Pioneer in Cardiology:
Adriana C. Gittenberger-de Groot, PhD, FESC

Pioneering Research to Explain How Coronary Arteries Develop and the Role of Genes in the Aetiology of Congenital Heart Disease

Adriana C. Gittenberger-de Groot, professor of anatomy and embryology, Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, the Netherlands, talks to Jennifer Taylor, BSc, MSc, MPhil.

The first major insight into the relationship of basic research and the clinical application of the results for Adriana C. Gittenberger-de Groot, PhD, FESC, professor of anatomy and embryology in the Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, the Netherlands, was that the lives of babies with ductus arteriosus-dependent heart malformations could be prolonged sufficiently with prostaglandins to enable them to make it to the operating room. Until this point, children with hypoplastic left heart syndrome died 2 to 7 days after birth when the ductus closed. She says, “The situation now, after many years and novel surgical techniques for repair of this malformation, is that we still do not know the underlying mechanism of the disease and whether such children will survive into adulthood and need to be included in heart transplantation programmes.”

The prostaglandin work is just 1 example where Professor Gittenberger-de Groot feels serendipity was at work because a unique combination of events kickstarted the project. She was knowledgeable about the ductus from her PhD on hypoplastic left heart syndrome, prostaglandins had just come on the scene and were being tested by a clinical colleague in Utrecht, the Netherlands, and she had just had her first baby and wanted a small project to work on part time. Her desire for a family also influenced her to choose a research rather than a clinical career. After her PhD, she realised that if you want to be really good at something, you can’t do everything, and she enjoyed research. She says, “I like to dive into a subject and understand why and how.”

Serendipity also played a role in Professor Gittenberger-de Groot’s career choice. She had wanted to study biology but instead studied medicine, during which she worked in an obstetrics department for 2 summers. She enjoyed the experience but thought she would prefer to work on the heart. Her father had a colleague whose sister, Arentje Oppenheimer-Dekker, MD, PhD, was professor of anatomy in the Anatomy Department at Leiden and her specialty was the new field of cardiovascular pathology of children operated on for heart malformations. Professor Gittenberger-de Groot says, “These were the exciting early years in the treatment of congenital heart disease. There were many human embryos available for study in the department, so the professors at that time combined the pathology of congenital heart disease with normal human development.”

Professor Gittenberger-de Groot joined Professor Oppenheimer-Dekker’s lab in 1965 as a student and never left. Professor Oppenheimer-Dekker, who trained in the United States with the founder of paediatric cardiology, Helen Taussig, MD, was not overambitious herself, but was a “wonderful mentor” for the young Gittenberger-de Groot, giving her ample freedom and support to develop her own...
The work was on human embryos and pathology specimens from the collection at Leiden and from around the world. At points in her career Professor Gittenberger-de Groot was offered professorships elsewhere, but she opted to stay in Leiden because of her family, including her husband’s position as a professor at the University of Leiden and curator at the Museum of Natural History (Naturalis). Professionally, the unique huge collection of human congenital heart disease specimens, which was not subject to the medical ethical problems seen in other countries, played an important role. When she became a professor, Margot Bartelings, MD, PhD, took over responsibility for performing the diagnostics on the specimens, including fetuses from spontaneous abortions or abortions induced for medical reasons.

Identifying and Coining the Term “Epicardium-Derived Cells (EPDCs)” (With Professor Robert Poelmann)

As head of the department, Professor Gittenberger-de Groot was free to direct the research. During the previous 20 years, she had witnessed many successful operations on children with congenital heart disease and the survival rate increased from 40% to 50% to ≥90%. Small adjustments to the surgery could result in improvements, but for Professor Gittenberger-de Groot, the area was no longer as exciting or challenging. She started working with a developmental biologist, Robert Poelmann, PhD, who at the time was working on neural tube closure rather than the heart. He remains her main colleague in the lab, and together they design almost all the projects. With him it became possible to move on to experimental research, always keeping in mind that they would link the research to the human problem.

The developing heart (the myocardial tube that loops and bends) does not need its own oxygen supply yet. The coronary arteries develop later. It had been thought that as soon as the aorta was in place, 2 vessels grew from it over the heart to form this vasculature. Professor Gittenberger-de Groot says, “We showed that that is not true, that instead a vascular network develops on the myocardium and it secondarily connects up to the aorta.” This was completely new thinking.” Coincidentally, this was also published in the same year by Professor Margaret Kirby, PhD, in the United States. This finding turned out to be a general rule; vessels do not always sprout from a main system but often grow into a main blood vessel.

Classifying Coronary Artery Variation in Transposition (the Leiden Convention) (With Dr Ursula Sauer)

Professor Gittenberger-de Groot’s ductus work was dominated by paediatric cardiac pathology, looking at specimens and describing them, and spanned from 1975 to 1985, during which time her principal colleagues were Arnold Wenink MD, PhD for whom she was a sparring partner in his research, Andre Moulaert, MD, PhD, a professor in paediatric cardiology in Utrecht, and Ursula Sauer, MD, a paediatric cardiologist at the famous German Heart Centre in Munich, Germany. She says, “The latter two are the main clinical colleagues who saw the relevance of looking into the morphology of the heart and linking it to clinical problems. All of the work was on human embryos and pathology specimens from the collection at Leiden and from around the world.”

With Dr Sauer, Professor Gittenberger-de Groot studied the variation in the coronary artery pattern in several heart malformations, including hypoplastic left heart, pulmonary atresia without ventricular septal defect, and transposition of the great arteries. One of the success stories in the early 1980s was surgery for transposition of the great arteries. The tiny coronary arteries had to be transplanted to the new aorta, but the 40 to 50 variations in these arteries complicated the surgery. For about 2 years, between 1985 and 1987, Professor Gittenberger-de Groot and Dr Sauer investigated the variations and classified them into 6 main categories. Professor Gittenberger-de Groot recalls, “I remember being almost in tears because I could not get it into a useful classification. But we succeeded in the end, and I was very happy with that.” Their resulting nomenclature on coronary artery variation in transposition of the great arteries, the Leiden Convention, is used by most thoracic surgeons performing the arterial switch operation.

Professor Gittenberger-de Groot and Dr Sauer became interested in the many variations in coronary artery origin, which started a new era of research for them that lasted from the late 1980s to the early 1990s. In the meantime, Gittenberger-de Groot was appointed professor as well as chair and head of the department. Although she will officially retire at age 65 in August 2010, she will continue as a guest researcher. She has already found her successor, who became chair and head of the department last April. At points in her career Professor Gittenberger-de Groot was offered professorships elsewhere, but she opted to stay in Leiden because of her family, including her husband’s position as a professor at the University of Leiden and curator at the Museum of Natural History (Naturalis). Professionally, the unique huge collection of human congenital heart disease specimens, which was not subject to the medical ethical problems seen in other countries, played an important role. When she became a professor, Margot Bartelings, MD, PhD, took over responsibility for performing the diagnostics on the specimens, including fetuses from spontaneous abortions or abortions induced for medical reasons.

Professor Gittenberger-de Groot in 1990 with Professor Dr Arie van der Leij and Professor Dr Ursula Sauer, who still works in Professor Gittenberger-de Groot’s lab. Photograph courtesy of Professor Gittenberger-de Groot.
Professor Gittenberger-de Groot and Professor Poelmann, and other colleagues headed by Professor Kirby, demonstrated that normal heart development is impossible without an extracardiac cellular source, the neural crest cells, which migrate from the neural tube region to the heart. Next they moved on to show that coronary artery development is dependent on the development of the epicardium, which originates from the proepicardial organ and grows over the myocardium. Using microsurgery they put pieces of quail proepicardial organ into a chicken embryo. The specific characteristics of quail cells allowed them to follow how the epicardium covered the heart. It turned out that “epicardium-derived cells (EPDCs),” a term coined by Professor Poelmann and Professor Gittenberger-de Groot, were important for the coronary vessels as well as the cardiac fibroblasts.

Others were also making discoveries about the epicardium. Professor Gittenberger-de Groot says, “When you have new scientific thoughts, I’ve found so often that others have tuned in on the problem at the same time. Even if you are completely convinced that you are the first, that you have never heard anybody else or spoken to anybody else on the subject, you see that all of a sudden others are coming up with it too, as if it’s in the air.” It happened with the ingrowth of the coronary arteries and also with the ductus research, an area that had gone quiet for 50 years. In the same year she published her article, a Brazilian she had never met published similar findings.

Subsequently, Professor Gittenberger-de Groot and Professor Poelmann showed that the epicardium is important for producing a thick myocardial layer. Professor Gittenberger-de Groot explains, “If you remove the proepicardial organ, the myocardium remains thin and the embryo dies. Disturbing epicardial outgrowth or differentiation leads to less severe myocardial hypoplasia.” They translated that finding to the idea that this embryonic capacity of epicardial cells might be recapitulated in adults. That led to the hypothesis that if EPDCs were injected as a type of stem cell into an adult heart after myocardial infarction, the injected EPDCs might do the same as they did in the embryo. “It’s the idea that you can reactivate this embryonic programme and use it as a sort of repair mechanism,” Professor Gittenberger-de Groot says. “By contrast, stem cell therapy is more like damage control. Stem cells taken from the blood and added to the heart are a completely different population, and the hope is that they will turn into cardiomyocytes.”

Hypothesizing That 85% of Congenital Cardiac Defects Are Associated With Defects in Epigenetic Regulation

Another major insight changed Professor Gittenberger-de Groot’s view on the development of congenital heart disease. The early 1990s, when she began working on developmental biology, was the big gene era, but in subsequent years there was no marked expansion in the knowledge of the genes important for congenital heart disease. After 20 years of study, 85% of congenital heart disease remains multifactorial with a genetic predisposition, but no responsible mutation has been identified.
system in the embryo is broader than in the adult. Her group has substantiated that many arrhythmias originate in sites that reflect embryonic stages.10

Professor Gittenberger-de Groot’s work has also been influenced by Marco DeRuiter, a former PhD student and now an associate professor in the department, plus a number of collaborators outside the Netherlands: the late Professor Thomas Pexieder, anatomist and developmental cardiologist in Lausanne, Switzerland; Professor Gaetano Thiene, MD, PhD, pathologist in Padua, Italy; Professor Drew Noden, PhD, developmental biologist at Cornell University in Ithaca, NY; Professor Ed Clark, MD, PhD, head of the Department of Paediatrics in Salt Lake City, Utah; and Professor Roger Markwald, PhD, a developmental biologist with a specialty in cardiovascular regeneration from Charleston, South Carolina, SC.

Funding has never been a problem for Professor Gittenberger-de Groot, with ~80% originating from the Netherlands Heart Foundation. However, as “somebody who likes to go for novel and daring hypotheses,” it can take time to get her ideas off the ground. She had the epicardium idea in 1998, but applications for funding were rejected because the idea was too risky. It was finally funded in 2004, and the articles were published in 2008 and 2009. She says, “I think it is such a waste of time and ideas. Ten years before you get a new idea somewhere in a production line.”

Professor Gittenberger-de Groot’s strategy for research follows a set pattern: choose a clinically relevant topic, read the literature and then put it aside, perform investigations alone or with students so there is the possibility of finding something novel, and then read the literature again and see how it fits in. Her approach has produced an impressive 5 cum laudes for PhD students. She says, “It is a struggle to combine innovative research and give credit to all that is currently published,” and adds, “It’s not so easy to get a novel thought if you’re constantly behind your computer pulling out all the literature that others have written.”

Professor Gittenberger-de Groot says, “This is the current group I’m doing research with photographed in 2009. From left to right: Noortje Bax, PhD student; Liesbeth Winter, MD, PhD, who has just completed her PhD on epicardium-derived progenitor cells stem cell research; Monique Jongbloed, MD, PhD, a clinical anatomist combining cardiology and basic science; me; Bert Wisse (in yellow shirt), senior research technician; Linda van der Graaf, a technician; sitting, Robert Notenboom, PhD, who has just joined our group; Rebecca Vicente-Stejn a current PhD student on development of the conduction system; Professor Robert Poelmann; Heleen Lie-Venema, PhD; and far right, Margot Bartelings, MD, PhD.” Photograph courtesy of Professor Gittenberger-de Groot.

References

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Spotlight: Lars Køber, MD, PhD, FESC
The Trandolapril Cardiac Evaluation (TRACE) trial “Was My Baby in Research Terms and It Really Changed Medicine”

Lars Køber, professor of cardiology, University of Copenhagen, Copenhagen, Denmark, talks to Judy Ozkan, BA.

A Scandinavian of Swedish, Danish, and Norwegian ancestry, Lars Køber, MD, PhD, FESC, professor of cardiology, University of Copenhagen, Copenhagen, Denmark was born in 1958 in Sweden into a family he describes as “crowded with physicians.” Many of them worked as general practitioners and were happy in their line of work. This sense of satisfaction and fulfillment inspired Køber to enroll at the medical school of the University of Copenhagen in the late 1970s.

During his undergraduate years, Køber met Vilhelm A. Bohr, MD, PhD, whose father and grandfather were both noted physicists and Nobel Prize winners. Dr Bohr convinced Køber to take a year’s sabbatical to study pure science. It was an eye-opening experience. He says, “This was totally new for me and opened up a new way of doing things.”

After graduating in 1985, Dr Køber combined clinical and scientific work as he progressed towards becoming a cardiologist in 1998. His thesis, completed in 1999, was on left ventricular systolic function after acute myocardial infarction. In 2000 he became a consultant at the National Hospital of Denmark, Rigshospitalet.

“We Had 27 Different Departments Working on It [TRACE] and a Good Team Spirit”

Dr Køber’s attraction to cardiology came from his early years working as a physician and his desire to push back the boundaries that he saw were limiting the treatment of patients. He explains, “What I liked about research was being part of advancing the treatment of patients. A cornerstone inspiration was a heart failure study published in 1987, when I had been working as a physician for 2 years.”

The study spelled out the benefits of angiotensin-converting enzyme inhibitors in patients with severe heart failure. The implications and therapeutic options were dramatic. Heart disease was as malignant as cancer, but suddenly there was hope that you could really change that.”

Spurred on by these findings, Dr Køber embarked on an area of work that would define his career. If his group had given in to initial scepticism about their ability to attract funding, the trial might never have happened, but they raised funds that amounted to $5 million to run what would become the Trandolapril Cardiac Evaluation (TRACE) trial.

Dr Køber lived with TRACE for more than 5 years and describes it as a mixture of fun and hard work. Although the initial sponsor pulled out after the first 2 years, perseverance paid off, and Dr Køber remains proud of the trial. He remembers all the facts and figures because he saw them so many times. He says, “This was my baby in research terms, and it really changed medicine. We did an enormous job of not just doing a medical trial but creating a data set of the deceased. We did this by screening all patients in Denmark who had a myocardial infarction over a 2-year period. We created a system in which everyone with an infarction was registered and followed up. To follow up what happened to every patient with acute myocardial infarction in an entire country is still quite unique.”

He estimates that ≥80 articles have followed on the back of TRACE and suggests it illustrates how effective epidemiology can be when applied to clinical data.

Professor Køber identifies the years spent working on TRACE as his most satisfying. Despite the long hours spent poring over echocardiograms, this time was also the most enjoyable. He recalls, “Although I was getting up at 3 or 4 in the morning to work on the study and then do my day job and probably something else after, it was a lot of fun. We had 27 different departments working on it and a good team spirit. We had to train a lot of people in echocardiography because it wasn’t widely used at the time. It was good for a lot of people. I know at least 10 consultants who in their career paths have carried out research in association with TRACE.”

A $4 Million Grant From the Danish Government for Investigations Into Acute Coronary Syndrome

Professor Køber feels that his job has improved with age, and he enjoys the prospect of a day at work facing new challenges. He understands that “we are all fighting for funding,” but he accepts it as part of the game. He enjoys teaching and interacting with PhD students. He believes he has found the right balance at the moment with 4 days of teaching and interacting with PhD students. He believes he has found the right balance at the moment with 4 days of teaching and interacting with PhD students. He believes he has found the right balance at the moment with 4 days of teaching and interacting with PhD students. He believes he has found the right balance at the moment with 4 days of teaching and interacting with PhD students. He believes he has found the right balance at the moment with 4 days of teaching and interacting with PhD students. He believes he has found the right balance at the moment with 4 days of teaching and interacting with PhD students. 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friend. Professor Køber describes himself as being “lucky to work with these people.”

Professor Køber’s research group numbers ≈15, including physicians and students, and together they produce ≈20 articles each year and work in collaboration with Professor Torp-Pederson’s group.

The next few years are mapped out for Professor Køber with a full programme of work, including sitting on the steering committee of 4 major trials. A $4 million grant has just been secured from the Danish government for investigations into acute coronary syndrome and Professor Køber plans to train as many PhD students as possible.

“We Started With Individualised Medicine and Then Moved Into 1 Size Fits All, and I Think We Will Move Back to Individualised Tailored Treatment”

Professor Køber has held leadership roles on the steering committees of more than 10 international clinical trials and has been principal investigator in 3 of them. To date he has produced 264 peer-reviewed articles. He is a fellow of the European Society of Cardiology, a member of the Heart Failure working group, a previous chair for the Danish Heart Failure nucleus, and a referee for a number of major journals, including Circulation and The Lancet.

Looking back, Professor Køber suggests that the advances made in treating heart failure have probably not been as widely acknowledged as they should be. He also suggests that the era of a uniform approach to treating patients with heart disease is over. He says, “We started with individualised medicine and then moved into 1 size fits all, and I think we will move back to individualised tailored treatments again. This is particularly true in heart failure, where we started by giving everyone the same treatment. But nonischaemic patients need different treatment to ischaemic patients and this is an example of where we could tailor treatment and drug development. My belief is that genes are going to help us here.”

Unlike most senior academics, Professor Køber has been based in Denmark for his entire career, and as a father of 4, he tries not to travel excessively. His wife is a cardiologist in another institute. When not at work, he runs, skis, and reads.

Given more time, he would immerse himself in the novels and literature he enjoys reading.

His advice for anyone who wants to succeed in a medical or research career is this; “Write down your goals and make a plan. I see a lot of physicians who haven’t really found their path or their specialty. Finding out what you want to do is a very good investment of time.” He also suggests that stamina is important. Being bright is not enough alone; it needs to be coupled with dedication to make progress. Trying to inject some humour into the day’s work and using the opportunity to cultivate friends are also recommended. Professor Køber characterises himself as someone who recognises innovation in others and is still striving to be more innovative in his own work and ideas.

References


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