[MUSIC PLAYING]

ROBERT ANDERSON: So over the years, the course has developed in such a way that I now lead off with each of the topics. We're going to discuss normal cardiac development, I explained, and when we started doing this, for quite some time, I thought embryology was a hindrance rather than a [INAUDIBLE]. But it's all changed in recent years because we can now see what is happening.

So the material I'm going to start with normal development will then progress as we go through the course. So some of the images that you see over the next few minutes, you'll see again in subsequent parts of this course. And hopefully, they will eventually make sense to you.

So it used to be when I started, when I thought that cardiac development was a hindrance, but we thought all the relevant chambers were already there in the primordium of the heart when it was not more than a single tube. And when I started teaching cardiac development, we would liken the single tube to my tie. Then I would bend my tie, and I would bring it up, and I would go through the most amazing contortions, and I would say, that is how the heart develops. And you can see by the state of my tie as it is at the moment why people will have difficulty understanding that. And we know now that it wasn't like that at all.

So I think it is marginally easier to describe what is going on, but I still recognize that it is quite difficult for some of you who have never seen a developing heart before to know what's happening. But the thing that transformed my own understanding was the development of the technique that I call episcopic microscopy. So Bill Lyons the now-retired curator of the archive-- he's moved on to greater things. He now assists the [INAUDIBLE]. When he is the [INAUDIBLE] maestro here in Pittsburgh. And he calls it EPIC. What does EPIC stand for?

MALE SPEAKER: Same thing.

ROBERT ANDERSON: Same thing, high-resolution episcopic microscopy. So I'm going to show you hearts that are demonstrating in that way. I'm also go to couple it with some pictures of scanning electron micrographs.

So we know now that the heart is not developed by bending and separation of the initial tube. What I meant to say before I got side-tracked is that if you understand echocardiography-- and the majority of you, all of you, I hope, understand echocardiography-- if you understand the images of echocardiography, I believe you can then understand the images I'm going to show you today. If I'm wrong, please tell me.

So the reason we know that all of it is not all coming from that initial tube, is that it has been shown, over the past 20 years or so by molecular biologists that new material is added to both ends of what we see at the initial heart tube. And so we know what we see initially was little more [INAUDIBLE]. And we know call that the first heart field.

The right-hand manifold is that the arterial pole, and that is called the second heart field And then, it's then we're going to need to be out back, because the exactly why biologists have now divide the second heart field. [INAUDIBLE] There's [INAUDIBLE] relevance of the right ventricle in the outflow tract arterial pole, and the path contributes to the atrial chambers at the venous pole.

So you would like, after all, to see pictures. So this one is, now, a scanning electron microgram. This has been made by my good friend and colleague Nigel Graham, who works here at St. George's Hospital. In fact, Nigel has now retired. We are all departing into the sunset, the difference being that I am still making trouble. Nigel is really enjoying his retirement.

But this is what he did quite some time ago, is he cut away the pericardial cavity so that you looking at the front edge of the developing thoracic region of a mouse heart that is on the 8 and 1/2 days of development. E stands for every other day.

And you can actually see the developing heart tube. So there it is. And as I said, we used to think that all of the components of the developing heart were within that tube. We now know that path we see initially forms little more than a ventricle. In fact, already, at this stage, there has been new material added at both poles.

So this growth at the venous pole eventually will produce atrial chambers. The growth at the arterial pole will produce, initially, the right ventricle and then the outgrow tract. On the true additions, two poles are coming from the second heart field.

So we can then grow our mice, and we can look at them a little later. So here's another, [INAUDIBLE] most beautiful scanning electron micrographs. And what you see is, that, as the tube has grown with the addition of material [INAUDIBLE] exposed, it has bent. And this is what we call the ventricular loop. So here you see the ventricular loop. We knew that from the outset, and now we can see it's really happening.

And now we can begin to make out more of the components of the heart. So that growth at the venous pole has produced a common chamber that eventually will become the right and left atrial chambers. And we'll look at that tomorrow when we discuss interatrial communications. Or is that this afternoon?

MALE SPEAKER: Yes.

ROBERT ANDERSON: Later this afternoon. So later this afternoon, I will show you pictures looking at the atrial component.

The atrial component then links up to the developing ventricle, which was part of that initial heart tube. And we can see a discrete connecting segment in this space, which is the atrioventricular canal. We now see the left ventricle is coming towards us, and that is via the initial linear tube. But the addition of the new material at the venous pole produces a second swelling that will become the new [INAUDIBLE] ventricle. That, then, turns back on itself, and the additional component, the outflow tract, extends to the margins of the pericardial cavity.

Very shortly, I'm going to show you a picture where I sliced away these atrial components so that you can look into the ventricular loop to show the relationships of the AV canal, the outflow tract, to the developing ventricles. It I write a summary at this stage, that is still the primary option. As yet, there are no formations of chambers. And so the chambers develop by what we'd call "ballooning." They grow out of this primary heart tube.

And the key point here-- and this is particularly pertinent to what we will discuss on Friday afternoon relative to isomerism-- is that from the atrial component of the tube, the appendages balloon out in parallel.

But as we've already seen, the ventricles themselves will form in series-- the left ventricle first, the right ventricle second-- and so the apical components of the ventricles will balloon out in series. And the difference between ballooning in parallel and ballooning in series will be the key to understand what is going on in the setting amid isomerism.

So this is a cartoon to illustrate the notion of ballooning that was made by my colleagues in Amsterdam. And it was they hey introduce this notion of ballooning, although it was there in the literature quite some time previously. So what you are looking at here in silver is that initial heart tube. This is the atrial component. And coming from there, you have the venous tributaries.

And then this is the ventricular loop, and this is the outflow tract. At the margins of the pericardial cavity here, the silver gives way to green, and green are the channels arising from the aortic sac. And we'll discuss a the certain of capacity of rings.

The key point from the atrial component in blue, you see how the appendages are ballooning in parallel, whereas from the ventricular loop, the apical components of the left ventricle balloons from the inlet part of the tube. The apical components of the right ventricle balloons from the outlet.

Let me show you that is the real situation. And this, now, is the picture that's taken by slicing away the apical parts of the ventricular loop and looking towards the cardiac base. So this is the same picture. As cardiographically, you see the show, the atrioventricular junctions-- this being the right side, this being the left side, this, obviously, being inferior, and this being superior.

So you are now looking from the apex of the developing right-left ventricles towards the base. And there, you can see the ventricular aspect of the atrioventricular canal Does that makes sense to everybody? I see nodding heads, so that is good news.

Within the atrioventricular canal, you see the two cushions that, eventually, you put forth the valve and leaflets. The key point that I want to establish was that at this very stage, the atrial ventricular canal is exclusively entering the left ventricle.

You can then see that, from the outlet of the ventricular root, there is another atrial component developing, and that will the right ventricle. You could then appreciate that at this early stage, the entirety of the outflow tract is supported by the right ventricle. So initially, [INAUDIBLE], that's double [INAUDIBLE] the ventricle, double [INAUDIBLE] right ventricle.

That is the developing muscular ventricular septum. And it develops concomitant with the ballooning of the apical components. Then we see the inner heart curvature. And in this respect, we liken the heart to the stomach. So this is the inner curve. This is the outer curve.

And the key point at this stage is that the interventricular communication is bounded poorly by the muscular ventricular septum. It is bounded cranially by the inner heart curvature. And this relationship of the, inter? To the communications, to the editor, as opposed to what will be the output septum, is a key point to understand ventricular septal defects.

However, if we look at this from the right side, and I slice the parietal walls at the right and left-- atrium chamber on the right, atrial on the right ventricular chamber-- you see a picture that looks like this. This guy that I'm showing you a picture of is human heart, so we have a limited number of human data sets that we have analyzed using endoscopic microscopy. And this parallels what we see in a mouse.

So [INAUDIBLE], we've seen the for [INAUDIBLE] of the right atrium. Entering it here, you see the inferior caval vein, surrounded by venous valves. And you note that at this early stage. The heart lacks any connection between the atrial chamber and the developing one.

Already [INAUDIBLE] developing right ventricle processes as the outlet is apical confirmed, And as You see, it supports the entirety of the outflow tract. And there, separating the outflow tract, are the outflow tract cushions that will separate it into the aortic and pulmonary pathways.

So there is the primary inter-ventricular communication. And all of that coming into the left ventricle has to pass through that primary interventricular communication to reach the outflow tract. It follows, therefore, it is not possible for the embryo to close this conditional into a ventricular patient.

So suffering again-- subsequent ballooning. The embryo has double inlet. The outflow tract arises through the right ventricle, hence double outlet. The right ventricle is incomplete. It doesn't have an inlet. As is the left ventricle, because it lacks its outlet. So the key to future development is to transfer an inlet to the right ventricle and an outlet to the left ventricle.

Does all that make sense? So that will need extensive remodeling, what I will now call the primary interventricular communication. Concomitant with that remodeling, we will see a second interventricular communication, and eventually, the embryo will close a tertiary interventricular communication.

So how do we transfer the inlet component by expansion of the atrioventricular canal? I've reverted to that initial picture I showed you, but this time, I've covered it in full chain refresh. And you should all immediately recognize the similarity to what you see in doubling left-left ventricle. Because the right atrium has it's bicuspid valve or orifice, but at this stage, it's just looking into the developing left ventricle.

The right ventricle is incomplete, and now you can see it is incomplete because it lacks that inlet component. But already, the floor of the right atrium, with the parietal margin of that tricuspid orifice is continuous with the roof of the right ventricle.

So all we have to do is get the right atrium [INAUDIBLE] the right ventricle is to expand the atrioventricular canal. And the beauty of having these [INAUDIBLE] data sets is that we could see, that is exactly what happens. So here we are, later on embryonic day 10.5. The right atria ventricular junction has, indeed, expanded. And in doing so, it has remodeled and called upon the atrioventricular junction so that it surrounds the right atrioventricular orifice.

So now I've jumped a couple of days. Here we are now on embryonic day 12.5. Here is a cut that resembles what you see in the OD subcostal echo configuration. And you see the right ventricle has now developed its own inlet.

You can also now see the cushions that are dividing the outflow tract into the pulmonary and the aortal elements. But the aortic root remains positioned above the right ventricle. The embryo still has double outlet right ventricle so that the communication unanimously here is the secondary into ventricular mutation. Does that make sense? [INAUDIBLE] adds, "Thank you." So all we now have to do to complete separation is transfer the aortic root. And we cannot complete separation until the aortic root is converging.

So that same day we said, I showed you just a moment ago, we've changed our cunning plan so that we can look through the aortic root. Here it is-- the aortic root. Unequivocally, the aortic root is positioned above the right ventricle. The embryo still has double outlet right ventricle.

So there is our secondary intervention in communication. But once more, the embryo cannot close that hole. Because if the embryo closed off that hole, no blood would get through to the aorta.

So here is where cardiac surgery recapitulates cardiac development. Because the embryo creates a shelf in the roof of the right ventricle so as to put the aortic root into [INAUDIBLE] for that ventricle. We can then trace back, and we can see the spectrum. A moment ago, it resembled [INAUDIBLE] right ventricle. And now, as the embryo is closing that space, it resembles tetralogy of Fallot.

And the geometric interventricular communication is the continuation of the long axis of the septum. Once more, the embryo cannot close that hole. The embryo closes the persisting communication between the cavity of the right ventricle passes to the aortic root. And that, now, is a tertiary interventricular communication, because the secondary communication has become the subaortic outflow tract as we see here. Just prior to closure, the aortic root is now looking directly out of the left ventricle. And there is the gap which will be closed before the [INAUDIBLE].

And that is done by a fusion of these so-called "tubicles," [INAUDIBLE] questions but fuse with the proximal portions that have become the infundibulum of the right ventricle. So now the right ventricle has inlets. Moments, how is that practical? How separation is complete.

In terms of normal development, the e was then, derived 80%. The arterial valves developed in the [INAUDIBLE] of the outflow tract to the distal part of the outflow, with the proximal cushions having been separated with the [INAUDIBLE] outflow tracts, must [INAUDIBLE] rising on the right side to become the subpulmonary infundibulum.

So there is an introduction to development. You will see many of those picture again, We'll [INAUDIBLE] provide them [INAUDIBLE] we'll expand them. So we talk about atrial septation, ventricular septation, and development of the arterial trunks.