A scientific whodunit

How the drive to understand a close friend's death may lead to one of Canada's greatest medical discoveries of all time

by Michael Smith

Robert Kisilevsky (left) and Walter Szarek: a collaboration "made in heaven."

Colin Rowe

Queen's University, 1975. Professor Michael Axelrad is dying. He has ankylosing spondylitis, a chronic inflammation of the spine, which has caused deposits of a mysterious substance called amyloid throughout his body. Ironically, the tough matted fibres of amyloid are Dr. Axelrad's research subject. In a novel or movie, he would come up with a last-minute cure, but reality ruthlessly blue-pencilled that particular plot twist.

Dr. Axelrad did not live to see the secrets of amyloid unravelled. But he did pass the torch.

Early in 2005, a Montreal company called Neurochem will – if all goes well – begin selling a drug called Fibrillex, which will be the first treatment for amyloidosis, the technical name for what killed Dr. Axelrad. Also in the Neurochem pipeline is another drug that targets both Alzheimer's disease and a condition called cerebral amyloid angiopathy. Another company, a startup called Atherochem, is developing a drug to treat and perhaps reverse atherosclerosis.

The intellectual and scientific roots of all these drugs go directly back to Dr. Axelrad's work 30 years ago.

The story of these drugs is long and tangled. It's a tale of scientific insight, married to effervescent research collaboration. It's a cautionary tale about the attractions and drawbacks of commercializing basic research, both for scientists and their universities. It may also be a lesson on how to foster good science for the people who run Canada's research bureaucracies. And if all the drugs work as hoped – especially the Alzheimer's drug – it will also be the story of one of the greatest medical advances in human history.

Insight

In 1977, Michael Axelrad succumbs to amyloidosis – widespread deposits of amyloid that have destroyed his kidneys. He leaves his last Medical Research Council grant in the hands of Robert Kisilevsky, a pathologist and biochemist whose research will be more and more consumed by a desire to understand the disease that killed his friend. Sitting in a quiet conference room on the Queen's campus, Dr. Kisilevsky, now 67, confides that his goal then wasn't mainly to find a cure, and even now, with a drug on the horizon, that's not what excites him. "If the drugs [work], fine," he says, "but if not, I have had a great time doing the science."

The science, of course, concerns amyloid, found in diseases ranging from Alzheimer's to rheumatoid arthritis. Originally, amyloid was thought to be a starch, a carbohydrate, and indeed the very word means "starch-like." But after heated dispute, amyloid was decided to be mainly a protein – and for nearly a century, that's where matters stood. A single protein, with some odd starch-like characteristics, was causing a wide range of diseases.

Fast forward to Queen's in the late 1960s and early '70s, where Dr. Axelrad was studying amyloid, trying to figure out what it was and how it caused disease. After an ingenious series of experiments with mice, Dr. Axelrad found that *something* – he dubbed it "amyloid enhancing factor" or AEF – was triggering the deposits of amyloid that were involved in so many diseases. He spent the last years of his life trying to characterize AEF, now working with young Bob Kisilevsky.

By then, he and Dr. Kisilevsky knew the wisdom of a century was wrong. There isn't a single amyloid, but dozens. Each amyloid disease has its own amyloid protein. What's more, the amyloid proteins are chemically identical to other, perfectly normal proteins. They're just folded differently, in the same way identical sheets of paper can be folded to make either a flying plane or a floating crane. For those who've been following the medical news, this story might ring some bells. The key players in spongiform encephalopathies – the most famous of which is mad cow disease – are misfolded proteins called prions. In the amyloid diseases, something was causing normal proteins to misfold.

It could have been something in the chemical structure of the various proteins, but when Dr. Kisilevsky looked, there was nothing obvious – no common patterns that might lead to misfolding. That's when Dr. Kisilevsky looked back at the debate over the composition of amyloid – protein or starch? It turned out that, while all the amyloid proteins are different, the carbohydrate component is always the same. It's a molecule called heparan sulphate. And Dr. Kisilevsky was able to show that heparan sulphate is Dr. Axelrad's AEF. "It was very exciting," he says. "This was the first time people had shown there was a molecular entity that could influence the conformal state of a protein."

Collaboration

But if a single molecule is the key player, shouldn't it be possible to interfere with it somehow? Maybe the proper chemical intervention could prevent amyloidosis, Alzheimer's and all the other amyloid diseases. "It was at that point that I contacted Walter," says Dr. Kisilevsky. "I realized that if the protein was interacting with the carbohydrate, there might be ways of preventing that interaction."

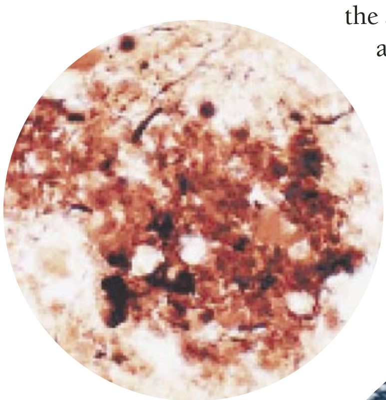
"Walter" is Walter Szarek, a world-famous expert on the chemistry of carbohydrates and one of the stars of the Queen's chemistry department. Born in the Niagara pensinsula, Dr. Szarek, now 66, still bears traces of the accent of his Polish immigrant parents. He's unabashedly enthusiastic about the 20 years of collaborating with Dr. Kisilevsky: "It was a marriage made in heaven – Bob and myself," Dr. Szarek says. The picture both men paint of their work together is of bubbling, constant excitement and eagerness to share. "He gets a result at maybe 11 o'clock at night and he calls me because he knows I want to know about it right away," is the way Dr. Szarek puts it.

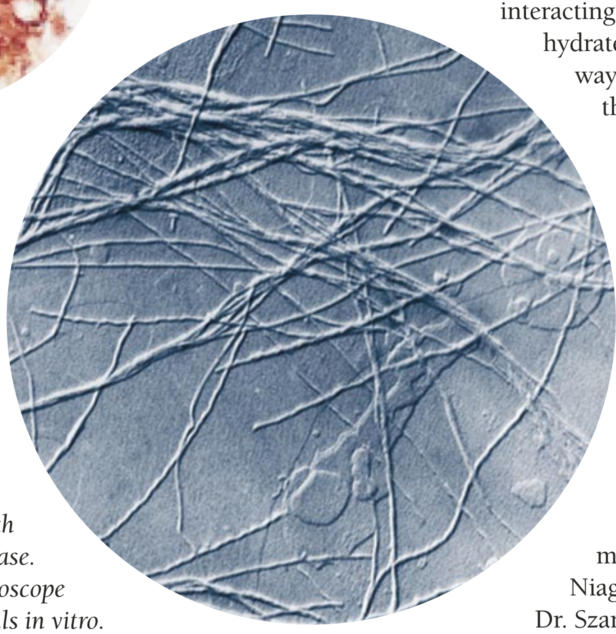
By the time he came on board, the goal had narrowed: to find a compound that would block heparan sulphate in test animals, without serious side-effects. This was Dr. Szarek's home territory, but what made it exciting, he says, is that he was working on the edge of two fields – chemistry and biology. To do innovative science, "you need broadness of vision," Dr. Szarek says. "You need expertise in some area, but you also need to be able to work out in the interface areas."

This is by now, of course, almost conventional wisdom. Canada formally encourages collaboration in basic research, with dozens of centres of excellence dotted about the countryside. But that's what the Nobel laureate Richard Feynman called a Cargo Cult approach: Because the big planes used to bring goodies and have stopped, you build a runway, complete with mock air traffic control towers and hangars, to entice them back. Because scientists like Professors Kisilevsky and Szarek have worked together with dramatic success, science bureaucrats think every basic science project should be a collaboration and so they mandate group research.

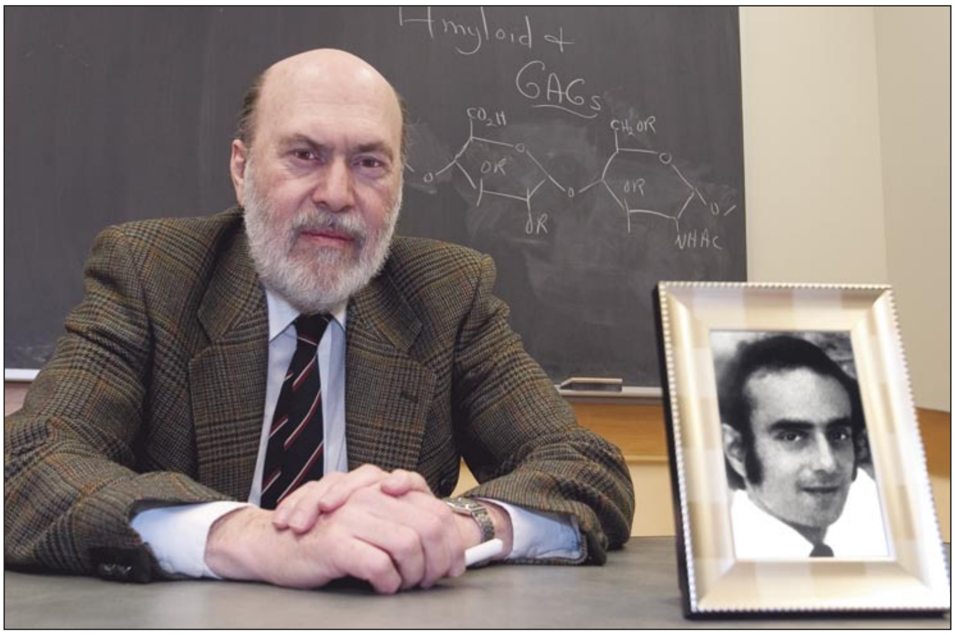
That's nonsense, says Dr. Kisilevsky. "Had Walter and I gotten together in the 1970s, I wouldn't have known what to do with him and he wouldn't have known what to do with me." The big thing, he says, is to have good ideas and then find partners as you need them. Dr. Kisilevsky and Dr. Szarek built a research group, alright, but they did it after they had the goods, not before. "We didn't build a group ahead of time," Dr. Kisilevsky says.

That low-key approach worked. In 1992, the two discovered the first of several compounds that block deposits of amyloid, at least in mice. But curing mice was just the first step.





Above: amyloid fibrils, stained, from the brain tissue of a patient with Alzheimer's disease. At right: an electron microscope image of amyloid fibrils in vitro.



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Dr. Kisilevsky was consumed by the desire to know how amyloidosis killed his friend Michael Axelrad (in photo frame).

Money, money, money

Even the most basic science needs money. And the mid-'80s and early '90s were what Dr. Kisilevsky calls "the lean times" for government support. The obvious step was to look to the private sector, especially since the government was encouraging those links. The first tentative step into the world of commercial science was rebuffed. "We were only looking for $10,000 to get us going," Dr. Kisilevsky recalls, but the university's tech transfer office said the scientists didn't really have anything of commercial interest. Still, they managed to get a few thousand from a university fund, and some seed money from the U.S. Alzheimer's Association – enough to do a bit more research.

That science attracted the interest of a pharmaceutical company, Upjohn Co. "Upjohn was very, very good to us," Dr. Kisilevsky says. "They gave us a lot of money and there were some very good people to work with."

But in 1992, Upjohn changed its business priorities and cut its entire Alzheimer's research program – ironically, only a few months before the two Queen's scientists finally found a compound that would do the trick. With Upjohn out of the picture, they went back to the Queen's tech transfer office (now renamed PARTEQ Innovations) and this time, it was clear they had something. "We knew the value of the discovery," says PARTEQ president John Molloy. PARTEQ also knew it was time to start a company. Neurochem was born in 1993, based in Kingston and looking for corporate alliances and investors.

Hopes and dreams

Fast forward again, to 2004. Dr. Kisilevsky is no longer associated with Neurochem, and is somewhat disillusioned about the whole experience. The disappointment hasn't stopped him from starting another company, Atherochem, which may do for atherosclerosis what Neurochem hopes to do for Alzheimer's and amyloidosis. Dr. Szarek retains a connection with Neurochem and still considers commercialization a "great adventure." He too is involved with other start-ups, with some of the same people who helped start Neurochem. Neurochem itself has moved to Montreal, where it employs 125 people, is worth more than $625 million on the market and is run by one of the big names in Canadian pharmaceuticals, Francesco Bellini, founder of Biochem Pharma, one of the original big players in the world of AIDS drugs. In late December, Neurochem sold distribution rights to Fibrillex (the amyloidosis drug candidate) to Johnson & Johnson for up to $54 million US.

What happened?

Neurochem entered the world with high hopes riding on it. For Dr. Kisilevsky, it would be an important source of support, letting him piggyback his basic science on the back of commercially useful applied research. Alas, that view was naïve, he now says. "It was government policy, pushing us to form companies . . . to get money for research," he says. But companies, once created, have wills of their own; and basic research is usually not a priority. "They want to take the cherries you've already got," Dr. Kisilevsky says. It was a disappointment to find that Neurochem, the company founded on his and Dr. Szarek's basic science, wasn't much interested in paying for more fundamental research. And the applied science that Neurochem needed wasn't interesting to him – "I didn't want to just screen compounds, one through 50,000" – so he left.

Dr. Szarek, though, maintained his links. For starters, the chemistry remains interesting. It's one thing, he says, to synthesize a smidgeon of some new compound in your university lab. It's quite another – and equally fascinating – to find ways of making that same compound in industrial quantities, so that it can make sick people better. Equally, "there's a phenomenal amount of personal satisfaction that we can actually see the drug come to market," he says. "If the Alzheimer's drug works out, we've literally changed the course of history."

Over at PARTEQ, John Molloy was hoping that Neurochem would be the template for economic development in Kingston founded on science from Queen's. Again, this was one of the reasons government favoured commercialization – found a company and turn your town into an economic powerhouse, in the same way

John Molloy: high hopes for Kingston.

Neurochem's head office is located in Laval, Quebec, just north of Montreal.

Palo Alto became Silicon Valley. Alas, that too is naïve. Kingston – like most university towns in Canada – has lots of good science, but very little in the way of management expertise, production facilities, or home-grown venture capital. Neurochem needed money and research facilities to expand from the start-up stage. It could have gone to the Boston area, where capital was available. Instead, it moved to Montreal, attracted by the government of Quebec, which lavishes attention (and support) on the biotechnology sector. "At least," sighs Mr. Molloy, "it's still in Canada." But it's not in Kingston.

Pharmaceutical companies in particular are tough. They face enormous scientific, financial, and regulatory challenges and eventually they need top people in the management suite, according to Ottawa-based Robert Bender of ARGIL Management Corp. "You wouldn't get Francesco [Bellini] coming into a small company," says Mr. Bender, who is a manager with a particular expertise – he takes small companies from their inception through the first few years, while they assemble cash, partners, and management.

He played that role with Neurochem, and he's doing it again with Dr. Kisilevsky's new venture, Atherochem. Can you develop a major pharmaceutical company in a small city? "My personal prejudice is you shouldn't even try," Mr. Bender says. "You're looking at tens of millions of dollars and five-year-minimum projects to have something that's even recognizable as valuable." So, most of the time, a drug born at Queen's or Guelph or Dalhousie is going to wind up being developed somewhere else. (He says other types of start-ups are plausible in small cities.)

There are, of course, other hopes. To the outside eye, the chance of getting rich seems a compelling dream and if Neurochem's drugs prove out, Queen's, Dr. Szarek and Dr. Kisilevsky are likely to do very well indeed. In fact, the researchers have already made some money, although neither has traded in the professorial Hush Puppies for entrepreneurial Guccis. "We've clearly gained on this," says Dr. Szarek, "but without sounding corny, I believe that a feast is having enough. I didn't sit down with Bob and say, 'Let's develop a drug for Alzheimer's so we can become wealthy.'"

More important, both men say, is the chance to do some good in the world. And even that goal, Dr. Kisilevsky admits, isn't what prompted him. Like many apparently quiet and retiring scientists, Dr. Kisilevsky says he's motivated, at bottom, by ego. "The most satisfying thing is that your hypothesis has turned out to be, if not completely correct, at least substantially correct," he says. "The fact that [the discoveries] may be useful is to me a secondary thing."

The morals of the story

What can we learn from the story of Bob and Walter and their excellent adventure?

Perhaps the first lesson is that good people have good ideas. Since they started Neurochem, Professors Kisilevsky and Szarek have been involved in other start-ups. Dr. Szarek is working with a company called PainCeptor, whose chief executive officer is Louis Lamontagne, the former CEO of Neurochem who moved it to Montreal to take advantage of Quebec's largesse. Dr. Kisilevsky's Atherochem is in the hands of Robert Bender, who says he was eager to work with the Queen's researcher again because "we have tremendous respect for the quality of his work." Indeed, unlike Neurochem and mainly because of Dr. Kisilevsky's involvement, Atherochem starts with cash in hand – $200,000 from the Canadian Institutes of Health Research and another $200,000 raised privately by ARGIL, which is now looking for even more cash from early-stage investors.

A nucleus of good people, supported by a knowledgeable tech transfer office, can generate enormous energy. "You look to the people," Mr. Bender says. On the other hand, science, not spin-offs, must be the goal: "It's the basic science that leads to [companies]," says Dr. Szarek.

The second lesson, though, may be that we should limit our expectations. Commercializing pharmaceutical compounds is probably not going to pay for basic research or revitalize the local economy. What it will do – again with the enormous caveat "if it works" – is improve the lives of people. If Neurochem's Alzheimer's drug works, for instance, it's going to remove one of the main terrors of aging.

But even if the aspirations aren't quite so high, it's a Good Thing to translate basic science into useful products. Dr. Kisilevsky's Atherochem is a case in point. The company is taking aim at atherosclerosis – the build-up of plaque in arteries that leads to strokes. Disgruntled by his experience with Neurochem, Dr. Kisilevsky is still determined to try again. Why? Well, the science is interesting, he says. And this time he's not expecting the fledgling company to do anything more than develop a drug. Finding a way to treat and perhaps reverse atherosclerosis, he says, would be "a good thing to do."

And that, in the end, may be the biggest lesson. Sometimes science leads to new cures and treatments or new widgets and gadgets. Most of the time, it doesn't. But the goal of science is to understand how the world works, and if that results in changing the world, it's a bonus. Michael Axelrad would have understood that. "I'm fairly sure," says Dr. Kisilevsky of his late friend, that his motive "was to understand the science behind amyloid disorders, not to find a 'cure'."

That said, it will be entirely fitting if, come this spring, the work of Dr. Kisilevsky and Dr. Szarek, sparked by Michael Axelrad's research 30 years ago, results in a treatment for the disease that killed him. AU•UA