AUTHOR COMMENTARIES - From Special Topics

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David Nathan
From the Special Topic of Diabetes

In our Special Topics analysis on diabetes research over the past decade, the work of Dr. David Nathan ranks at #7 by total cites, and #1 by cites/paper, based on 72 papers cited a total of 6,040 times. According to Essential Science Indicators℠ from Thomson Reuters, his record includes 102 papers, the majority of which are classified in Clinical Medicine, cited a total of 8,333 times between January 1, 1999 and February 28, 2009.

Dr. Nathan is Professor of Medicine at Harvard Medical School, as well as the Director of the General Clinical Research Center of the Diabetes Center at Massachusetts General Hospital. He is the chairman of the Diabetes Prevention Program, and co-chairman of the Epidemiology of Diabetes Interventions and Complications Study, both NIH-sponsored trials in diabetes research.

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

SW: Your 2002 *New England Journal of Medicine* article on the Diabetes Prevention Program (DPP) is cited more times, by a factor of 10, than any other paper you've published in the last decade. Do you consider this your major contribution to diabetes research?

Actually, what I'm probably best known for is the Diabetes Control and Complications Trial (DCCT), which was a multi-center, NIH-funded study in type 1 diabetic patients. But the major results from that were published in 1993, before the Special Topics analysis. We eventually published about 150 papers out of that study and many of them are among my most-cited papers. The original 1993 paper, of which I was the first author, may be the most frequently cited paper in all of medicine—virtually every clinical and clinical research diabetes paper cites it. Of course, these multicenter studies represent the work of hundreds of investigators and the invaluable contributions of thousands of volunteers.

In the past decade, the two papers that are most cited are that DPP study, again one of those wonderful NIH-supported opportunities to study important clinical questions across the US, and a paper from the DCCT published in the *New England Journal of Medicine* in 2005 that looked at the effectiveness of glucose control on heart disease. (Nathan DM, *et al*., "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes," 353[25]:2643-53, 22 December 2005).

The DPP study was important because it showed how to combat the epidemic of type 2 diabetes. The DCCT study was the first to show that controlling blood sugar can beneficially affect heart disease, which is a major killer of persons with diabetes. From

the science point of view, both are similarly important; from the clinical point of view, they are as well.

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SW: How did the Diabetes Prevention Program get started, and what question did you set out to ask?

The institute at the NIH that supports my work, and to which I am forever indebted, is the NIDDK. Historically, it was not as active as the two other large NIH institutes—NHLBI and NCI—with regard to clinical trials. The DCCT was really the first great clinical trial hit for NIDDK in the 1980-90s. With it came tremendous enthusiasm that we can successfully perform these multicenter trials and that it was important that we do more. After the DCCT was published, the NIDDK started thinking about what directions should be taken next.

I was part of a small working group, along with leadership people at the NIDDK, that looked at a number of different studies that might be done with money put aside to do large clinical trials. Two large ones came out of the planning. One was the Diabetes Prevention Trial 1 (DPT1) to study whether type 1 diabetes could be prevented from occurring in high-risk individuals. The results of that study were essentially negative—the selected interventions didn't work.

SW: What was the intervention used in the study to try to prevent type 1 diabetes?

The intervention selected was insulin, not to treat diabetes, but to prevent it. More than 100,000 young relatives—mostly siblings and children—of patients with type 1 diabetes, who were at high risk were identified while their blood glucose levels were still normal, but with decreased insulin secretion. They were on the way to developing diabetes. They were treated with insulin, injected or oral. It was a very experimental approach to see whether it could prevent diabetes, and it turned out that neither of the approaches worked.

SW: And the DPP?

That was the second of the two large multicenter clinical trials that were proposed and funded by NIDDK in the mid-1990s. It was originally called DPT2, like type 2 diabetes, but we didn't like that name and changed the name to the Diabetes Prevention Program or DPP. The NIDDK put out a request for applications, and numerous universities, academic hospitals, research centers applied. The most meritorious applications and centers were selected with a peer-review process, and the selected Principal Investigators subsequently designed and conducted the study. Again, these types of studies depend on a large group of talented investigators including, in the case of the DPP, research coordinators, dietitians and experts in behavioral medicine, and, of course a committed and loyal group of research volunteers. We showed that we were able to prevent diabetes—dramatically.

SW: What interventions were used and how did they work individually?

We had a control group, of course, which was given a diabetes education that everyone received in the study. The volunteers were randomly assigned either to lifestyle interventions—the goal was to achieve 7% weight loss and increase activity to 150 minutes per week—to metformin, the most commonly used diabetes drug in the world, here used to prevent diabetes, to the thiazolidinedione troglitazone, or to placebo. We stopped the troglitazone part of the study early, because of concern regarding the liver problems associated with it.

SW: Did you see in the other groups what you expected to see?

We had a hypothesis we were testing, which was that we would see a decrease in the development of diabetes in these very high-risk people we selected. But the magnitude of the effect was surprising. The 58% reduction in the development of diabetes in the lifestyle group was much more dramatic than we expected; in fact, we ended up stopping that study ahead of time because we got such a large effect. That was also what happened with the DCCT—we stopped that trial ahead of time since we were seeing such a large effect. The 31% reduction of diabetes development with metformin was also impressive.

SW: Did you continue to follow your subjects after the study ended?

When the study ended, we informed the patients of the main results. We actually taught them all, or offered to teach them all, how to do the lifestyle changes that had been so effective. Then we proposed a follow-up of the study and the vast majority of the participants enrolled in the DPP Outcome Study.

SW: You started planning DPP well before the research community became aware of the existence

of the obesity epidemic, so you must have been quite prescient to be anticipating a diabetes epidemic.

"The current projection is that there will be 225 million persons with diabetes worldwide in the next 15 years."

I like to think we were, but it was clear that an epidemic was coming. In 1984-85, the worldwide population of type 2 diabetics was said to be about 35 million. By 1995, it was clearly on the upswing, increasing along with obesity. While we knew type 2 diabetes was increasing, we'd never have guessed by how much. The current projection is that there will be 225 million persons with diabetes worldwide in the next 15 years.

SW: Do you have other large diabetes studies in the works that we should know about?

I have recently written an editorial in *JAMA* about clinical research and what's coming up ("Progress in diabetes research—what's next," 301[15]: 1599-1601, 15 April 2009). I suggested that we now have a wealth of information about how to treat type 1 and type 2 diabetes better and how to prevent type 2 diabetes. The challenge is to make sure that the interventions are being used effectively and cost effectively.

I have become increasingly focused on the public health implications of diabetes research. We have to make certain, as best we can afford, that as many people as possible are offered the interventions that have been proven to work. Prevention must be given a high priority.

It requires real research to determine how to translate the results of clinical research into clinical care most effectively and cost effectively, for the largest number of people.

SW: When you're looking at prevention, were you able to show in the DPP that increasing physical activity prevented diabetes, since physical activity was a part of your lifestyle intervention?

There's only been one study, in China, that looked at exercise independently. That study randomized people to diet, exercise, and diet plus exercise. The design of the study made it a little difficult to interpret, but the investigators couldn't show any independent or added effect of exercise. In the DPP, we could only look at the effects of exercise alone in a secondary analysis, because we didn't have a separate exercise group.

When we did the secondary analysis it looked like the major effect on diabetes prevention was through weight loss. We did notice, though, that those who exercised had the best weight loss. For example, the participants who reached their exercise *and* weight-loss goals, they had the best results. The people who didn't reach their weight-loss goals, but did reach their exercise goal also benefited. Exercise apparently plays an important, supportive role.

SW: So these were all overweight individuals to begin with?

Their average body mass index was 34, which qualifies as obesity. These were big Americans, selected specifically to be at least overweight. Seventy percent or so had a family history of diabetes. We also recruited from ethnic and racial groups that were known to be at particularly high risk to develop diabetes. Our study population was a very high-risk group.

SW: What do you consider the biggest challenge to doing the type of diabetes research you've been doing?

The biggest challenge from the investigators point of view? I think the biggest challenge is to create a study and a study environment in which the research volunteers are respected and feel respected. In the really successful studies in which I've been fortunate to participate, the adherence and retention of our study volunteers has been extraordinarily high—often exceeding 95% over many years. This is in contrast to many – often less demanding studies—in which as many as 20% of the volunteers "drop out" in the first six months.

Keeping study volunteers actively involved in studies requires planning and effort. It is important to make certain that the subjects feel respected, that they're involved in a critical way. If participants are just told what to do and don't understand why they are doing it, they may be made to feel like lab rats. Volunteers should feel part of the research team.

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David Nathan's current most-cited paper in *Essential Science Indicators*, with 3,045 cites:

Knowler WC, *et al.*, "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin," *N. Engl. J. Med*. 346(6): 393-403, 7 February 2002. Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: TYPE 2 DIABETES, DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT), DIABETES PREVENTION PROGRAM (DPP), BLOOD SUGAR, HEART DISEASE, NIDDK, LARGE CLINICAL TRIALS, DIABETES PREVENTION TRIAL 1 (DPT1), INSULIN, LIFESTYLE INTERVENTIONS, METFORMIN, TROGLITAZONE, LIVER FUNCTION, OUTCOME STUDY, OBESITY, STUDY DESIGN.

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