[MUSIC PLAYING]

ROBERT ANDERSON: So I'm sure that you all call the series of lesions that we did, we are going to be talking, you call them heterotaxy. And it's amazing to me that many people use words with no knowledge of what they really mean. I've done it myself over the years.

So what is heterotaxy? There is a nice definition given by Dr. Kim, who wrote this nice review in the current circulation journal. And it comes from the Greek. There are probably some of you here who know it from in its original form. And it is anything other than the usual or the normal arrangement.

And that immediately gives us a problem, because if we take the word "heterotaxy" literally, then individuals that have a mirror-image arrangement-- situs inversus, if you will-- are other than usual and, hence, should be heterotaxic. But the Nomenclature Working Group, of which we discussed yesterday in the setting of ventricular septal defect, they have actually defined what they mean by heterotaxy.

I have to say, I wasn't part of the committee that produced this definition. And they, again, defined it as an abnormality where the internal thoracoabdominal organs demonstrate an abnormal arrangement across the left-right axis. So within that definition, also, patients having situs inversus-- mirror imagery-- would be heterotaxy. But for better or worse, the working group excluded mirror imagery from the setting of heterotaxy. And I think it's also the case that in most centers dealing with patients with congenital heart disease, those that have situs inversus or mirror imagery are not included within these particular groupings.

There's no question also however that within the groupings, there are two subsets of patients. So the conundrum remains, how best should we segregate and describe them? And I firmly believe that the approach is based on isomerism.

So here you see a picture of two entities that are themselves isomeric. They are mirror images of each other. So what is the definition of isomerism? Nowadays, the fount of all knowledge, as you know, is *Wikipedia.* So you see that they are enantiomers-- two stereoisomers that are related to each other by a reflection. They are mirror images of each other.

And as far as the thoracic organs go, then, and the lesions we are discussing, isomerism, I believe, is the way forward. So if we go back to Dr. Kim, he says that isomerism has become the conventional description for which morphologically right or more logically left structures are found on both sides of the body in the same individual. In other words, within the same individual, the organs themselves are mirror-imaged.

And in fact, that is not unusual, because we all have examples of bodily isomerism. So this is the palm-- of the dorsal surface, the back surface of my hand. There is the other one. And they are mirror images of each other.

And all of our parietal components-- the musculature of the arms, the musculature of the limbs, the musculature of the trunk-- the two sides are isomeric because they are mirror images of each other. But that is what about the-- the heart is missing. In your books, you will have, what about the heart? Can the heart exhibit isomerism?

And that has been an ongoing problem. We first started examining the potential presence of isomerism way back in 1982 or the early 1980s. In fact, the first paper I wrote on it was done in collaboration with Dr. Zuberbuhler, who was the chief of pediatric cardiology here at the time.

So let's look at the way the heart develops and see if that helps us to determine whether it can be truly isomeric. And you will now know that the chambers, the distinctive part of the chambers formed by ballooning from the primary heart tube and those distinctive components within the atrial segment are the appendages. Within the ventricular segment, they are the apical components. How do they become morphologically right as opposed to left? This is all under the influence of a cascade of so-called laterality genes. And these laterality genes are also involved in producing mirror imagery. And so that's another reason why we should be including mirror imagery in the overall grouping of heterotaxy.

So we know that amongst these genes, there is one, called PITX2c, which goes along with another one called CITED2, and they produce morphologically leftness. And in the developing embryo, the default option is morphologically leftness.

So we know that these genes that produce morphologically leftness don't turn the entirety of the normal embryo into an embryo with two left sides because there are another set of genes. And they include LEFTY1, NODAL, another gene in this cascade has the wonderful name of sonic hedgehog. The molecular biologists, when they started producing these genes, had very fertile minds, so they came up with the most wonderful names. Another one, as you probably know, is tinman. And if you knock out tinman, you don't have a heart. So that's why they call it the tinman gene. I

Don't know why they came across sonic hedgehog, but I'm told it's a ninja turtle or something? So there you go. Anyway, LEFTY1 and nodal stop PITX2c reaching the right side of the embryo. They produce a midline barrier.

So we have these two sets of genes, of which PITX2c is the exemplar on the one, LEFTY1 and NODAL on the other. And they influence the way that these structures develop. Now, you will remember that I showed you this picture before. And I pointed out that on the atrial chamber of the primary heart tube, the appendages balloon in parallel. So that means that if we stop the gene in the midline, this appendage is going to respond to morphological leftness. This is going to respond to morphologically rightness.

I then pointed out that in the ventricular loop, the apical components balloon in series. And that means that here, the right and left genes affect both of the developing ventricles in comparable fashion. And that is why when we are considering isomerism, which is the consequence of failure of those genes, we should be looking at it in terms of the atrial component rather than the ventricular component.

And so if PITX2 produces morphologically leftness, if we knock it out in a mouse, then we would produce bilateral morphological rightness. And these are the under-surface of the atrial chambers in a mouse prepared by Dr. Jim Martin, who was a colleague of Nigel Brown, worked closely with Nigel Brown. Jim Martin works in Houston. And he developed the PITX2 knock-out mouse. So you are looking here at the undersurface of the two atrial chambers. And I hope you will agree that here, the one side of the atrial component is the mirror image of the other side. There are bilaterally morphologically right appendages.

And then there's a molecular biologist in Japan called Professor Meno. And Professor Meno knocked out LEFTY1. And having knocked out LEFTY1, the gene for morphological leftness is able to reach both sides of the embryo. And here, in Dr. Meno's LEFTY1 knockout mouse, I hope you will all agree again that we have bilateral morphologically left appendages.

So now we know that by manipulating developing mice unequivocally we can produce isomerism the atrial appendages. The question then is, can you, as physicians and cardiologists, recognize the isomeric features in the postnatal heart? And that just been the problem. And my very good friend Richard Van Praagh has suggested, in fact, that isomerism is no more than a useful mnemonic.

That all depends on how we look for the features of isomerism. So how do we distinguish rightness from leftness in the atrial chambers? So we come back to the method put forward die by Dr. Van Praagh to help us recognize, specifically, chambers and their components.

And the point he made in the morphological method is we should use the most constant part of any chamber to decide whether it was morphologically right or morphologically left. And this is the work in which he put forward the morphological method. He was criticizing, in fact, a paper that we had written suggesting that in the setting of double and left-right ventricle, we could disqualify the incomplete left ventricle from being a ventricle. And he was 100% correct. So we took on board the notion of the morphological method, and we've used it as our guide ever since.

So which is the most constant atrial component? It is not necessarily the most obvious. For example, consider the venous connections. In the normal heart, of course, the most obvious feature of the morphologically left atrium is the pulmonary veins. And Dr. Van Praagh still uses the pulmonary veins as the marker of the morphologically left atrium.

Now, you all have seen pictures and illustrations this morning showing this lesion. So which lesion am I showing you?

AUDIENCE: [INAUDIBLE]

ROBERT ANDERSON: Total anomalous pulmonary venous connection. And you see perfectly well that the vertical vein is turning downwards. So if we use the pulmonary veins as the marker of the morphologically left atrium, in this setting, what would we have to identify as the morphological left atrium?

AUDIENCE: The liver.

ROBERT ANDERSON: The liver. So it is a no-no to use the venous connections as the arbiter, as the final arbiter for atrial identification, the more so when you see that here, we can recognize the left atrium. It still has its body, and it still has its obvious appendix.

So the appendage is the most constant atrial component. The question then becomes, can we distinguish rightness and leftness on the basis of the morphology of the appendages? And for quite some time, we tried to use shape as an indicator of the appendages. And here, again, in Pittsburgh, when I was here in the early 1980s, one of the fellows here at the time, Shiv Sharma, worked together with Bill Devine and myself. Diane hadn't even joined us at that stage. Or had you joined us?

- I was here.

ROBERT ANDERSON: She was here. So we got out 1,800 hearts that were present in Pittsburgh at the time. And Bill hid them behind his back. And he held them so I could only see one or other appendage. And then he produced the heart, and I had to say, is it morphologically right or is it morphologically left based on shape? And I think I was right in all but about half a dozen cases.

So we published this paper saying that on the basis of shape of the atrial appendages, we could recognize isomerism. Richard Van Praagh then made the very substantial point that shape can be altered by hemodynamics, and the hearts that come from patients with heterotaxy often show the evidence of abnormal hemodynamics. So shape is not a good arbiter.

So then a Japanese fellow came to work with me in London, and he came up with the notion of finding a better way of distinguishing the appendage-- namely, the extent of the pectinate muscles. So here, to your left hand, you're looking down on the tricuspid valvar orifice. Bill and Diane-- Bill, in particular-- has emphasized this many times as he's been showing you hearts during our meeting over the past two days. And you all know that the pectinate muscles encircle the vestibule of the tricuspid valve, and they reach to the crux. Whereas, when you look into the left ventricle, the vestibule is smooth, the pectinate muscles are confined within the appendage.

So this is the study that my Japanese fellow did when he came to work with me in London. He also came here, in fact, and he looked at the hearts in Pittsburgh. And all together we collected 182 hearts coming from patients known to have so-called heterotaxy. And Urimura looked for the features that permitted him to distinguish what was bilaterally morphologically right, what was bilaterally morphologically left, and what he could not distinguish with certainty.

And when he used shape, he wasn't as good as I was. He had a small proportion of hearts he couldn't tell the difference. When he added to that features such as the terminal crest, again, it was not absolute. But when he took the pectinate muscles, all of those 182 hearts could be distinguished as showing either isomeric right appendages or isomeric left appendages.

So when you have the hearts in your hand, there is no question that you can identify isomeric appendages. Since then, we've extended our study to another 300 hearts. Diane helped us coordinate. We looked at the hearts in Toronto. Diane looked at them in Chicago and in Gainesville. And in all of those, using the pectinate muscles, we were able to distinguish rightness from leftness.

So now we know, with the hearts in our hands and using the extent of the pectinate muscles, all individuals will fit into one of four groups. And so this is the starting point, as we discussed on Wednesday, now, for our own approach to sequential segmental analysis.

But what about the correlation with the other organs? Because the big problem is that you cannot always see the pectinate muscles. So we know the correlation with the bronchial tree is excellent. The spleen, however, which previously was used to discriminate heterotaxy into the settings of asplenia and polysplenia, is far from perfect. And Urimura, when he was working with the 182 body parts and hearts, examined that.

So here you see the situation when he looked at splenic morphology, knowing that the individual had isomeric left appendages. We would expect there to be multiple spleens, but in only 2/3 of cases was he able to show that those individuals had multiple spleens. In 1/4, he didn't know because the information wasn't available. But in 10%, either the spleen was absent, or there was a solitary spleen in the setting of left isomerism.

And then, when he looked at right isomerism, it was much the same. In a proportion, we didn't know what was happening. But in the patients with right isomerism, 14% had a solitary spleen, whereas 4% had multiple spleens. So using the spleen as a marker of so-called isomerism is not very good.

And Bill Devine also wrote a nice paper saying that when Ivermark wrote his first paper, had he not concentrated on the spleen, we might never have got here in the first place. But for better or worse, this is where we are.

So the most important feature-- what is isomeric? And in the atriums, it is only the appendages. So we need to describe the variables. And they are particularly important, the venoatrial connections, because they are particularly varied in the setting of isomeric appendages. We need to take note of a-v junctional morphology, ventricular morphology, and, indeed, all of the features of the heart and all of the features of the other organs.

So finding isomeric appendages gives you no information about the venous connections. But we need to describe them, and we need to describe them with sufficient accuracy that we take away ambiguity. And we know that in some instances, the venous connections may seem to be normal. All the systemic venous connections come to one side. All the pulmonary veins come to the other side. Or they may be mirror-imaged when they come to the wrong sides. But that is very much in the minority, but the cases like that do exist.

Despite of that, however, the arrangements are different in many respects, and finding and recognizing the venoatrial connections can give you a clue as to whether or not the actual appendages are isomeric. So if we consider right isomerism, for example, as Bill stated this morning, always, in the setting of right isomerism, there is absence of the coronary sinus. So that's a very useful marker.

We also anticipate bilateral superior caval veins. And if they come back to the heart, they do so to the atrial roof because the coronary sinus is absence. The coronary veins connect directly to the atrial chambers in absence of the coronary sinus-- another feature. Always, in right isomerism, there is total anomalous pulmonary venous connection. This does not mean that the pulmonary veins might not come back to the heart. What it does mean, however, is that if the pulmonary veins do come back to the heart, they do so in anomalous fashion because both of the appendages are morphologically right.

So in the setting of isomeric right appendages, in about half the individuals, the anomalous pulmonary veins drain to an extracardiac systemic vein. In the other half, they come back directly to the heart. And many do not recognize that as being total anomalous pulmonary venous connection of cardiac type.

Rarely, they are directly to the right atrial roof. More usually, they come to a midline confluence which can, itself, be restricted. So how does that distinguishes from left isomerism? Because in left isomerism, also, there are often bilateral superior caval veins. But in that setting, most frequently, one will come back to the coronary sinus because the coronary sinus is usually present.

We have emphasized at several points during our meeting this week that the coronary sinus is a morphologically left structure, despite the fact it drains to the morphologically right atrium. So it's not unexpected to find the coronary sinus when there is isomerism of the morphologically left appendages. But should the coronary sinus be absent, then once again, the coronary veins will drain directly.

The preliminary veins are frequently symmetrical. And again, that is not unexpected because the pulmonary veins are morphologically left structures. And if you have atrial chambers with bilateral morphologically left appendages, why shouldn't the pulmonary veins drain symmetrically? But symmetric drainage is certainly not normal. It is bilateral and symmetrical.

We anticipate interruption of the inferior caval vein with azygos continuation. But again, that is not universal. However, when there is interruption of the inferior caval vein, the hepatic veins usually drain directly into the atrial chambers, although they can drain via an infradiaphragmatic confluence.

So all of this is pertinent to the question as to whether there is any such thing as situs ambiguus. Because my friend Richard Van Praagh still will describe situs solitus, situs inversus, situs ambiguus. And I would suggest that is no longer justified, because there is no ambiguity if, in any individual with so-called visceral heterotaxy, we describe each of the organ systems.

The lungs and the bronchial tree can only be usual, mirror-imaged, or show right or left isomerism. The spleen can be solitary, typically multiple in the setting of left isomerism, but not always, usually absent, but again not always, in the setting of right isomerism. How do we get across that information? We describe what is present.

Is there intestinal malrotation? A very important feature. And it can exist with either right or left isomerism. But again, it's not always present. And then, within the heart, the appendages will only be, usually, mirror-imaged isomeric right, or isomeric left. But that is but the first part of the analysis of cardiac structure.

And the key point-- the arrangements are not always in harmony. But that doesn't disturb us if we describe them each. So when we judge on the extent of the pectinate muscles, we know from our extensive investigations that the evidence of isomerism is unequivocal, that only the appendages are isomeric. The rest of the features are variable, as is bronchial and splenic status, and they need to be described. Again, description has been removed. There, you can just see it on the bottom.

So does isomerism exist? For sure, it does. The whole body, however, is not isomeric. It is only the thoracic organs that are isomeric. The abdominal organs are jumbled up. They are truly heterotaxic. But the answer is simple description.

[APPLAUSE]