had to the past. And so the past really is prologue.

This is one of my favorite paintings, which hangs in the Wellcome Library. John Collier painted a century ago, actually, and it's talking of the death sentence. The patient, you can see here, is pale. The physician really is behind that closed door, one-on-one with the patient. The accoutrements of his practice are on the desk. The microscope you can see there, you can see a hemoglobinometer that's there, some of the rudimentary things that we're seeing. This obviously is a very anemic patient. As you carefully scan through what's on the physician's desk, you can see that he likely has some sort of hematologic malignancy, and the tragedy of the diagnosis is coming through.

With respect to heart failure, we deal with much of the same issues. All of you in this room know how we often refer to heart failure as being the cancer of the cardiologist. The prognosis, in fact, is much more dismal than many patients in heart failure. But what does the past tell us about it? What do the definitions of the Greeks, the Romans, the Renaissance clinicians and physicians, and even the more modern clinicians tell us about what heart failure is? I like to get to definitions of heart failure using Frank Netter's drawing. Who here doesn't know who Frank Netter is? I mean, everybody grew up with the Frank Netter montages, the Frank Netter pictures of the milieu of heart failure, the milieu of a variety of disease states, and it's something which gives us, I think, great insight.

You can see here what heart failure is, by my definition, as so elegantly demonstrated by Kirk. Really it's remodeling of the heart. It's not fluid retention, it's not a depressed ejection fraction necessarily, it's remodeling of the heart into a hypertrophied ventricle, a dilated ventricle, and then the heart not performing up to a certain standard. That is the definition of failure. Actually, I hate the term "failure." When you are sitting in that room talking to the patient and you are talking about heart failure, it is a pretty devastating thing for some people to understand.

The etiologies obviously have been quite different. Dilated cardiomyopathy in the first panel and inflammatory cardiomyopathy there, hypertrophic ischemic cardiomyopathies, and producing different clinical syndromes that we all, in our mind, think of, ranging from the typical bloated, congestive patient, to the patient with acute pulmonary edema that might present in the middle of the night to the emergency room, to today's better understanding of heart failure, the asymptomatic individual that we try so hard to one, pick out of the crowd, who is at risk for becoming the patient on the left of the patient in the middle. How do we prevent the progression to the disease?

The concept of heart failure, from the bloated, dropsical patient as Hector demonstrated and I love those pictures from Avicenna's time, because they parallel the pictures that Frank Netter showed -- to the patient with acute pulmonary edema, and they come back around to the historical documentation of what the clinical observations were, the description of the heart failure signs and symptoms. We have seen the fact that nothing under the sun is new, that the disease process was described and well characterized by the Egyptians. You see that the understanding and the anatomic path of physiology and pathology correlates with things like the hypertrophy that was just nicely detailed by Kirk. You look at the circulatory physiology, and you see how we've gained an understanding for the consequences of cardiac failure.

You look at the hemodynamics, and you can relate how pressure and volume overload then translates into the metabolic perturbations that occur to give you perpetuation syndrome, and also, by the way, give us targets for therapies that are indeed "modern," which I sort of shudder at, because think of what's going to happen a decade from now, two decades from now, 50 years from now when they are looking at the stuff that we write about how we treat heart failure and they are laughing at us talking about modern therapies. Then when we are trying to relate that to the biochemistry and biophysics, and particularly, as we drill down deeper, to the molecular biology of the pathophysiology of the heart failure syndrome.

So we see how the concept of heart failure has evolved from the past into the modern times. It has evolved from the clinical observation of a dropsical individual, all swollen up, the Michelin Man, the Pillsbury Doughboy, fluid retention that is problematic, drilling down then to the molecular biology of the hypertensive patient who's at risk for developing concentric or eccentric left ventricular hypertrophy.

By the way, that concept really comes from Arnie Katz, who unfortunately can't be with us tonight. Arnie has really done an incredible job of trying to teach us how to understand the nuances of the development of the heart failure syndrome.

The way I look at it, and when I pick up my favorite book, the Oxford American Dictionary (Laughter) There's a lot of good words in there. Maybe some not so good, but it's entertaining; you can read it sometime. But when you look at failure, it just comments that it's the inability to measure up to certain normal standards. Again, when you're sitting with a patient behind closed doors in a room and you're talking about heart failure, it's not necessarily a death sentence, but it does imply the failure of a variety of dynamics secondary to some sort of injury.

Then again, it comes back to the molecular biodynamic responses that are there, that are creating the heart failure milieu -- sorry that I've used milieu at least three times tonight already -- but the heart failure milieu, which is based on fluid retention and hemodynamic perturbation that we well have characterized and that we understand it leads to congestion, pulmonary edema, the shock syndrome. And again, coming back to the Netter montage, gives you the picture that we all know about and that we all see.

Now the problem, to take it from ancient days into more modern days, the problem is huge, as I alluded to. This data comes from Dan Levy and the Framingham Heart Study. Who doesn't know about the Framingham Heart Trial?

It is an unbelievable database. This information, published about five years ago, demonstrates that during the different eras, at least the modern eras of medicine, defined as 1950 and forward. Arguably we can say that might not necessarily be the modern era of medicine -- but you can see that the survival curves have substantially increased. If you were diagnosed in the 1950s, between 1950 and 1969, with congestive heart failure, your five-year survival was extraordinarily dismal. There has been a step-wise improvement, a step-wise increase with the therapies over time. If you really critically look at the most modern data that's available, the era up until the turn of the century, you can see that for men, in the top part of this slide, the five-year survival rates for all comers with congestive heart failure is only 40 percent. That data really has not changed very much. Women have a little bit of an edge, between 55 and 60 percent five-year survival. But it is pretty dramatic, and I think it is something that the public is finally beginning to understand, finally coming to some awareness about.

Now, the other thing that's interesting from a historical perspective is that it ain't nothing unless it's on TV. There's no question about that. The media drives a tremendous amount of understanding, a tremendous amount of focus, and in fact, a tremendous amount of funding that gives rise to what we do with research into heart failure. One of the things that we haven't talked about yet is how the concept of heart failure gets out of the clinician's office, out of the hospital, out of the outpatient department, and into the public so that you can begin public campaigns against a variety of diseases.

Perhaps, arguably, the best-demonstrated public campaigns have been against HIV/AIDS recently, and certainly campaigns against cancer with early diagnosis of breast cancer, etcetera, are classic examples of taking observations that are important in the clinic and then moving them out into the public to generate awareness, to generate insight, to generate education, and to help us move forward with the partnership with the patient for treatment.

But how did heart failure make its entry? From a historical perspective, I think one of the important things is looking at the history of FDR, a fascinating individual. Sometimes people forget that the cold war was caused by congestive heart failure, an absolutely fascinating thing that I'll explain more about in a minute. FDR had very long-standing hypertension. Back in the 1940s, this was a controversial diagnosis. Everybody remembers the definition of hypertension at that time was a systolic blood pressure of 120, plus the patient's age. Well, that's crazy. That means that a patient who was 80 years old was allowed to have a systolic blood pressure all the way up to 200 millimeters of mercury. Gives you a little bit of insight into how definitions have evolved, changed, how history has set the stage for looking at things a little bit differently.

FDR was seen by a cardiologist -- very early cardiologist, Howard Bruenn, who was in Bethesda, who practiced at the Naval Medical Center. And in 1944, the height of World War II, right before the Alta negotiations, right before he was talking to Stalin and Churchill about the splitting up of Eastern Europe -- as I see some of my friends here from Belgrade nodding -- found FDR to be cyanotic, breathless, with an enlarged heart, blood pressure of 186/108. He diagnosed hypertension, and obviously what he had was hypertensive heart disease, perhaps hypertensive encephalopathy, and certainly had congestive heart failure. As a matter of fact, if you look at the classic picture of Stalin, Roosevelt, and Churchill at Yalta, you can see he is holding a cigar, he is falling asleep. He has sleep apnea and congestive heart failure with swollen feet, a plethoric description, and if you look really carefully at the portrait, you can see the jugular venous distention. Film clips from the era show the head nod that occurs was something with pretty wide-open tricuspid insufficiency.

Well, FDR died on April 12th, 1945 of a cerebral vascular accident. Now, somebody who is walking around with a blood pressure of 200 millimeters of mercury, it's no surprise that he died of that. As beautifully documented by Franz Messerli a while back, everybody was absolutely shocked that the president died of a cerebral vascular accident, and even more shocked that he actually had congestive heart failure.

So a lot of talk about heart failure emerged, a lot of talk about hypertension, and that really was the beginning of the modern era of our understanding of hypertension and heart failure, at least from the public perspective. It is a lesson well learned, because today, as we look at disease processes in the public, particularly in the presidential candidates who are all talking about McCain's melanoma that he had and it was resected -- very public documentation of information in our presidential candidates -- we look at things quite differently.

The second example of the public learning about heart failure comes from Eisenhower. Here we see Eisenhower and his billion-dollar heart attack. The day Ike had his myocardial infarction, the stock market lost $1 billion in value over a four-hour period of time and had to be closed early in the afternoon. There was a dramatic economic impact. What a lot of people don't know, however, is that Eisenhower had an extraordinarily severe ischemic cardiomyopathy with, as you can see here, multiple myocardial infarction. He died an absolutely miserable death of congestive heart failure. He was in bed; he was resuscitated multiple times, and basically was tortured to death because of the heart failure syndrome. As this got out, the public awareness campaigns really evolved to prevention and treatment of this syndrome, and we began to see the coalescence of data, in the '50s and in the '60s, of how best to treat heart failure.

So where did modern therapies come from? I love to show things about William Withering, 1785, the first real writings that were picked up by clinicians. The use of foxglove, and of course one of my favorite drugs today, digitalis preparations, clearly comes of the observations that were made by Withering on ill dropsical patients and the affect of foxglove tea. The commentary about astute clinicians looking at their patients, picking out the patients that respond to drugs, and then designing clinical trials, in the case of William Withering, a simple case series of 150-some-odd cases, it gives you some insight.

We jump, then, to things of the more modern era, and we see the same exact types of things in an iterative process, recapitulating themselves. Just like William Withering back in 1785 watching dropsical patients with congestive heart failure getting better with foxglove tea, we see things such as this, the Amazon pit viper -- I hate snakes. Is there anybody here -- I hate snakes. I mean, I really get all shook up about snakes. I dream about snakes sometimes! (Laughter) All right, I'm glad we're on the same page. So arguably the most venomous snake in the world is *Bothrops jararaca*, the Brazilian pit viper. Whose bite kills, still, some 50,000 individuals in the world today. It kills by three mechanisms. One, a neurotoxin -- patients get paralyzed. Two, a pro-coagulant affect -- the patients start bleeding from their gums and all of their mucus membranes. Then three, the thing that really gets them, is they have sudden vascular collapse, where they faint and their lungs turn white from what turns out to be Bradykinin release. In fact, a very smart herpetologist by the name of Sergio Ferreira took the venom, back in the '60s, and synthesized the elements that turned out to be the neurotoxin, turned out to be the pro-coagulant, and turned out to be the "Bradykinin potentiating factor," which caused the hypertension and the white lung syndrome. BPF turned out to be nothing other than the eight amino-acid sequence, which is now captopril, which is the first ACE inhibitor used to treat congestive heart failure.

The story of historical observation and iteration, I think is one that we see over and over again. Then of course, we see fascinating observation by individuals like Finn Waagstein back in the 1970s, taking patients with acute pulmonary edema and giving them heretical treatment beta-blockers and demonstrating rather substantial impact with beta-blockers. For those of you that were in medical school or training back in the 1970s -- way before I trained, I tell you (Laughter) -- this was a radical intervention. Why did they do it? Well, it was simple. There was a lot of thyrotoxicosis going on at that time, Inderal, the first beta-blocker was available, there were some very brave people that gave Inderal intravenously to people who were tachycardic in a hypermetabolic state with thyrotoxicosis, and demonstrated resolution of acute pulmonary edema and the high-output heart failure that is so much a component of the thyrotoxicosis syndrome, which fortunately we see so rarely today.

Waagstein and a few other smart individuals said, "Hey, why not try this therapeutic tactic in the individuals with pulmonary edema and acutely decompensated congestive heart failure?" Now we know where beta-blocker therapy is in heart failure. I don't need to go through that in much more detail.

There were other dramas that occurred. This slide shows the transplant drama, here, looking at patients cachectic with horrible congestive heart failure and demonstrating the unbelievable impact. This particular picture here, just a year later, an individual that successfully underwent cardiac transplantation, again demonstrating the benefits, 20-some-odd years later again, demonstrating the outcomes that we can expect now in individuals with advanced diseases.

So really what was the modern evolution? Well, it's a complicated intertwining of observations that really was rooted in just that -- sitting with the patient behind the closed door in the clinic and trying to take observations and interventions that had been developed in the past and applying them to therapies. So you can see how there was -- and I'm not going to go through this in detail -- see how there was the development of the vasodilator hypothesis, a tremendous amount of radical drugs that were used, leading to common things that we felt were important. You can see the neurohormonal and neurohumoral process appearing with utilization of drugs that ultimately modulated the neurohumoral systems. Again, an alphabet soup of evidence is based in clinical trials.

You can also see some very important things emerging. That is, in evidenced-based medicine today, when you design a clinical trial that has a bona fide hypothesis, where there really is equipoise and we don't know what the results are going to be, we do see negative trials, we do see negative results.

I have to admit, one of my pet peeves is when a negative trial rolls in, the media jumps all over it and says, "Well, you know, who was watching the store? How could you be so stupid? Why did you design a trial like this that comes out with something that might actually harm somebody? The point being, well we didn't know that. The point being that you've got to move science forward. You've got to move clinical reality with hardcore evidence. You will see some classic observations that result in negative studies here.

I saw Jerry Griffin in the back room remembering when the CAST trial emerged. Everybody thought it was unethical to do that because we all knew suppressing PVCs after a myocardial infarction in patients with heart failure saved lives. When we gave anti-arrhythmic drugs we actually killed the patients.

So as we move forward then, the other thing that has occurred is a tremendous innovative spirit. Drugs don't do enough. I showed you that despite best therapies there still is about a 50 percent five-year mortality rate in symptomatic congestive heart failure patients. Turning to devices, cardiac resynchronization devices, ventricular-assist devices, total artificial hearts and CRT produced some very successful trials and now they're a part of our core armamentarium with the future perhaps being pharmacogenetics of picking patients out in whom we can prevent the development of heart failure, and the development of ventricular hypertrophy, the development of clinical deterioration.

Now let me go back and look again at some historical developments of some fascinating things that give us insight into the hard work, the tremendous energy that it takes to uncover things. I don't think many realize that George Palade should be credited as the father of cell biology. He was at the Rockefeller Institute back in the 1950's. He was interested in the electron microscopy to dissect out the subcellular components of a variety of cells. If you look at his studies on the heart, he uncovered something called Palades bodies which were first reported in the early 1960's were these granular secretory bodies spread out in the heart in his observations primarily in the atrium. Well it took a heck of a long time to figure out that those secretory nodules, those secretory bodies were produced in response to that dilatation that was commented on a minute ago in terms of hypertrophy of the heart and the production of natriuretic peptides which would ultimately cause peripheral vasodilation, natriuresis, diuresis and other beneficial effects including an anti-hypertrophy effect that then led to the development of atrial natriuretic peptides as therapeutic interventions, B-type natriuretic peptides as therapeutic interventions and even set the stage for futuristic therapies such as urodilatin and other natriuretic peptides that are coming to fore. Again the link, the historical link, going back to Palade's original observations and even springing on the other historical observations of hypertrophy. We see that over and over and over again with new therapeutics coming out. How do we manage volume overload? How do we manage fluid retention? How do we manage the difficult problem of cardiorenal syndrome, and new drugs such as AVP blocking and manipulating agents coming out? We are seeing clinical trials with Tolvaptan as one particular example of a new agent that can give us therapeutic benefits that are in troublesome patients with fluid retention when we use drugs that just don't help us anymore.

I mentioned the fact that FDR had sleep apnea; he did. He clearly had sleep apnea, nodding off at the Yalta conferences. I think that's why he gave away Eastern Europe. I don't know. He fell asleep. But sleep apnea in heart failure has recently been recognized as another syndrome of extraordinary importance that we can go after. Who would have thought 10 years ago or even 5 years ago that sleep apnea would have been something that is a trick of the trade?

I'm a little reluctant to tell everybody what the tricks of heart failure cardiologists are because if you know you won't send your patients anymore. So the patients come in and they fail standard therapies. What do we do? We look for somebody that can respond to CRT. We look for somebody that can respond to new diuretics. We look for somebody that has sleep apnea and we can use CPAP respiratory devices and monitor them and see some bona fide improvement.

This just particularly points out one study which shows improvement in ejection fraction in individuals who are treated with positive pressure airway breathing devices and the fact that we have a whole variety of new devices that are coming out to be able to monitor that and new guidelines. Again, who would have thought that we as cardiologists would be looking at a pulmonary difficulty like sleep apnea? Who would have thought that we would have been using hormonal measurements to mark, diagnose, quantify the severity of heart failure 10 years ago and now such a common thing that we do with pro-BNP, BNP measurements and even use that as therapy?

Ultrafiltration, is another -- who would have thought that we would have become nephrologists? So the cardiologist is not only pretty damn good general practitioner but a cardiologist is a pulmonologist with sleep apnea, and now we're shoving away our renal colleagues, "Get out of the way." How many of you have trouble calling a nephrologist in the middle of the night to the ICU to suck out some fluid in a patient who isn't hyperkalemic and azotemic and in a coma due to renal insufficiency? So we are learning a lot about how to manage heart failure syndromes with other more radical ways, and ultrafiltration is another example of that. Of course one of my passions, mechanical circulatory support devices, it's the 50th anniversary of the first successful implantation by Willem Kolff at the Cleveland Clinic of a total artificial heart in a dog. Now people might laugh at that and say, "Look how far we've come." Not too far. But at least if you do check out the history of mechanical circulatory support we have made tremendous progress. We have come from the days in the 1960's of the very first successful LVAD patient. This patient here was treated by Mike DeBakey in Houston. You can see the paracliporial device which exited the chest. It's dangling down the front of this woman's chest. The inflow cannula by the way is in her right axillary artery. The patient had rheumatic heart disease, mitral aortic insufficiency, couldn't come off the pump after an attempt at bivalve replacement, was dead basically, had the LVAD device put in, was weaned from cardiopulmonary bypass, was in the ICU for 48 hours, woke up, pumped for five days, had the device removed, and we'll talk about when women were women and men were men under local anesthesia at the bedside with the arterial repair being done under lidocaine and the device explanted with just clamping off the inflow cannula. She did well, lived for five years. Actually what's peaked my interest in mechanical circulatory support was I actually saw this patient down the road when I was a medical school student. She ultimately was killed crossing the street in Mexico City which again places things in perspective about the morbidity and mortality of these things. But many things are happening, lots of circulatory devices are coming on board including some really creative things, Orqis or the CANCION system here just one example of creative devices that are in clinical trials that are rooted in this historic evolution. Of course there was a landmark FDA decision about three weeks ago when they approved the HeartMate II device, the first non-pulsatile, continuous flow, left ventricular system that we can now use as a bridge to cardiac transplantation.

Other things that really excite me in terms of moving in this historical timeline, this constant yin and yang, this push to innovation, things like cell therapies. Perhaps just around the corner as Norm Shumway used to say about xenotransplantation, around the corner and it will always be around the corner. I'm not sure I believe that. I do think cells are going to be real. I'm not sure I'll see it in my professional career, however. But I do believe that these are going to be therapeutic agents.

To conclude, where are we going based on this historic information? Well, we are going to be going into the history. One of the things I think we constantly need to do is innovate and think of new ways to do things, new changes that can occur, both simple modifications of what is already out there as well as innovative new arenas. I think one of the most important things is to clarify the pathophysiology of heart failure, particularly as we relate it to the pharmacogenomics and tailored therapy issues. One of the things that bugs the heck out of me is that in heart failure we give ACE inhibitors, beta blockers, whatever to 100 patients with congestive heart failure and it benefits maybe 20, maybe 40, arguably as many as 50 patients out of that 100.

It doesn't dramatically affect the vast majority of patients. Yes, it does do wonders in many situations. You take a patient with pneumococcal pneumonia who presents with an infiltrate. You culture that. You identify the Pneumococci. You do platings. You do sensitivity testings. You identify the fact that you have an antibiotic that the bacteria is sensitive to. You give the antibiotic to the patient. What's the cure rate of pneumococcal pneumonia in a sensitive patient to penicillin or amoxicillin? It's 100 percent. Why can't we identify in the heart failure patient the heart failure combination of drugs that is going to be tailored to the pharmacogenomics of that individual so that we pick out the medications and treat them?

We do have a long way that we can go I think. There are many exciting things on the horizon and I think that putting what we are doing today in historic context, both the public, and the media as well as the scientific history that underlies things is absolutely critical and maintaining an innovative spirit and, if you will, preserving the passion of treating these patients with new approaches. Thank you. Here is Clyde Yancy to talk about another fascinating subject. Thanks.
(Applause)

"History of Diversity in Cardiovascular Research"

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Good evening. How are you? I want to thank you for being here. When this idea first came to mind I wasn't quite sure where we were going with it. I am not a student of history. My own personal history would make me feel fairly repulsed by most history to be frank, and I am much more of the mindset of being engaged with the present. But after understanding the passion that my good friends have for this topic I thought I should be a part of this. So how is it that what I plan to discuss has anything to do with heart failure? Heart failure unfortunately is not an equal opportunity illness. There are too many patients with heart failure who seemingly because of their gender or their age or their race have outcomes that are not the same as they should be. So as I was thinking about the context in which I would present the information this evening and was sitting at the back table about an hour and a half ago reviewing my slides, I had the most incredible experience happen. The gentleman that works with Laura came in and said, "Dr. Yancy, there's a woman here who'd like to say hello to you." I thought, this is my lucky night. This is just great. (Laughter)

So I look up and it's a schoolmate with whom I graduated from high school in 1975 and hadn't seen her since, 33 years ago. She was walking through the lobby of this hotel to meet her husband so they could go home and saw my name on a sign and said, "I wonder if . . ." and she comes in and it's Michelle Rodian. We went to grade school together. We hated each other actually. (Laughter)

We went to grade school together. My mind has been clicking ever since because history is just a collection of sterile facts until you have a context. Michelle actually helped me establish my context. My context for this is not only to discuss the history of diversity in medicine but to do something that I haven't done in a public audience, gosh, in a long time. Jim Young has known me since I took my first faculty appointment maybe 17, 18 years and he has been my sounding board, my mentor. I'm going to tell you some things that I haven't even shared with Jim.

I grew up in a violently segregated environment, and we had to be very careful growing up. Until I was in college I really never had an experience with the other side, so to speak. They were on television, but I never went to school with them, I never went to church with them, I didn't get a chance to compete against them athletically, I didn't get a chance to play against them with my instrument. It was a totally segregated world. I drank from the fountains that said those were where I should drink. I went to the balcony to watch movies. So that's my indoctrination. When I decided I wanted to be a physician I went to college. Even though I went to a majority minority school I was told it was a long shot at best that I could go to medical school. So during one of my summers in college I went to Tennessee and studied biochemistry with a medical school professor who happened to be white.

We had a very good rapport, but when I told him I not only wanted to go to medical school but I wanted to go to Tulane he said, "You'll never get in. Forget about it." So I went back that fall and took the MCAT at the age of 19 and got early admission. I go to Tulane and I get in, and the first week I want to find out what happens to people who come here that are early-entrance admits and I was told they all flunk out.

So I didn't flunk out. I then decided I wanted to study biochemistry and maybe even get some basic research experience. I went to my favorite biochemistry professor and he said, "No, basic research is not for you." So that opportunity was closed. I kept wondering when am I ever going to find somebody that would be positive, that would be a mentor?

I hadn't met Jim yet. I finally get to residency internship and I'm a fellow in cardiology and it's time to pick a lab so we can do our research experiments. This is 1987, and I've given you a perspective of my history. The only laboratory assignment that was left was either, one, working in a dog lab and tying off LADs all day long and that didn't appeal to me much or, two, working in a human physiology lab with a South African physician. I thought I'm totally hosed. There was just no way that I will ever be a cardiologist. (Laughter)

I finally found a mentor from the most unlikely of all sources, and he taught me how to write, how to do clinical research, how to do a right heart catheterization, how to do clinical trials. His name is Brian Firth. He works for a major pharmaceutical firm now. But I finally found a mentor, and finding a mentor makes a lot of difference. So when Laura and I sat down a few months ago and she invited me to be a part of this and I knew I didn't have exactly the same passion for history as all of my good friends, I knew that I did have a curiosity about who are the people that could have been mentors? Who are the people that could have been an inspiration? Who are the people that could have convinced me that I can do what I do now?

Who are the people that are looking for someone to inspire them to do some of the things that we try to do? So that encouraged us to think about who those people are. There is a history, and I'm going to try to share that history with you.

None of these disclosures make a whit of difference to what I'm about to tell you. So let's look at this timeline. This timeline starts at the end of the 19th century. And the first prominent African-American physician we can identify is perhaps the most prominent physician and that's Daniel Williams. Now I'll tell you more about him as time goes on, but the timeline starts at 1889. You can see that he is credited with doing the first open heart surgery successfully. An African-American physician is credited with that. He started the first nursing school for African-Americans. If you move further there's another name that enters this cascade and it's Vivian Thomas.

The story about Vivian Thomas is nothing short of extraordinary. Concurrent with that is another figure of interest -- Charles Drew. The reason that we have blood banks now is because of Charles Drew. And then there's Levi Watkins and then there's Daniel Savage. If any of us in this room respect the deleterious consequences of having left ventricular hypertrophy we should thank Dan Savage because he is the person responsible for that observation. So when we put this together, we realized that African-American physicians have been deeply involved in the history of cardiovascular medicine.

Let's start with Daniel Hale Williams who was born before the Civil War, 1856, and died in 1931 and was born in Pennsylvania. Like the situation was for most African-Americans born in the 19th century, and early 20th century, the only way you could get a quality education was to either be born in the north or go to the north. He was educated ironically here in Chicago at Chicago Medical College which we now know is the Feinberg School of Medicine. He was the first African-American appointed to the Illinois State Board of Health. He was chief surgeon at Freedmen's Hospital and you can see he started his first nursing school and established a first professorship for clinical surgery at Meharry Medical College.

Now if we follow the trajectory, here is where he became really important. In 1893, a patient presented with a stab wound to the chest. It turns out this patient had tamponade, and it was Dr. Williams who had either the wherewithal intellectually or the guts emotionally to try to fix this and was able to suture the pericardium. Not only did the patient live through the exercise for five days in the hospital but lived another 50 years. Now he also did some other surgical issues, but this truly is a first documented successful cardiovascular surgery done by someone of color.

One of the issues at that point in time was how do you overcome the risk of infection? He was able to understand that it was necessary to practice sterile technique in order to make the surgery work. He went on to found the National Medical Association and was the first vice president of that. This is not that unusual for this point in time, but there was a strong, prevailing, perverse logic that the physiology of black individuals was overtly different from non-black individuals. He discovered that such was not the case, that black women had ovarian cysts just as frequently and just as often as white women. One of the things that are important here is that apart from anything that was racially directed, he gained entry into the American College of Surgeons in 1913 and several schools bear his name-ship, so I believe that he had significant contributions, and he's responsible for the phrase "code blue." He coined that phrase because of cyanotic children that came under his care. So whenever we say "code blue" it was a physician of color who innovated that name.

Here are the last pictures of Dr. Drew. Now we are talking about someone different now who is considered to be the father of the American Red Cross. He was born in Washington D.C. and was educated at Amherst College.

Now I have two daughters of college age; one is in college and one that's thinking about college, and I know for a fact that Amherst has an admission threshold that's even higher than Harvard, so one automatically respects Dr. Drew for the accomplishments that he made. He had his original appointment at Montreal General Hospital, again, not unusual for an African-American to have to leave this country to forward their career, residencies at Columbia and Howard University and several appointments at Howard University as you see here and one of the early directors of the American Red Cross and helped to really refine that.

One of the things that is so disheartening, is that this is the father of the blood bank. When we order blood, we can attribute the success of blood banking to Dr. Drew. When he was in World War II it was unacceptable to use African-American blood to resuscitate someone injured in the field. He had the courage to walk away and say, "This is not right." That is one of the early examples of someone exercising a silent protest in the face of injustice.

He was the first African-American to service and examine on the American Board of Surgery. The United States Post Office honored him, and a university is named for him and has established a cardiology fellowship.

I've taken you through Daniel Williams who was the first person to successfully perform cardiac surgery, race irrespective, and I've taken you through Charles Drew who established blood banking in this country. I don't know that this is corroborated, but the real tragedy of Dr. Drew's life, because it was a truncated life, is that he had a traumatic death, and part of his death was the reluctance of the physicians caring for him to give him a blood transfusion even though he was the father of blood banking.

What about Vivien Theodore Thomas? Tonight in the audience we have a few people who have a connection with Dr. Thomas and so they may be able to speak up and share even more perspective. But this truly is a giant in American medicine. He was born in my home state, Louisiana, and went on to Tennessee to get his high school degree. Now do you notice something? There's nothing about a college degree. There's nothing about going to medical school. He was a lab tech, and he worked in the lab of Dr. Alfred Blalock who was a partner with Dr. Helen Taussig. He followed Dr. Blalock from Vanderbilt to Johns Hopkins. As his notoriety and his fame grew he eventually was recognized in an honorary way for his notoriety. What is it that constitutes the significance of his life and his contributions? Well he literally solved the problem of cyanotic heart disease in the setting of Tetralogy of Fallot. He is a person who conceptualized the Blalock-Taussig shunt and invented the clamp that allowed for sufficient occlusion of the pulmonary arteries so that the anastomosis between the subclavian artery and the pulmonary artery could be done successfully. This lab tech trained chiefs of surgery in other major institutions. Now there are any number of things that have been written about his prowess, about his intellect, about his demeanor. Here are some of the things that I can share with you that have been discussed. This was published just about five years ago and it says that Thomas' essential contribution is to the development of the Blalock-Taussig shunt remain obscured by the stature of Alfred Blalock and Helen Taussig. This oversight should be corrected, and I couldn't agree more. For those of you that may not be exactly in line with what we are discussing, let me just remind you of the problem with Tetralogy of Fallot.

The problem with Tetralogy of Fallot was an acronym that we were taught in medical school, sophomore, SOPH, so a septal defect, an overriding aorta, pulmonary hypertension with pulmonary stenosis and right ventricular hypertrophy. He conceptualized that the way to go from this defective part and to get at least normal physiology was to construct this conduit so that there could be oxygenated blood delivered into the systemic circulation. Now as a result of this he ultimately became recognized for his novelty, his innovativeness. You see a list of awards here in his name including the Young Investigator Award from the Council in Cardiovascular Surgery and Anesthesiology. You see the Congressional Black Caucus has recognized a Vivien Thomas Scholarship Fund. You can see that the Johns Hopkins School of Medicine in 2004 established a fund for diversity in his name, and at least one college at that university is named after honorary Dr. Thomas. But I think this quote really captures the heft and the importance of who he was and what he did and it's from Dr. Denton Cooley. "Even if you've never seen surgery before, you can do it because Vivien made it look so simple. There was not a false move, not a wasted motion when he operated." And even Dr. Blalock, his lab supervisor, upon examining the suture line during an atrial septectomy, and Thomas developed that procedure as well, "Vivien, this looks like something the Lord made," truly a gifted individual. Dr. Vincent Gott, "Mr. Thomas was almost legendary among cardiac surgeons. It is safe to say there is not a cardiac surgeon over 40 who doesn't know of him and his tremendous contributions to the specialty." And Dr. J. Alex Haller said, "Dr. Blalock once said that Vivien Thomas' hands were more important to him in the development of the blue baby operation than his own" and he meant it.

What else do we know about him? Remarkably in the same situation as many African-Americans were at this time, he was penniless and had no opportunities. His family lost everything during the stock market crash of 1929, something that was not specific to African-Americans, many people did. But the way that he made extra money, and I have to use the vernacular, "check this out," the way he made extra money was to bartend at Dr. Blalock's parties, this man who invented this procedure bartended so he could make extra money.

Let me go to someone a bit more contemporary, another life cut short, and that's Daniel Douglas Savage. Again, this gentleman has a significant footprint in American medicine because he really is the father of left ventricular hypertrophy, and he did so by working through the Framingham Heart Study and identifying that it was LVH that was so problematic regarding the risk of developing cardiovascular disease. One of his early collaborators was Dan Levy. If you've ever spoken to Dan as I have, Dan will quickly credit Dr. Savage as really being the father of the science behind left ventricular hypertrophy. The same scenario, again, someone born in the south but educated in the north for obvious reasons. He went to the University of Wisconsin and had an excellent matriculation all the way through to his MD degree and ended up with an appointment with the National Center for Health Statistics. He again was the sole proprietor and director of the Minority Framingham Report. In 1987 he established the premise of left ventricular hypertrophy. It was a bad thing. Then in 1974 he founded the Association of Black Cardiologists, an organization to which I belong. In 1990, the Association of Black Cardiologists established the Dan Savage Award. I had the humble privilege of being awarded that prize in 2005.

Here are some notable quotes about him. He has been described by his colleagues as a man of ideas, an innovator and a scientist who fervently served his community. I especially embrace his challenge to students and his challenge is thusly -- to set your standards high, sacrifice to achieve your goal, and don't stop until you've done your best, certainly an edict that should go forward even in contemporary medicine.

So one of the only real reasons I think you look at history is because it gives you a perspective of where we are. So if you look at this history of these physicians or people who should have been physicians who made significant contributions and recognized the barriers that prevented them from attaining professional recognition for what they've done, you'd like to think that we're in a better circumstance now. Well is that true?

We are dealing with yet another healthcare crisis. And a healthcare crisis is healthcare disparities. But we have to think about what we mean when we say disparities versus differences. This is lifted directly from the Institute of Medicine report, and it is a fact that there are differences in healthcare outcomes based on race, non-minority versus minority; however, some of those differences are appropriate because procedures may not be indicated, therapies may not be indicated, and patients have a choice. But there is this disturbing group of reasons why these differences exist that are best explained as a disparity because they are based on non-objective issues. They are based on the arbitrariness of our decision making which reflects our biases, our prejudice and our stereotypes.

Very quickly, a number of reports now have demonstrated that no matter what the metric is, there is consistent evidence that persons of color receive less appropriate care even in contemporary medicine.
So we're no longer talking about the 19th century or the early 20th century. I think this is the best example we can give you. Here are African-Americans. Here are Caucasians: Breast screening -- a major difference, eye exams for glaucoma and cataracts -- a major difference, the use of beta blockers in post-MI LV dysfunction you can see here, a major difference, even routine follow-up -- a major difference, so clearly these issues persist.

Now when one tries to think about why this is happening, we have to start to embrace some very disturbing concepts, the very sorts of things that I dealt with as a young adult and then all of the biographies I've shared with you dealt with throughout their lifetimes and may have even been responsible for their premature death. Why do we have disparate healthcare? Perhaps because of economic issues, perhaps because of infrastructure issues, perhaps because of cultural ignorance, and admittedly there are some patient-level issues that have to do with awareness, which have to do with some inherent biological differences, but we clearly are not where we should be.

Several of you have seen me share this with audiences before, but I think it paints a great picture, and it's best to think about this figure from your right to your left. Consider the blue stars as excellent care, the black stars as poor care. Look at the patient physician interface. This interface is a critical juncture because there is incorporation not only of data from the history but objective data as well, but it has modified our process by our ability to interpret this and we interpret it in the context of our social, economic and cultural persuasions. When we are in synch with the person with whom we are visiting, our interpretations incline us to do the most appropriate interventions and make the best decisions. When we are not in synch and that absence of being in synch is guided by our stereotypes, then we end up making faulty decisions.

It doesn't mean that any of us are inherently bad people but that all of us bring to the table our own biases. How could that be? How could well-meaning people practice medicine in such an arbitrary way? Well, again, there are these four big buckets that are, if you will, subliminal, that are subconscious but they're very real and they include bias, stereotyping and uncertainty. But there is a solution. The solution is cultural competency. That is if we take governmental policies, employ best practices, exercise tolerant behavior, have open-minded attitudes and have appropriate infrastructure to deliver care that is culturally sensitive we should be able to overcome this. It is pretty evident that if we want to improve circumstances then we really want to optimize a patient-provided communication regardless of who the patient and provider are. We obviously want to achieve mutual respect in shared decision making. If we are persuaded by costs, if we are impacted by inequalities, then there will be a decrement in the quality of care. This is why we should be aware of our history because just knowing the history and knowing what we should do is not enough. We really must apply the knowledge appropriately. Willing is not enough. We really must do it. If we are to be students of history then we need to learn from history and be certain that we don't leave people by the wayside and that we allow excellence and talent to spring forth no matter what the source is and that we not duplicate these areas in our care of patients who have heart disease but that we really practice open-minded, culturally-sensitive medicine. Thank you very much. (Applause)

Presentation of Materials and Discussion

Hector Ventura: Now if you have any questions, not for me, for everybody else I hope, please do ask. I know that I want to talk about what Clyde just said, but I had the opportunity to go to Johns Hopkins and I met Vincent Gott who was the Chairman of Surgery at Hopkins for a long time, and I asked the very same question about Vivien Thomas. I don't know if you watch HBO, but there was a movie about Vivien Thomas.

I think we came a long way though; however, in some ways we know the area but we have come a long way. I wish I could have the command of the English like Clyde has. But look out because Clyde is going to be it; I promise you. That's what I said in my state, Louisiana. I'm in Louisiana too. I think you've got to look out because Clyde is in a leadership position that I don't think could have happened back when Vivien Thomas was alive. I do believe in some ways we have come a long way. I've seen the picture of the operation of the blue baby, and one of the people behind Dr. Blalock was Vivien Thomas. He didn't know what to do. Now then next year we talk about Hispanics which is the other story, right? That would be my kind of people. (Applause)

Hector Ventura: But I don't think there were any Hispanics before me. I don't think so. I'm sure there are plenty though. The people that you hurt have a passion for this. I think Clyde's lecture is -- what's that? Oh, there is a question. I hope it's not for me. Oh, this is for you, Clyde. See, I cannot answer any science. I apologize. I have no science; I'm history.

So the question reads, "Why is heart failure more prevalent in African-American women, anything to do with salt retention? Is there a gene that might have been modified? Well I don't know if somebody can answer this. I don't think it is more prevalent. I mean, salt is not a good thing, especially in Mississippi and Louisiana, I promise you. I had a patient once who told me, "I don't eat with salt, but I eat crawfish." Yeah, salt is not a good thing for the heart; in some people it's not. So now it's more prevalent in African-American women, yeah it is more prevalent. I think some of it is risk factors are more prevalent in African-American women I think diet makes a lot of difference. I don't think it has to do with culture, but diet -- you know, I'm always very amazed that the Essence Festival is sponsored by McDonald's and Coca Cola. There's a lot of food that has a lot of fat in it. I think one of the things that is clear is that the environment has changed. Now whether the environment has anything to do with it to with modifying the disease is a really good question for one reason: I always ask myself like Emeril Lagasse, "How old is heart failure? Has it been there from the beginning of time?" The renin angiotensin system and sympathetic nervous systems are there from the beginning of time. When the hunters and gatherers were going and trying to get food they bled and they had to have a lot of renin angiotensin and sympathetic nervous system activity to survive. But I don't know if they had heart failure because they died too young, so I have no idea. But I always ask myself, this retention of sodium in compensatory mechanisms happens to you every time you jog or run and every time you bleed. So maybe it is old. I have no idea. But I'm sure Jim can answer these better too by the way. Are there any other questions? I think this program is one of the best programs that I ever attended. (Applause)

Question: Are we designing medicines in the basic lab that are translating or is it really still sort of this accidental discovery?

Hector Ventura: No, if you're talking about serendipity. Beta blockers and ACE inhibitors have been designed. That was by design; it was not by chance. This is my own opinion and I don't want to speak for Jim or Kirk or Clyde, but if you are talking about digoxin for heart failure was serendipity, but Captopril and beta blockers, Inderal, were all by design. It was done by design, not by chance. Now some drugs are developed by chance. Obviously Viagra was created to treat coronary artery disease and you know what happened to it. (Laughter)

Kirkwood Adams: Now the only comment I wanted to make is that a lot of advances that occur happen because of what is sometimes referred to as lateral thinking, so basically somebody's investigating snake venom and then it suddenly occurs to them that this might have a medical application. Now what happens usually is there are a lot of people that learn about what snake venom does, but then there are only a few people who do the lateral thinking and say, "Maybe this might have physiologic impact." The other thing that you mentioned was how we get new drugs, and there definitely are people who are doing what we call designer peptides, and I'll just acknowledge one of those people as John Burnett at the Mayo Clinic. So what he has done is he has taken the properties of different natriuretic peptides and combined some of those in one molecule. I think to the extent where things are known that they might be beneficial, I think we are at the level now where we could see designer drugs taking advantage of known knowledge and combining properties in a designer drug fashion. So there is always going to be serendipity in medicine. There is always going to be serendipity in the basic lab. If you talk to people in the basic lab who really work there very long, some of the most fundamental breakthroughs have come from mistakes and experiments. Now what can they do that is very difficult for us to do in the clinical world is they can replicate that mistake and reconfirm that discovery.

But you see that is their fundamental attention to the scientific method, so they accept serendipity as a part of scientific discovery. They don't want to assume that it comes from brilliance. Like most things useful in life it comes from a tremendous amount of hard work and a consistent methodology and attention to detail.

Hector Ventura: Okay, so now we need to conclude. If you want to stay for an hour more that's fine, but we don't have anymore wine so I don't know if you want to stay. (Laughter)

Hector Ventura: Let me say a few things: First of all, thank you very much for coming here. I know that all of us have a passion for this. Even we got Clyde to talk about history, which is unusual. He said, "I always look at the past" but now he knows why. The other thing is we have in the slide show some more slides that we haven't mentioned for Dr. Katz. There are some about drug discovery that you asked about, sir. So you might look at that yourself. We wanted to do this for a long time, and this is amazing that you came first of all and second of all that you stayed. Hopefully we will continue to do this. We also thank the companies who help us to do this in a wonderful place. Again to Laura and the staff, thank you very much for everything and everybody else, thank you for coming. Good night.