



The business of sleep

An interview with Prof. Peretz Lavie, the outgoing Technion president

IN SEPTEMBER, Prof. Peretz Lavie will complete a decade as president of the Technion – two full four-year terms and two additional years. His successor will be Prof. Uri Sivan, a physicist famous for creating a tiny transistor based on strands of gold wire and DNA.

During his stint as Technion president, Lavie engineered a remarkable joint venture with Cornell University to create a new university on Manhattan's Roosevelt Island, initiated by former New York Mayor Michael Bloomberg, along with a new science and technology university in Shantou, China, and funded by the Guangdong provincial government with the support of the billionaire Li Ka Shing.

Lavie is exceptional because he has combined three careers, one as a pioneering researcher of sleep disorders, a second as a successful entrepreneur and a third as an effective academic administrator – the first president in the history of the Technion to be elected for a third term in office. This is rare, because generally the conjunction scholars confront is either-or (research or business), rather than both-and (scholarly research and business).

The Technion (Israel Institute of Technology) is a public research university in Haifa that was established in 1912.

Each year Lavie shares his start-up insights with students of the entrepreneurship course launched by Nobel Laureate Dan Shechtman over 30 years ago. I interviewed him at length about his sleep research and resulting start-ups.

How did you first become interested in sleep research?

It started when I was a student at Tel Aviv University in 1968. One of the lecturers in the department of psychology, Prof. Zvi Giora, had an interest in dreams. At that time, the area of sleep research was in its infancy. The turning point was 1953; it was discovered when that when you record brain waves and eye movements during sleep, you can identify the periods when people dream. This was a landmark discovery and

slowly this field of research has emerged.

Together with Zvi Giora we established a tiny sleep lab and starting some pioneering sleep recordings. When I thought about graduate studies I decided to continue with sleep research. I was fascinated by the fact that when you stand next to a machine, you can precisely identify when the person sleeping in the next room is dreaming. You can wake them up and get the detailed dream story. This is how I found myself in W.B. (Bernie) Webb's sleep lab at the University of Florida, Gainesville, one of the meccas of sleep research in the '70s and '80s.

I joined the Technion in 1975, came to the School of Medicine that opened its gates four years earlier, and set up the first sleep research lab. In between Florida and Haifa, I spent a year at the University of San Diego, California, specializing in sleep medicine. I was exposed to the use of sleep lab recordings in order to diagnose sleep disorders.

I think it was my mother who first referred to me a relative or neighbor, who suffered from from sleep disorder. She said, can you see her and give her good advice? Now, I am not a medical doctor, but a PhD. I could only be a consultant. I saw the person, then another and another... I found myself dedicating quite some time to seeing people with all sorts of complaints about sleep. At that time there was a neurologist, Dr. Ronnie Peled, doing research in my lab.

Together with Ronnie and some other physicians, we formed a team that together provided diagnostics and treatment, and this is how the Technion Sleep Disorders Center was born. Once the number of referred people increased, I said to the vice president for research, "Look, I am seeing many patients. We are the only ones in Israel. Let me open a service clinic, the Technion Sleep Disorder Center."

"Dr. Ronnie Peled was the clinical director, and we started to see patients. At night, we used to do sleep recordings; some of the physicians provided treatment. We started in the Technion, and then we opened clinics in Tel Aviv, Jerusalem, Hadera and Holon. Today we have two – in Haifa, Rambam

Medical Center, and in Givatayim. Many of our students opened similar clinics in other places as well. This was the first company that I started, but soon others followed. I would estimate that up to now some 200,000 people spent at least one night in a Technion sleep disorder center.

What causes snoring and why do men snore more than women? Why is snoring, and sleep disorders in general, related to serious threats to our health?

One of the first patients referred to me came as a delegation of three. A snorer and two neighbors in the apartment block in which he lived. They spoke; he did not. They said, "If you do not solve this problem, we are going to kick him out of the apartment. The entire block cannot sleep because of his snoring!"

Snoring is caused by the vibration of the soft tissue around the throat. With aging, the control of the smooth muscles around the pharynx (the cavity behind the nose and mouth, connecting them to the esophagus) is weakened. As air moves along the tissue, the tissue vibrates. For instance – take this window shade, move your hand along it, it vibrates, and makes noise. This is snoring. In sleep apnea, it is intermittent. It occurs when there is a collapse of the airways during breathing.

Sleep apnea syndrome (breathing repeatedly stops and starts during sleep) is caused by the intermittent collapse of the airways. Once the airways collapse, airflow is blocked; once the blockade is opened there is a snorting sound that is very alarming.

For most of the couples who come to me, the wife is complaining, because snoring is much more common in men than in women. Women say, "I am not bothered by the snoring, but by the silence in between snores. Suddenly there is a silence, it is like he has died, and it can last up to 70 seconds, this blockade of breathing."

Why are men more prone to sleep apnea than women? There are many reasons. First, the shape and length of the airway. Usually, men have longer and thicker airways than

women. Second, it's hormonal. Progesterone, the female sex hormone, facilitates breathing. Testosterone, the male hormone, inhibits breathing. We men pay the price; we are more prone to sleep apnea.

When and why did you launch your sleep-related business venture?

Starting our second business was a byproduct of our clinical and research activities. When we started sleep recording, it was in its infancy. We needed to provide technological solutions to improve some of the devices and gadgets that we used in the laboratory. One of my assistants, Jacob Zomer, developed a very efficient respiratory belt; placed around the chest, it measured respiration. Most of the commercially available belts had problems. This one was a very efficient noise-free one. Many of the visitors who came to our lab and saw the belt said, can you give me one? After the 10th such request, we said, "Why not produce and sell them?" This was our first commercial activity.

It led to SLP-Scientific Laboratory Products Ltd., which specialized in building a variety of sensors for sleep laboratories. The company was a Technion company, 50% owned by my group and 50% by the Technion. We are now selling a variety of sleep market sensors around the world.

The third company we started was Itamar Medical. This wasn't our own initiative – the story is very interesting. One of my areas of research was Sleep Apnea Syndrome, a disease characterized by repeated breathing arrests during sleep. The patient falls asleep and stops breathing. This can happen throughout the night. Severe patients have this once per minute! These patients are not aware of their breathing disorder. They complain about their tendency to fall asleep during the day. Often their snoring is very disturbing and loud, and many have hypertension.

At that time one of my postdoc fellows, Dr. Bob Schnell, and I began to look into the link between hypertension and sleep apnea. It was obvious to us that blood pressure dramatically increased during sleep; when you stop breathing, then resume breathing, a sharp increase in blood pressure occurs. How can this be measured? At the time, to measure blood pressure during sleep, you had to go into the arteries with an invasive measurement, which was very risky. So we decided to develop a device that would allow us to measure blood pressure continuously

during sleep – from the finger.

Measuring blood pressure through the finger is based on physiology. The finger has the capacity to change blood flow 100-fold within seconds. It has numerous nerve endings, and hence is almost the perfect site to measure changes in blood pressure. We built a device that was a sensor mounted on the finger; it imposes uniform pressure and allows us to measure the changes in blood flow in the finger in very sensitive way.

We decided to look for investment, to build a blood pressure monitor based on this device. In 1997, I was dean of medicine, and got a phone call from someone I did not know, Dr. Giora Yaron, an entrepreneur and physicist who was the CEO of Indigo, and before that National Semiconductors.

He had heard about our device, heard we were looking for investment money, and said he wanted to meet with me to tell me about a different application of our device. He said he had been looking for two years to solve a technical problem that we had solved.

"When shall we meet?" I asked.

"In 30 minutes, I will be in your office," he said.

He told me he was working with a heart surgeon who, while doing open heart surgery, looked at the fingers of his patients, and noticed the fingers turned blue. Why? Because blood is squeezed out of the fingers as the body reroutes the blood to the heart to protect the heart during surgery. We could use our device as a sensitive indicator of ischemia – an inadequate blood supply to the heart.

We tested it on 40 patients who underwent heart surgery, and in 39 of them found signs of ischemia in the finger. Convinced that our technology was able to detect ischemia, we started a company. The founders were myself, the cardiac surgeon, and Giora. Giora brought in another partner, Martin Gerstel, who was the CEO of ALZA, a large pharmaceutical company, and had immigrated to Israel.

As for the fourth company, I was on an American Technion Society fundraising mission. Now, sleep is a sexy subject. I gave a talk in Boston about sleep apnea and about the model we had developed to diagnose and treat it. Someone approached me. "My name is David Baron," he said. "I am a Technion graduate in electrical engineering. Is there anything in the US similar to what you are doing in the Technion sleep clinics?" I said, "Unlike in Israel, in the US there is a separa-

tion between treatment and diagnosis."

"Would you like to open a sleep lab in the US?" he asked. I said, "OK, but I am not a businessman."

"I am," he said.

A month later, I flew back to Boston, and met with the head of all Harvard Medical School hospitals and told him about our sleep labs. "You came from Haifa, and you teach us here in the US about sleep medicine!" he said. He gave us the OK to team up with Brigham and Women's Hospital, and we opened the Sleep Health Center, a service modeled after the one we had in Israel.

There were many unexpected twists and turns over the last 15 years. At its peak, there were some 33 clinics in five different states.

Today "big data" is a watchword for many new businesses. What role did big data play in your business success?

One of my contributions to the sleep centers was the database. From the beginning, I was determined that any information we collected during sleep from our patients should be kept and stored. In 10 years, we had accumulated data from over 50,000 patients, and then later, from more than 100,000 patients. This was a gold mine! It allowed us to prepare protocols based on patients' demographic characteristics, their medical complaints, etcetera. We knew precisely when patients came in, what kind of test they required, and more than that – having big data allowed us to do demographic and epidemiologic studies.

We were the first to document the prevalence of sleep apnea in the general population. In 1981, I published the first study of this subject, and we estimated that about one in 25 of all adult males had sleep apnea. But this did not make an impression, even though it was published in *Sleep*, a leading journal, in 1983. Ten years later, when a good friend from Wisconsin published the same result, but this time in *The New England Journal of Medicine*, all hell broke loose.

We were the first to show the link between hypertension and sleep apnea, in 1984. This was a turning point. Sleep apnea was seen to be a major risk factor in cardiovascular diseases. All this had much to do with the fact that we had kept the data, and with the concept of big data, now a buzzword.

I brought with me to Boston a database comprising more than 60,000 patients, invaluable with respect to understanding the demographics of sleep disorder. It turned out

that our sleep centers had gathered massive amounts of big data – the key to our business success.

After we opened the sleep health centers and wanted to convince the insurance companies to approve payment, we sent them information for about 100,000 patients. Until then, they had not seen any database that convinced them. We had the largest experience in diagnosis of sleep disorders.

What advice do you give to Technion students who aspire to become start-up entrepreneurs?

Introducing a new medical device is a tortuous procedure. You learn while on the move and sometimes it costs you a lot of money. With Itamar Medical, we built a device to measure ischemia. We invested many millions in building a medical device, as an add-on to an exercise stress test. But we found it has very little commercial value. An exercise stress test, even if you double the price, is too inexpensive; it's not profitable. At that time, I introduced the company to the area of sleep disorders. We hired a market research firm, and we asked them to provide data on the size of the sleep market.

I remember meeting with the firm, Wilkerson. They came back and said, "There are three typical responses to customers. 1. Drop it, there is no market. 2. It's an OK market; and 3. It's a big wow. This is a big wow."

That was when, in the early 2000s, we moved into the sleep market. We set out to build a device that would provide all the information on the structure of sleep solely from the finger – when people stop breathing, when they wake up, and so on. It was a perfect device. We thought, all we need is US FDA (Food and Drug Administration) approval, and then, onto the market!

The FDA approval was easy, almost immediately. We showed our device, correlated with lab recordings, giving the same results. We're in business! Then we realized that to use it in the practice of physicians, you need a CPT (Current Procedural Terminology) code, a code set used to report medical, surgical, and diagnostic procedures and services to entities such as physicians, health insurance companies and accreditation organizations. This is the endorsement of the insurance companies to use the device. No one will use a device that has no CPT code, because you will not get reimbursement from medical insurance.



TECHNION

Prof. Peretz Lavie

How did you end up "cannibalizing" (making irrelevant) one of your own sleep businesses?

To obtain the CPT code you have to get approval of neurologists, otolaryngologists, psychiatrists, etcetera, and some have sleep clinics. "What you are doing?" they asked. Cannibalizing the sleep clinic market! Because instead of spending a night in a sleep lab, you place the device on your finger and sleep at home; all your sleep data is automatically recorded.

In the Sleep Health Center, we used to charge \$1,300 for a night in the sleep lab. I joked that this was an eight-star hotel. "Come sleep in an uncomfortable position, and pay \$1,300 for it! The same service with the finger device cost \$300 or \$350. The sleep labs will lose their clients."

Getting the CPT code, lobbying with each one of the medical societies, and then the insurance companies, was tortuous. It took several years. Whenever you have a medical device, think about not only FDA approval, think about who is going to make money with the device and who will lose money. Somebody is going to lose!

By the way, we paid the price – personally. Our Sleep Health Centers opened in the US under the umbrella of Brigham and Women's Hospital, which at one time had 33 clinics. We had clinics in Massachusetts, Arizona, Connecticut, New York and Rhode

Island. At its peak, annual revenues were \$30 million. Then one day – one night – the finger device.

The three major insurance companies in Massachusetts decided that there would be no more lab recordings, only home monitoring using our finger device. Itamar Medical was one of them. This killed Sleep Health Centers overnight. No more sleep studies in a lab!

I was a board member of SHC. At every meeting I warned that the day soon comes when there will be no more sleep lab recordings. Be prepared! They did not listen. Since I was elected president of the Technion, I left all my board memberships, and placed a Chinese wall between me and the companies.

Overnight the SHC business was closed. Today there is not a single sleep clinic in the US. In Israel, there are still three to five of them, specializing in complex sleep lab recordings, but most of this is actually done at home.

The finger device is known as "Watch PAT" – peripheral arterial tonometry. The patient sleeps with it. It stores all the data and in the morning, in 90 seconds, the physician has the data and a diagnosis. ■

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