



## Masterminds of Ardian: An Interview With Inventors Mark Gelfand and Howard Levin

By **Mary Stuart**, *Start-Up 01/01/2011*

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### EXECUTIVE SUMMARY

Start-Up interviews the inventors behind Ardian, the object of one of the highest priced venture capital-backed medical device acquisitions, and between them, five other medical device companies. The team uniquely brings a perspective of applied physiology, and the integration of systems, to the goal of device innovation. In CHF Solutions, they've addressed heart failure with a device from nephrology, in Cardiac Conetps, heart failure by way of a neurological approach to sleep apnea, and in Ardian, hypertension, by studying the functioning of the kidney.

### ARTICLE

## Masterminds of Ardian: An Interview With Inventors Mark Gelfand and Howard Levin

***Start-Up* interviews the inventors behind Ardian, the object of one of the highest-priced venture capital-backed medical device acquisitions, and between the two of them, five other medical device companies.**

By Mary Stuart

The acquisition of **Ardian Inc.** by **Medtronic Inc.** announced in November was, by many measures, remarkable. [201010155] Medtronic offered \$800 million for the 89% of the company that it didn't already own, with a potential upside of \$500 million more in milestone payments. The price was one of highest ever paid for a venture capital-backed medical device company, all the more surprising since Ardian's technology is still at the pre-commercialization stage. Ardian's *Symplicity Catheter System* is CE marked but hasn't yet been launched in Europe, and is awaiting its pivotal clinical trial in the US, where it's not expected to see a launch before 2014.

Ardian has developed a catheter-based intervention for the treatment of hypertension, and is unusual in targeting, with a device, a condition in which drugs have always held sway. Pharmacologic treatments for hypertension make up a \$26 billion dollar market in the US. In this Ardian is again unique, in actually being

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able to offer the multi-billion dollar markets that so many device start-ups promise in their business plans. Finally, points out Hanson Gifford, III, a partner at the Foundry LLC, the incubator that has helped shepherd Ardian to its commercial form, this was a rare case in which, for once, the technology worked even better than everyone thought it would. Says Gifford, "We were hoping for a 15% reduction in blood pressure, and actually got more than 30%," in results announced during the American Heart Association meeting in November 2010.

Ardian may be unusual in the device world, but it is a fairly typical example of the kind of work done by the inventors behind its core technology. The team of Mark Gelfand and Howard Levin, MD, who run an incubator called Coridea, has founded three companies: **CHF Solutions Inc.**, **Cardiac Concepts Inc.** and Ardian. As individuals, they have filed many patents, and together or singly have licensed them to companies like Evalve (now part of **Abbott Laboratories Inc.**), **Zoll Medical Corp.**, **Nephros Inc.**, **PLC Systems Inc.**, **Biophan Technologies Inc.** and others. ( *See Exhibit 1.*) On the surface, these companies cross several clinical specialties: cardiology, nephrology, neurology, even pulmonology, but they all have one thing in common; they are outgrowths of the team's work in heart failure, the place where they both began their careers.

Howard Levin, who gained his MD at the Mount Sinai School of Medicine in New York, received his training in cardiology at the Johns Hopkins University School of Medicine, later becoming one of the heart failure/transplant cardiologists and the medical director of the Ventricular Assist Program at the Columbia Presbyterian Medical Center. Levin was instrumental in the clinical trials and regulatory approval of one of the first-generation left-ventricular assist devices from Thermo Cardiosystems (now **Thoratec Cardiosystems Inc.**, a division of **Thoratec Corp.**). He is the author of 41 issued US patents.


Gelfand grew up in the Soviet Union during the Cold War. At the St. Petersburg State Institute of Technology, he trained in electrical and controls engineering. In 1987 he emigrated to the US, where he became a senior research engineer in the division of cardiology at Johns Hopkins, working on a project in cardiopulmonary resuscitation that became the core of **Johns Hopkins University's** first spin-out, **CardioLogic Systems Inc.** Gelfand is the author of 47 issued US patents in the fields of heart failure, resuscitation and hemofiltration.

Ardian is a great example of the strengths of this inventive team. The Foundry's Gifford points out that they uniquely bring the perspective of applied physiology to the world of medical device creation, which means that they often solve clinical problems by tackling their root cause. So while other device innovators seek to improve on previous generations of devices, or to replicate or assist the functioning of a particular organ, the Gelfand and Levin group often come up with something that is very different from what has been done before, because they've gone back to a basic understanding of how multiple organ systems function together. In CHF Solutions, they've addressed heart failure with a device from the nephrology specialty, in Cardiac Concepts, heart failure by way of a neurological approach to


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sleep apnea, and finally, in Ardian, hypertension by studying the functioning of the kidney.

At the start of Ardian, the team of Gelfand and Levin reviewed physiology literature published as far back as the 1930s and found that the renal sympathetic nerves were implicated in hypertension, heart failure, and other diseases. While those early studies isolated the contribution of the nerves with invasive surgeries that brought with them unwanted and unintended complications, the team found a way to disrupt the nerves with a minimally invasive catheter delivering radiofrequency energy. What they have done in Ardian, and elsewhere, is successfully manage the tension between proposing something that's so new that nobody has ever done it before, and a product that's adoptable by physicians.

Now the two entrepreneurs have codified the knowledge gained in 21 or so years of working together in their new incubator, Coridea. Their goal is to use the incubator to prove out new concepts, give them a fair shot but at the same time get to a go-no go decision before too many funds or people have been committed. Levin says, "One of the hardest things is knowing when to switch or modify an approach. You want to stay in there long enough to know if it's right or wrong, but you also want to be flexible enough to change when change is warranted." Coridea fulfills those requirements.

*Start-Up* spoke with Gelfand and Levin to try to glean some of their learnings about the invention process in the medical device world. They share with us their five fundamental rules: Use the power of observation; don't get wedded to your own ideas; prove the concept before getting too many people involved; reduce risk by validating the concept with off-the-shelf technologies, and finally, the most important one, think big.

**Q:** START-UP: I'd like to ask you both how you came to be inventors. Did it begin in childhood? What was your formation, as an inventor?

Mark Gelfand: You could say that inventing was in my blood. My grandmother was an inventor in her own right. She invented a dog jacket with a handle for lifting the dog while stepping up on the bus. The dog almost died of embarrassment! Actually, she was the first one in the family to design a medical device. She had heart failure, and she created for herself a harness out of suspenders so she could sleep upright.

Howard Levin: That's a brilliant idea. It makes the blood volume pool in the lower part of the body so it gets rid of the shortness of breath.

Gelfand: I grew up in St. Petersburg, Russia, which was then the Soviet Union. It was a different world, a different time. I probably got involved in inventing early on because my father was an inventor. He was a university professor but his true profession was engineering and there are lots of anecdotes I could tell you about him. For example, as a very young engineer he was tasked with automating a mill for the grinding of cement. This was a challenging task because the process was a closed system, and there was no way to see the coarseness of the cement during the

process.

He noticed that some operators of the machine were getting much better results than others. He was mystified, so he decided to sit in the plant and watch them. He noticed that the good operators actually listened to the mill. That was their secret. So he brought in an oscilloscope and a microphone and sure enough, he discovered that there was a frequency shift in the noise that the mill makes as it grinds.

That leads to my main point about inventing. Much of what later becomes an invention is based on observation.

**Q:** How did you end up in the medical device industry?

Gelfand: Out of the university, I started working in the pulp-and-paper industry, which is about as far from medicine as possible. I didn't want to stay in graduate school forever, and I wanted to find a place where I could run my own show as soon as possible. My gamble actually paid off. In two or three years I was running my own engineering group, and it was based on trying to control processes in the pulp industry. I was responsible for automation of an enormous plant, and I was primarily looking at control software. This was in the early 1980s. The software industry was just emerging, and there were no software experts there, which was why I got this chance at such an early point in my career.

There was very little room for innovation in the paper industry, but there was a lot to learn about making the different parts of the system interact, which later on, oddly enough, helped me with my studies of physiology.

**Q:** So your first experience was in manufacturing paper?

Gelfand: Yes. The world consumes a lot of paper, and my job was to make the paper bright because there is a premium for light colored paper. The lightening process is very destructive to the paper (not to mention the environment) so there was always this balance of bleaching the paper without destroying it. That taught me my second lesson about inventing: engineering is about the art of compromise. Those who find the best compromises win.

**Q:** I can understand that because my father was an engineer, and he could always be very decisive even when I thought things were confounding, vague and less than ideal.

Gelfand: Being an industrial engineer was good training, because you are forced to make decisions even if you don't have enough data. You can't wait until you are sure; you have to go with a hypothesis, on a project on which a lot of money is riding.

**Q:** So, in 1987, how did you make the crossing from a paper mill in the Soviet Union to biomedical engineering at Johns Hopkins?

Gelfand: It wasn't really a career choice. During the Cold War I moved to America and I needed a job to make money. Some friends of a friend worked for Johns Hopkins and I interviewed with them. Dr. Henry Halperin, who was to become a lifelong friend and collaborator, interviewed me and hired me. He was also

Howard's scientific advisor. That was serendipity.

At that time, the modern medical device industry was just being born in a regulated environment, and it was a great time for applied physiology and cardiology, which was what was going on at Johns Hopkins. There were people there like Dr. Myron Weisfeldt, the director of our cardiology division. They wanted to work on devices and they realized that they needed to hire some engineers.

**Q:** What kinds of projects did you work on at Hopkins?

Gelfand: The project that I was hired for was a pet project of my boss Henry Halperin and of our division chief Myron Weisfeldt. The idea was to improve upon cardiopulmonary resuscitation. Everybody agreed that current methods were inefficient and that more people ought to be able to be resuscitated. There was a lot of experimentation going on in the lab on how to improve upon chest compressions. You wouldn't believe the crazy things that were tried – there was one theory called high impulse CPR and it involved dropping weights on the chest to stimulate blood flow.

In the end, we ended up with a circumferential chest compression idea, and now you can see the successor to the device in ambulances as the *AutoPulse*, sold by Zoll Medical [Zoll acquired AutoPulse manufacturer Revivant, which in turn had acquired the assets of CardioLogic – the Johns Hopkins start-up – in 1999].

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It was an inflatable vest that wrapped around a patient's chest so you could apply more energy to the chest without breaking any ribs. I was put in charge of building the prototype. There was funding for the project from Dr. Richard Ross, the Dean of the Hopkins medical school. He was the driver behind those kinds of projects and later became a scientific adviser to my first start-up.

We built the device, literally by hand, using parts available at hardware stores, and did a study at Johns Hopkins. The results of the study were astoundingly good, and were published in the *New England Journal of Medicine*.

**Q:** That project was the basis for CardioLogic?

Gelfand: Yes. On the strength of those results, Johns Hopkins decided to do its first spin-off, CardioLogic, to commercialize the cardiopulmonary resuscitation device. For me it was a logical choice to go with the company, so I took a job as the chief engineer of CardioLogic. That was 1992.

**Q:** And how did that product do in the marketplace?

Gelfand: This was a great learning experience. The first generation pseudo-commercial device was tested in Europe. In the US, there were huge obstacles for doing clinical trials on this kind of device. As the chief engineer, I equipped every device with a black box that would record what was actually going on out in the field. We discovered why resuscitation wasn't as effective as it should be. In reality, very little chest compression was being done. Operators were actually spending a

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lot of the time looking for a signal from the heart to see if it was beating. While they were doing chest compressions, they could not see the ECG; the noise would eliminate the signal. We realized that the biggest obstacle was not the inefficiency of chest compressions per se, but the interruptions. We learned that what people reported about what they did wasn't what had actually happened.

The AHA eventually changed its guidelines to address this issue, and now there is a new generation of devices for CPR that allows the paramedics to look at the ECG without interrupting compressions. Dr. Halperin from John Hopkins and Zoll Medical were instrumental in making this happen, but it took decades.

**Q:** That's an interesting example of why experience in the field might not reproduce success in the laboratory. Howard, tell us how you got into inventing. Did you take things apart around the house when you were a child?

Levin: I grew up in Staten Island, New York. When I grew up, it was a borough of New York City that everyone considered "The Sticks."

Gelfand: They still do.

Levin: I'm 53 now. I grew up during the Space Race. My first goal was to be an astronaut. Everyone was interested in science; we all had chemistry kits, radio building kits, things like that.

**Q:** Did you do any early inventing?

Levin: I can't say I changed the world back then, but I did get tired of holding the phone, so I took the rotary phone apart and wired in an old Ma Bell headset so that it was easier to talk on the phone.

My father was a lawyer who really wanted to be an entrepreneur. He got involved in all sorts of things. We found out quickly that in the entrepreneurial world you can do really well and you can do really terrible. But we were taught that one shouldn't be afraid to fail. It's how you recover from failure that's important. Mark and I used to discover that the first time we would do a clinical trial with a new device, almost immediately after it started, we would invariably say, "Oh, how could I not have thought of that? So we learn, we recover, and that makes the invention.

**Q:** Remind me later to ask you if you two have been involved in any spectacular failures.

Gelfand: Oh, it will come up.

**Q:** So what do you think makes a person an inventor?

Levin: A physician friend of my father taught me the art of observation. You notice that someone favors one leg, holds their arm in a certain way, or breathes in a certain pattern. This information is available to anyone who looks or listens with an open mind, but not everyone does. So it's like they say, "Invention favors the prepared mind."

**Q:** You ended up becoming a doctor yourself. What about your training prepared

you for the role you have today as an inventor?

Levin: I followed the standard track – college, medical school, residency, fellowship, attending. I was trained as a heart failure transplantation cardiologist, but along the way I really enjoyed clinical medicine and thinking about the underlying physiology. I found that I enjoyed working in the ICU world because it required a deep understanding of physiology and the ability to integrate everything I knew about different areas of medicine into what was happening with the patient. There one would commonly get to the end of the available therapies and have to innovate or kludge together therapies, that is, it required a little inventiveness about applying things.

In fact, this is one thing that I think separates Mark and me from other inventors in the medical device space. We come to it with a focus on physiology.

**Q:** Would you explain what you mean by that?

Levin: Physicians in general are not scientists, for very good reasons. They learn symptoms and patterns of symptoms and apply them to disease states and there is a set pattern of therapies for a particular disease state. Now, if 2,000 years ago somebody clutched their chest, it was evil spirits; 1,000 years ago, it was an imbalance of humors, 20 years ago, it was hemodynamics, 10 years ago, there was a molecular cause, now it's genetics and so on. The underlying reasons – the disease states – that you learn in medical school might change over the years, so if you go by that, you might be interpreting something totally wrong. But if you go by the symptoms, the clinical patterns, you are still going to be right.

Today, there are very good molecular and genetic scientists who are also physicians, but there seem to be very few remaining systems physiologists, which is what I believe Mark and I are.

Gelfand: Right, we became obsolete in the 80s and 90s because everybody was moving toward that other stuff, but conversely, we were among the few left standing that understood how organ systems interacted with each other, and that's what people say is one of our unique qualities. We can be "cross cultural." We understand the physiology of how different systems interact.

**Q:** What was the first medical invention you got involved with?

Levin: It was at Hopkins in the late 1980s when I was working on a project called cardiomyoplasty for heart failure.

Gelfand: You wanted an example of a spectacular failure, now you have one.

Levin: Cardiomyoplasty involves taking one of the back muscles, the latissimus dorsi, and wrapping it around the heart, stimulating it in synchrony with the heart in order to squeeze the heart. Medtronic was actually doing the project. We found that the best way to look at the interaction between the skeletal muscle and the heart was using MRI. The problem is that standard pacemakers wouldn't work in the MRI. So we developed a system to pace safely in the MRI and that was the first invention that I was associated with.

**Q:** But the cardiomyoplasty project failed?

Levin: It's a good example of how scientific thinking evolves into engineering thinking and then into business thinking. Once we were able to use the MRI, we found that in fact, the part of the muscle that wrapped around the heart was not contracting. When it was taken from the back and wrapped around the chest the blood supply was so disrupted that the muscle became ischemic and couldn't contract any more.

But there were people who benefitted from cardiomyoplasty even though the muscle wasn't contracting, and the question became, why? The hypothesis was that the heart was being constrained by the wrap, and that's how companies like Acorn [**Acorn Cardiovascular Inc.**] and Paracor [**Paracor Medical Inc.**] got started, on the concept of constraining the heart to prevent dilation and improve heart failure.

That's what good inventors or entrepreneurs do; they continually evaluate what they have. Most of the time what you start with isn't what you end up with. You have to keep reevaluating at every point where you are, what you've got and where you have to go.

Gelfand: Howard published the very first human paper on external myocardial constraint for heart failure and we still both firmly believe in the physiological foundation behind constraining and preventing heart dilation.

[Gelfand notes that the duo has done a great deal of development on a third-generation alternative to the devices of Acorn and Paracor for heart failure, an injectable, interventional device that uses a biodegradable polymer to constrain the heart. That project remains on the back burner in this funding environment, especially since both of those first-generation companies have experienced setbacks.]

**Q:** How did you two meet?

Levin: In the late 80s Mark and I met in the lab at Hopkins - we called it a lab, but it was really a machine shop where our desk was. We shared a desk and a computer. I was a cardiology fellow and Mark was an engineer and we hit it off.

The other thing we had in common was that we were both broke. A person whom we eventually came to know well and who worked with us in more than one company was working for a Holter screening company at the time. They had a contract with a drug company, and they were looking for a new way of analyzing the data that they had. I sort of pretended that I knew what I was talking about and made some suggestions about what they should do, and then I went to Mark and said, "I have no idea how to do this, you need to help me." We figured out a way to do it, it worked pretty well, and we got "X" dollars per hour, which we split 50-50.

**Q:** It sounds like the two of you have complementary strengths.

Levin: We have different backgrounds than most medical device inventors. Mark was trained as a systems engineer who learned about physiology; I was originally a

cardiologist who was good at physiology. Over time we have meshed, we have learned how to talk to each other about things. We will express our opinions and not back down, but we will also defer to the other's area of expertise.

**Q:** Let's talk about some of your companies, starting with the first one that you did together, CHF Solutions, which developed a way to remove excess fluid in heart failure patients admitted to the hospital for fluid overload. What was that first experience together like?

Levin: For me, CHF Solutions was the most fun company, because it helped people immediately. In an hour, people who couldn't breathe before were sitting comfortably. The next day they looked like completely different people and they said, "Thank you, thank you, I haven't slept this well for 10 years." That positive feedback was great.

Gelfand: We were actually in charge of CHF Solutions, all the way to the approval. Howard was the president and I was the chief technology officer. It's a good example that helps to illustrate what we've learned and how we've changed the way we do things.

Levin: When we came out of academics, we were inclined to focus on the clinical question and come up with an answer for it, and that's what we did with CHF Solutions. It has a great clinical answer to people who are resistant to diuretics or for people in whom you need to get fluid off controllably and quickly. But it does not fit into a business model that cardiology companies normally deal with. We had to learn everything from call points, to cross cultural referrals, to who carries the bag and how it fits into an acquirer, to how things work within a hospital in terms of logistics with catheter placement, what happens after 5:00 and before 8:00 in the morning and how that all affects your cost-benefit and reimbursement. It was a great medical idea that became more of a business issue than a medical issue. That was our introduction to the real world of selling stuff.

Gelfand: I think we were way too focused on development of the devices and working on the clinical aspect with a few physicians who loved doing it but we totally missed on the market development. We never asked ourselves the question, where is the reimbursement? Who is going to pay for this?

**Q:** One of the great talents the two of you have is that you look at diseases from the broader systems standpoint, a perspective that you describe as "cross cultural." While that means you come up with innovative ways of doing things, doesn't crossing boundaries in fact sometimes present problems because medical specialties can be siloed?

Levin: One of the big problems with CHF Solutions is that heart failure cardiologists don't have a device budget. They prescribe the drugs that are on formulary at the hospital. When it comes to paying for a piece of capital equipment for heart failure, the heart failure guy has no budget; it's not in the cath lab's budget, it's not in the electrophysiologist's budget, and we got some push back from nephrologists because we were stepping on some toes [The device was

essentially a kind of hemodialysis, made simple enough for any clinical specialty to use.]

Levin: All these things were great learning experiences for us. The problem is very cross cultural. For somebody in one specialty to refer to someone in another specialty immediately, it had better be a lifesaving therapy, otherwise it might get used to some extent but you won't get rapid adoption.

In the end CHF Solutions worked out well and got picked up by Gambro. It is doing well clinically, and Gambro is doing well financially. [**Gambro AB** acquired CHF Solutions in January 2010.] [W#201010018 ]

**Q:** Since Gambro is a leader in dialysis, that makes a lot of sense. It occurs to me that I don't see a lot of venture capital-backed start-ups in nephrology.

Levin: Exactly! There should be, though. We need to figure out a way to get rid of dialysis, or to improve it so that it is not only life-sustaining, but it makes peoples' lives better.

Gelfand: It is an area still looking for its innovators, and someday that will happen, but the economic constraints on dialysis make innovation tough. Actually, one of my favorite inventions was *RenalGuard*. It's not a classic start-up, but we licensed it to PLC Systems.

**Q:** I remember seeing that licensing deal and wondering what a TMR company was doing with a kidney product. [PLC Systems was a laser company delivering transmyocardial revascularization (TMR) for angina. They divested that business in November 2010 to **Novadaq Technologies Inc.**] [**201010159**]

Gelfand: PLC came to us [in 2003] and asked us to identify a new technology that they could pursue. They saw that TMR was losing ground and they had cash so they wanted to retarget. They wanted a relatively small market, they didn't want to compete with large corporations, and they wanted to solve a problem that was not addressed. We proposed quite a number of things, and among them was contrast-induced nephropathy.

Radiocontrast dye used in angioplasty is nephrotoxic and can lead to acute renal failure in some patients. It is well linked to mortality. It doesn't happen often, but when it happens it is really bad.

We proposed that as a target, and then they said, "Now invent the technology." They gave us some money and we started experimenting.

**Q:** Why is this your favorite project?

Gelfand: It was a challenging engineering / physiology project. The constraints were terrible. You are talking about a rare event that is not directly related to the activities of the cardiologist in the lab. Because the device is used preventatively, it has to present no risk whatsoever, and it has to be very cheap. It has to be so easy to implement that the cardiologist won't have to spend any time on it whatsoever.

We started experimenting with every possible thing that we could think of. We

learned that injury to the kidneys from contrast is primarily ischemic. The kidneys basically ruin themselves trying to remove and concentrate the radiocontrast, which is a heavy iodine molecule that generates a high osmotic gradient. The kidney tries to remove the contrast, and in the process become ischemic because the blood flow becomes like sludge.

We realized that when kidneys are making huge amounts of diluted urine, they aren't doing any work. Filtration is a passive process. The kidneys work very hard in the process of concentrating urine, removing all the toxins very slowly. That's why it can be dangerous when contrast is pushed rapidly during procedures.

We came up with this counterintuitive idea of changing the conditions, during or immediately after the procedure, under which the kidney lives. We tried all kinds of things, even ridiculous things like plugging the bladder and overinflating it bladder to sort of hibernate the kidney for an hour or two. Finally, we came up with the idea of giving the kidneys large amounts of IV fluid.

There were challenges with that strategy; the problem with high volume hydration is that it is very hard to track and it is easy to overload the kidneys and create pulmonary edema. So we created a closed loop system that would measure the amount of urine coming out of the patient and infuse the saline proportionately back into IV. We tested it in animals, and it worked extremely well. Now PLC is selling it in Europe, and positive European results were presented at the last TCT [Transcatheter Cardiovascular Therapeutics] meeting.

Levin: As a pure exercise in applied physiology and the process of invention, RenalGuard is an example where we really refined our model. In this case, we used a contract firm to manufacture the prototype. It allowed us to focus on the things we understand best and to do it without spending huge amounts of money, to quickly arrive at a practical solution, and to leverage our knowledge of systems-level physiology.

Gelfand: That's why we started our own company Coridea, to create an environment where we could engage in an experiment and go for a solution cheaply and fast, before a lot of other people or a lot of money get involved, because at that point it becomes very difficult to shift gears.

One thing that makes us different is that we believe that all the technologies that we need probably already exist inside or outside of the medical field. The medical industry doesn't usually lead with new technologies, it usually adapts from other fields. It simply can't compete with the pace and R&D budgets of industries like telecommunications. We try to do clever adaptations, and that saves us time and money.

Levin: The problem is that after you start a company and now you have people in the company, VCs and the management of the company don't like to make changes, and understandably so. They made their bet, and until it is clear that is not going to work, it is hard to get them to change or modify. In Coridea, we want to be able to try and compare different approaches quickly and cheaply.

**Q:** How is Coridea funded?

Levin: We have always been self-funded. After we left CHF Solutions in 2003, we used the money from that exit to fund our own testing. We could go through a couple of ideas and get it to the point where we personally believed it was viable and worthwhile to move forward and it was the right thing to do to start a company around it. Sometimes people have an idea, get some people to fund a company, and then they are stuck. We wanted to get to the point ourselves, where we can feel comfortable that something is a viable opportunity.

[Note: Coridea's next company, Coridea NC1, the subject of which is to be determined, was recently launched with funding from SV Life Sciences and Third Rock Ventures.]

**Q:** What is your definition, these days, of a viable opportunity?

Levin: Our view of that has changed over the years. As we said, we used to try to fix a problem that was of interest to us clinically. But we have learned that VCs want you to have identified the unmet clinical need and the market size. You have to be able to differentiate that market down to the base market and what they are at risk for. We have to articulate the technical risk, the IP risk, the clinical risk, the physiologic risk, identify the competitors and potential acquirers, and lay out the timelines, whether a pre-commercialization exit will be possible or whether we are going to need a sales ramp to get acquired. We are not business guys, but we have learned enough about those different areas to assess whether to go forward with an idea or not. We won't go forward with anything that doesn't have a base market of a half a billion dollars because VCs won't fund it. That locks us into certain areas, heart, lung, and kidney, but we have expertise in those fields. They are all related.

Gelfand: We had some IP in spine because we had an engineer that had some great ideas in that space, but we licensed that IP out. We quickly realized that we don't know anything about spine, and physicians in that field don't know us either. Today, if Howard makes a call to anyone in cardiology, he will get their time and attention.

**Q:** So Coridea is a sort of incubator?

Gelfand: Coridea will vet and sort out ideas. We have become good critics of our own work over time, and over the years, we have also acquired a body of advisers that we trust and discuss our ideas with.

Often we are not looking for a qualitative response from our advisers. A good example of this is renal denervation. Ardian is now getting so much attention but very early on it was incredibly hard to get this going because it was so new and counterintuitive. The first responses were highly negative. We heard, "You're crazy, it's not going to work." Instead of getting upset, we took that as a positive response because that meant we were doing something that is really new. If the advisers can tell you, "This is exactly what should be done," that probably means that it already has been done.

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**Q:** Ardian is being described as one of the biggest, if not *the* biggest, exit of a venture capital-backed company. Tell us how you came to found Ardian.

Levin: First, I'd like to go back to a person who had a great influence on us. At Hopkins, we both worked with Mike [Myron] Weisfeldt. He instilled in us this idea of thinking big. His point was that it takes as much brainpower and effort to think about a small problem as a big one, and your chances of actually solving them are also about the same. So he emphasized that we should not focus on small problems and not get bogged down in the details. It's always better to focus on something big.

Gelfand: In that sense we are probably not like other device inventors, who see something that's already been done and find a way to improve it. The trouble with those improvements is that they usually don't fall into the "think big" paradigm. They may turn out to be big by accident, but in most cases they are just improvements.

Levin: Ardian was a big idea. I will tell you, the number of people who told us initially that it was the stupidest idea they ever heard was countless. [Ardian treats hypertension with a catheter that delivers a low dose of radiofrequency energy to disrupt the renal sympathetic nerves.] And at that point, they were just as likely to be right as wrong. We were lucky to be able to move forward.

Gelfand: We had just come out of CHF Solutions, which, by contrast, was a classic improvement company.

**Q:** Really? But there was no other device for heart failure like it.

Gelfand: Yes, but we basically took a dialysis machine and packaged it into something usable. Everyone already knew that removing fluid from heart failure patients was good for them. And excellent clinical trials had been done on hemofiltration for heart failure that were very conclusive. It's just that the technology used to be clumsy.

Ardian grew out of our learning from CHF Solutions, though. We were working on the removal of fluid from every possible pathway because it is no secret that sodium overload is behind all those complications of renal failure, heart failure, or cardiorenal syndrome, and we doggedly focused on one fact: the kidneys in those patients can remove sodium but for some reason they just don't want to. I wondered, "Why don't they want to?" And, "How can we force them to?"

Levin: This is an example of how we work. A lot of the secrets of the world are found in the library. People from the 1920s to the 1960s did amazing clinical and physiological studies. They would practically cut people in half and sew them back together, resulting in a great clinical discovery, although you couldn't possibly implement that kind of an approach.

But we looked at those kinds of studies in order to build up a physiological theme. As we said, Mark and I do cross-cultural really well. Just because we are talking about hypertension doesn't mean that we are only working in the cardiology area.

We might look at nephrology, GI or the brain, if there's a common physiologic link.

Going back to the literature, we found that hypertension was a surgical disease until the 1960s. Basically they took out the sympathetic chain. In fact, if you looked at the literature in the 60s, until beta blockers came out, there was a debate about whether you should do surgery or use drugs. The problem with removing the sympathetic chain is that you get all kinds of side effects. It is a blunt instrument. We looked at all of that physiology, trying to figure out how we could remove the influence of external effectors on the kidney, to let the kidney do what it is supposed to do.

We also found some pediatric papers where there were malformations in the kidney in patients who were hypertensive, but when they removed the malformations the blood pressure went back to normal. We began to wonder what was the contribution of the kidney itself – apparently it wasn't only stuff on the way in to the kidney but on the way out as well. We then found a common pathway, the renal nerves.

**Q:** And the rest is history; I spoke to the Foundry's Hanson Gifford who said that the technology worked even better than they'd hoped it would. What kind of a role did you play in Ardian?

Gelfand: After our experience with Ardian we can be clear about where we fit best. If we had been in charge of executing it, I don't think we would have done as well. Hanson Gifford and the Foundry were fantastic. That group of people knows exactly what it is doing. They had enough patience to stay with it at the preclinical phase, to look at the technology embodiments and choose the one that was commercially viable. If we were doing it, we probably would have chosen a different approach. We learned an enormous amount from how they operate.

Levin: We have learned that different stages of a company require different types of people. There are people that come up with the idea and maybe take it through early clinical trials, perhaps to the Series B round, and there are people that operationalize the company and take it through clinical and to \$50 million in sales, and other kinds of people who take it from a \$50 million company to a \$100 million company. We fit into the early part.

**Q:** Let's talk about Cardiac Concepts. You are really breaking new ground there, with a neurostimulation approach to central sleep apnea (the rarer, neurological kind of sleep apnea, as opposed to obstructive sleep apnea, a respiratory disease). ( See *"Sleep Apnea Devices: The Changing Of The Guard,"* START-UP, October 2010 [[2010900199](#)].)

Levin: That's true. With Ardian, it was already accepted that lowering blood pressure has a positive impact on patients. If they could show that they lowered blood pressure, everyone would intrinsically accept that we did what we came to do.

With Cardiac Concepts, they are fixing a respiratory problem -- or rather a neurologic issue -- to have an impact on heart failure. We'll have to convince the

pulmonary physicians because they are the testing and referral guys. They have an idea of what they want their endpoints to be: AHI [Apnea Hypopnea Index]. The heart failure guys will want to know other things: how will it impact heart rate and other parameters related to heart failure.

Gelfand: With Cardiac Concepts we wanted to validate the physiological concept as early and cheaply as possible. You can develop an implantable stimulator, an implantable lead, take two years to do that, and then go do a study in humans. But you might find out that after you spent \$10 to \$20 million, the implant needs to be changed, or the lead needs to be changed. You really want to use things that you know to validate that concept so you can justify spending that money.

We wanted to find an acute or sub-acute way to test this device, so they went with a pacemaker system external to the body, oscilloscopes and a bunch of other equipment on a cart. Three Arch Partners and our other investors understand that reducing this all to an implant is just an engineering problem.

**Q:** What do you have in mind for some new projects?

Levin: We are generally interested in trying to keep the kidneys from failing.

Gelfand: We will never stop working on this. Like others, we first wondered how we could improve dialysis, but we learned from our adviser, Dr. Hans-Dietrich Polaschegg [who was a technical founder of **Fresenius SE**], that this is near to impossible. With dialysis, you are trying to do in four hours what the body does in three days. It is physically impossible to speed up the process of diffusion.

People have been working on nocturnal dialysis – dialysis that can be done daily in the home, but there are always going to be large numbers of people that can't benefit from this because of their education level, their co-morbidities, their support systems, access infection risk, and other reasons. So we have decided to do something else.

Howard has always been saying, instead of trying to improve dialysis, why don't we prevent renal failure? The progression of renal failure is known several years ahead of time. We have set as a goal to find all the possible ways to delay the need for dialysis.

**Q:** What do you think the role of innovation will be for emerging markets, like China, or Brazil, for example?

Levin: There is a lot of potential upside in emerging markets like China and India because of the huge number of people. Whether the US model of developing devices can take advantage of that, the jury is totally out. We have done a fair amount of work in China. There are cultural differences, practical differences, and the way that people approach things are different, but there's no doubt it is a great opportunity.

Gelfand: I know Brazil fairly well, and the reason why new heart surgeries like the Batista procedure come from a country like Brazil is because in that world and other emerging economies, medicine is centralized in large hospitals, and there is

no follow-up. They want procedures to fix patients definitively and send them off; they don't expect to see them back every six months for little tune-ups.

Levin: They also don't want to pay for lifetime maintenance with drugs, so they offer a huge device opportunity.

**Q:** It sounds like Ardian has the opportunity to change medical practice.

Gelfand: We are happy that our inventions have found their way into every day clinical practice all over the world. I was in an ICU in Poland where I saw the CHF Solutions Aquadex quietly spinning away. When I told the young attending that we invented it, he looked at me like I was a lunatic. For him, it was just a part of the landscape.

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