AUTHOR COMMENTARIES - From Special Topics

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Mark Cooper
From the Special Topic of Diabetes

According to our Special Topics analysis of diabetes research over the past decade, the work of Dr. Mark Cooper ranks at #6 by total cites, based on 130 papers cited a total of 6,085 times. In Essential Science Indicators℠ *from Thomson Reuters, Dr. Cooper's record includes 246 papers, the majority of which are classified under Clinical Medicine, cited a total of 7,787 times between January 1, 1999 and April 30, 2009.*

Dr. Cooper is the Director of the Danielle Alberti Memorial Centre for Diabetes Complications as well as the Head of the Diabetes Division of the Baker IDI Heart & Diabetes Institute in Australia.

In the interview below, ScienceWatch.com *correspondent Gary Taubes talks with Dr. Cooper about his highly cited work.*

SW: Your most-cited paper is the 2001 *New England Journal of Medicine* article on the "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy" (Brenner BM, *et al.*, 345[12]: 861-9, 20 September 2001). How did this project come about and what was your role in the research?

I'm an endocrinologist by training, and I've been interested in diabetes and kidney disease since the early 1980s. Then in the late 1980s, several groups suggested that diabetic kidney disease was not only related to high glucose, but also that there may actually be a hemodynamic pathway within the kidney, the renin-angiotensin system, that is both activating kidney injury and amplified by diabetes and high blood pressure. Over the next five years, a range of new ways of interrupting that pathway became available to clinicians.

In the early to mid-1990s, I became involved in experimental work looking at what are called angiotensin-II receptor antagonists. The original prototype was losartan, which was just being approved for use on high blood pressure. It was considered particularly useful in diabetics. So we launched a multinational trial to see if this drug could reduce the progression of kidney disease, independent of its effect on blood pressure. Brenner, the first author, was the chief investigator of this multi-national trial.

SW: What did the trial find and why do you think this paper is so highly cited?

Not only did losartan reduce the progression of kidney disease, but it also reduced heart failure, so it is now considered the first line of therapy in most international guidelines for people at risk of diabetic kidney disease. That's why this paper has been so influential. At the time, by the way, this

was the largest-ever trial on people with diabetic kidney disease.

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Mark Cooper with his team leaders.

SW: Do you know what losartan does—what the mechanism is—that leads to a reduction in two different diabetic complications—heart failure and kidney disease?

Since this was a clinical trial, we can never say we know exactly what the mechanism is. What we predicted is that by reducing the action of angiotensin II, which is a profibrotic, proinfammatory molecule that activates injury in end organs—the kidney, heart, and blood vessels—we'd be attenuating that injury, which is accelerated in diabetes. Many of my papers actually talk about this pathway and its implications for diabetic complications, including kidney disease.

SW: Your work spans a lot of different subdisciplines in diabetes and kidney disease. Can you describe your thought process in choosing journals for your publications?

It's become easier because of this world of impact factors. You work out how good the paper is, and what the readership will be, and then decide where to send it. If I have a paper that I think is very clinically relevant, I'll start with the *New England Journal of Medicine.* If I'm not successful, I'll go to *The Lancet,* then *JAMA* or the *BMJ*. The reason we went to the *BMJ* first with my second most-cited paper—the results from the CALM trial—is that the *BMJ* has a tradition of publishing nephropathy papers. As nephropathy is perceived as more and more important, more and more are appearing in the *New England Journal*. But in 2000, the *BMJ* seemed most appropriate.

In terms of the more research-oriented work, if I think it's an extremely strong paper I might try the *Journal of Clinical Investigations* first. If that doesn't work, and it's on the kidney, I'll probably go to *Kidney International* or the *Journal of the American Society of Nephrology*. If it's more about cardiovascular disease, I might try *Circulation* first. If it's one that bridges both but is very diabetes based, I would go to *Diabetes*. I actually follow the impact factors and I also look at where similarly directed work has been published. If some journal has taken a particular interest in a certain area, then I might go there. And then, of course, some are just invited by the journal—then it's easy.

SW: What are the most challenging aspects of doing research on diabetic complications and nephropathy and how has it affected your ability to make progress?

In these clinical trials, the big problem is recruitment and the heterogeneity of the populations you're studying. You have a lot of different ethnic, cultural, and racial groups. It's possible, for instance, that some racial groups respond differently than others. That is a kind of confounder that complicates these studies. The other problem is keeping people motivated. These studies take years. The first study we talked about was three years long. So you need a team of clinical trial nurses and investigators who have a good relationship with their patients and subjects and can keep them motivated.

We've learned a lot over the years about the basic science but we've been finding it very hard to translate that to therapies. One reason for that is this is a very chronic disorder. It takes many years to evolve. Even if you have a major new discovery, it can take 10 to 15 years to translate it to the clinic. It's not like cancer, where you have this malignant disease, and your treatment either works or works a bit, or it doesn't. With these conditions, such as diabetic complications, you can only learn whether your treatment has an overall beneficial effect by doing these trials with thousands of subjects, and following the disorders for years.

But this is a critically important area of research. Increasingly papers on diabetic complications are going to the top of the list of the most-cited papers in diabetes. This is the major burden of the disease—particularly cardiovascular complications—and increasingly we now know that these complications are linked together. They tend to cluster in patients, who tend to get all the complications, not just one or two.

SW: What do you consider the important areas of research in your field?

We're now looking at several different areas of study. One major one is why glucose continues to damage organs in diabetes even after you return the glucose back to normal levels. This is called metabolic memory, and we're trying to figure out the mechanisms of that. We've had two papers published in the last year suggesting that this memory may be partially related to epigenetic mechanisms. We're trying to work out how glucose affects the genome in this way. Why is glucose having this sustained effect on blood vessels, the kidney, the heart, and the eyes? We think it is through these sustained effects on epigenetic pathways.

SW: Can you give us an example of one of these potential epigenetic phenomena?

"We've learned a lot over the years about the basic science but we've been finding it very hard to translate that to therapies."

If you put cells in a high-glucose condition, then return them back to normal, they continue to generate proinflammatory molecules, particularly in a pathway known as NF-?B. These may be related to histone methylation of the promoter region of one of the genes that codes for a subunit of NF-?B.

SW: And the other areas you're now working on?

We're also very interested, not just in diabetic kidney disease, but in the relationship between diabetes and heart disease. Most diabetics die of cardiovascular disease. Surprisingly, this has not been very well studied. The animal models are not very good. We're trying to work out the pathways that cause atherosclerosis in diabetes. Some of these pathways that have been identified in diabetic kidney disease—like this renin-angiotensin system or advanced glycation end products—appear to participate in diabetic atherosclerosis as well. Three of my recent papers are looking at diabetic atherosclerosis and identifying some of these pathways that are also relevant to the kidney and participating in other diabetic complications.

You also asked what I think are important areas. One that I think is a big issue with diabetic kidney disease is that we have a treatment—these ACE inhibitors—but they only delay progression of the disease. They don't cure it. We need to find other pathways critical to the disease, and we have to find therapies that can add on to the ACE inhibitors. Recent studies have shown that glucose lowering is pretty good for kidney disease, but not so effective for cardiovascular disease. So we have to identify new add-on treatments. We have a few targets, but not that many. In the next few years, I think we'll see a significant amount of work focusing on finding new targets and validating the few we have.

SW: What would you like to convey to the general public about your work?

That the outlook for diabetic complications has improved dramatically over the last 20 years. Some of that is due to very good basic and clinical research which I was fortunate to be involved in. People with diabetes should not become despondent when they receive the diagnosis, because the outlook has improved significantly for both type 1 and type 2 diabetes, since managing diabetic complications is much better now than it used to be, although we still have plenty more to do.

SW: If you had an unlimited source of research funds, what research or clinical trial would you like to do that you can't do now?

That's a very hard question. I think what I would now do with this modern technology—with the big advances in epigenomics, genomics, and proteomics—is much more unbiased analysis of the human genome and the epigenome in people with or at risk of diabetic complications, and I would try to identify and accumulate a much bigger panel of potential targets to test. Those are very expensive experiments and the technology has not been widely available. The technology is now just on the verge of being much more comprehensive and robust.

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Mark Cooper's current most-cited paper in *Essential Science Indicators*, with 2,035 cites:

Brenner BM, *et al.*, "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy," *N. Engl. J. Med*. 345(12): 861-9, 20 September 2001. Source: *Essential Science Indicators* from Thomson Reuters.

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