

Controversies of the Sweet Urine Disease

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Before the discovery of insulin, the primary controversy in diabetes was what kind of reductive diet to use—rice diet, rancid fat diet, vegetables “cooked three times in their own water,” and so forth. All were restrictive and essentially treated diabetes by starvation. For type 2 diabetes, they probably worked out, in that they no doubt led to weight loss. (Perhaps we should try some of these again.)

With the advent of insulin, the problem of diabetes was thought to be solved, and indeed, those with type 1 diabetes did just fine, for a while. It didn't take long, however, for those now living longer to begin to develop vascular and neurological complications. And thus began a new round of controversy.

This controversy, which began in the 1930s, raged on for the next 60 years and was often very heated. The issue, simply put, was whether the vascular and neurological problems associated with diabetes were a genetic concomitant of the disease (and thus inevitable and unalterable) or instead were associated with the metabolic abnormalities of diabetes, such as high blood glucose levels (and thus preventable). Which side one took on this issue had great ramifications regarding the method of diabetes management one's practice adopted.

A classic debate on this topic took place in New York in the 1940s between Dr. Elliott Joslin and Dr. Edward Tolstoi. The debate, which was recorded and is available at the New York Hospital, Cornell University School of Medicine, was reenacted a few years ago.

In the late 1930s, Dr. Robert L. Jackson, then a pediatrician at the University of Iowa School of

Medicine, joined the debate. Dr. Jackson, supported by his wife, who was a nutritionist, questioned why the diets of children with diabetes were restricted in carbohydrate and calorie content. He observed that, with such restriction, children were not growing well. The diet of restricted calorie and carbohydrate contained a high fat content so that smaller or fewer doses of insulin would be required. (Only regular insulin was available then.)

Dr. Jackson began to experiment with a regular meal plan (he did not care for the word “diet”) and four injections/day of regular insulin and found that his method could control blood glucose levels in children while still allowing them to grow. He had the foresight to also document the effects of his method on the health of organs usually damaged by diabetes (eye and kidney). And, in the 1950s, he published landmark research^{1,2} documenting the prevention of retinopathy in children with well-controlled diabetes. Unfortunately, Dr. Jackson's data were not well received. This was in part because there was not a good method of measuring glucose control at the time, but primarily because both patients and doctors recognized how hard it was to achieve glucose control.

Longer-acting insulins (protamine zinc insulin, globin, NPH, and the lente series) were becoming available in the '40s and '50s, and physicians trying to be nice to patients were prescribing one dose of insulin per day. Their reasoning was that if control didn't make any difference anyway, why try to achieve it with numerous daily injections? This method of diabetes control was easier for patients

and physicians alike, so it was easy to develop this mindset. Specialists were not needed, and anyone could do it, they said. Physicians with this mindset tended to demand strict scientific evidence that control mattered, while accepting data to the contrary without rigorous scientific scrutiny.

I entered the fray in 1964 when I began training with Dr. Jackson at the University of Missouri. It was about this time that an article was published on muscle biopsy specimens and measurement of basement membrane thickness (BMT) of capillaries.³ The article concluded that control of blood glucose made no difference because thickening had occurred even in those who had not yet developed full-blown diabetes. This solidified the position of the loose-control advocates and made the position of the tight-control advocates very difficult. Nonetheless, Dr. Jackson and I and others stuck to our guns and continued to advocate physiological control, but proof was clearly needed.

Thus began our involvement in Dr. Charles Kilo's and Dr. J.R. Williamson's research on BMT.⁴ We published an article showing conclusively that tight control would not only prevent BMT, but also reverse it when poor control was improved.⁵ We also published an article on prevention of retinopathy.⁶

Dr. Jackson retired in 1972, and his mantle fell to me as a spokesman for the physiological method of tight control. I participated in many debates throughout the country, often against multiple opponents, to advocate for better control. These debates certainly raised emotions, but, confident in our position, we persisted for the sake of the children.

The debate was finally put to rest by the Diabetes Control and Complications Trial (DCCT) results in 1993.⁷ But the underlying problem remained.

In 1996, I participated in a debate with one of the principle investigators of the DCCT, who conceded that I had been right that the course of vascular disease was related to the degree of control of the metabolic abnormalities but claimed that the degree of control necessary simply couldn't be achieved. Tight control, he said, was too imposing on patients (more so than blindness or amputation?, I wondered), too labor intensive, and too costly.

There was also a respected fear of hypoglycemia, which was a concern, especially in children. However, we were finding that we had less difficulty with hypoglycemia when the methods we used brought about normal blood glucose levels more of the time.

Tools eventually became available to answer all of these arguments. Self-monitoring of blood glucose, hemoglobin A_{1c} measurement, and insulin analogs have solved many problems. But still, in 2003, a decade after the DCCT, physiological control still is not universally accepted.

Today, the controversies are centered not so much on "why" as on "how." Debates about how to get the most physiological management include:

- What kind of meal plan should we use—carbohydrate counting? Low-carbohydrate, high-protein diet? Calorie counting? Exchange lists?
- How should we monitor blood glucose levels—fasting and postprandial glucose measurements, or pre-meal and bedtime measurements?

- On what should we base our insulin adjustments—sliding scales, algorithms, or patterns?

Through the current debates, I remain an advocate of physiological diabetes management, as follows:

- A good, healthy, well-balanced meal plan
- Monitoring at fasting and 2 hours after meals
- Pattern control
- Either four doses per day of insulin using the bolus-basal concept, with lispro or aspart for bolus insulin and glargine for basal insulin, or bolus insulin injections with basal insulin administered with an insulin pump

I have been at this now for 40 years, and I will continue to insist that the closer to nature we can become in our management, i.e., the closer we can restore people with diabetes to physiological normalcy, the better off our patients will be.

We need to continue our research to find better ways to mimic nature and test all methodology, to look at the data critically, and to base management on scientific data outcomes. Why must we do this? Not simply to settle arguments and debates, but instead because the quality and length of the lives of our patients depend on it.

We must always look beyond the horizon to see how we can improve the quality of life for those we serve. If we always keep their welfare in mind, then there are no losers of debates, only winners—our patients.

References

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diabetes patients in relationship to level of control. *Pediatrics* 5:959, 1950

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Editor's note: Dr. Guthrie was recently named the American Diabetes Association's Outstanding Physician Clinician for 2003. He was honored at the Association's 63rd Annual Meeting and Scientific Sessions in New Orleans, La., in June. We appreciate his efforts as an associate editor of Diabetes Spectrum and his lifetime of service on behalf of all people with diabetes.