## About the Authors

Dr. David Miller did his clinical training at the University of Western Ontario and the University of British Columbia. He has been a consultant endocrinologist in Victoria BC since 1997, with a focus on diabetes of all types. He has been an active writer of diabetes and endocrinology guidelines provincially and nationally for two decades. He developed many of the interactive tools for the Diabetes Canada Clinical Practice Guidelines in 2013 and 2018. He is a Clinical Professor, Endocrinology, at UBC and University of Victoria and an Internal Medicine Physician Practice Enhancement Program assessor for the College of Physicians and Surgeons of BC.

**Affiliations**

Vancouver Island Health Authority

Sue Schaefer is a retired Certified Diabetes Educator who worked in a variety of settings through the course of her 34 year nursing career. Her last 15 years were spent working in First Nations communities on Southern Vancouver Island. Sue is best known for her work, "Sweet Success with Diabetes: Laugh and Learn with Mrs. Pudding." Sue and her alter-ego Mrs. Pudding have presented in over 100 towns and indigenous communities across Canada. Sue is the proud recipient of Queen Elizabeth II Diamond Jubilee Award for her work in diabetes.

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Judith Atkin is a white settler to Turtle Island (Canada), with a very colonial past from Sri Lanka, South Africa and England. Walking alongside Indigenous community members both as a home care nurse and as a diabetes educator for the past 20 odd years has given her insight into the resourcefulness and resilience of Indigenous peoples as they negotiate the societal and health challenges of the results of residential school, racism and past and on-going colonialism. It is her honour and privilege to live and work amongst families of the Coast Salish and Nuu Chah Nulth Nations on their unceded lands of southern Vancouver Island.

**Affiliations**

Vancouver Island Health Authority

# Case Report: A First Nation Man's Journey with Severe Insulin Resistance Syndrome

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## Introduction

James (a pseudonym) was born in the 1940s near Vancouver Island, British Columbia, to a Coast Salish family. His schooling was the imposed residential school system whereby Indigenous children were removed from their homes and communities and sent to schools in communities far away. His siblings attended various residential schools, so during his three years at such schools he saw them only in the summer time. His treatment during his schooling fostered a deep distrust of physicians and nurses. In addition he lost much of his native language and culture during this time. He graduated from Queen Elizabeth (High) School in North Surrey, British Columbia, where he was the only Indigenous student. James attended Vancouver Vocational School before returning to Vancouver Island to work as a band manager for his First Nation community. He married Mary (a pseudonym) and together they raised four children. Today he works as an Elder in Residence with post-secondary institutions on Vancouver Island.

## Diagnosis and Treatment

James was diagnosed with pre-Type 2 diabetes (T2DM) in November of 2006 and was treated with metformin. He remembers being told not to eat either salt or sugar, and that his diagnosis resurrected his feelings of distrust. The authors met James in December of 2008. His T2DM had suddenly changed. Two months earlier, while taking metformin, he had an HbA1c of 6.0%. He presented to a local hospital with classic symptoms of hyperglycemia, a random blood glucose of 28.7 mmol/L and an HbA1c of 11.4%. His medications at the time were metformin, atorvastatin, clopidogrel, felodipine, and quinapril. Treatment with insulin was initiated and he continued on his metformin, but his T2DM proved quite resistant to insulin up to 250 units per day, on a basal-bolus schedule.

James' history at that time was notable for the concurrent presentation of Guillain-Barré Syndrome and focal segmental glomerular sclerosis approximately 15 years earlier. He had spent close to six months in hospital at that time and retains a tracheostomy scar on his neck. When he presented with insulin resistance he had a stable eGFR of 65 mL/min/1.73m$^2$. In addition, he had an active urine sediment with with hyaline and granular casts in his urine and proteinuria, which had also been stable for many years. He weighed 75 kg (having unintentionally lost approximately 35 kg in the previous eight months) and had a BMI of 23 kg/m$^2$. The first clue to his diagnosis was an antinuclear antibodies test (ANA) which was strongly positive, with a titer of 1:640, with a homogenous and chromosomal pattern. Subsequently, his double stranded DNA was also positive. He had none of the cutaneous or rheumatologic issues normally associated with lupus. At this point the authors suspected that James had type B severe insulin resistance and consulted with Dr. Philip Gorden at the National Institutes of Health (NIH) in Bethesda, Maryland, a recognized expert in insulin resistance syndromes. From the onset, Dr. Gorden and his research team were very interested and engaged in James' care. At that time they were treating patients with type B with rituximab, cyclophosphamide and pulse corticosteroids,[1] and the same combination therapy was administered to James.

## National Institutes of Health

In March of 2009, three months after his diagnosis, James and Mary travelled to the National Institutes of Health (NIH) to meet with Dr. Gorden and his team. They had never previously travelled outside of British Columbia. James recalls being fearful but with Mary's encouragement to trust his care team, proceeded to Bethesda. All travel and care expenses were paid for by the NIH. Mary was able to stay in an adjacent guest building and visit James daily during his three-week stay. During that time he received cyclophosphamide 100 mg daily, two cycles of pulse dexamethasone (40 mg daily x 4 days), and two dose of rituximab (each 1000 mg IV). The complete protocol is described by Malek et al.[1] In addition, the patient was administered Humulin R U-500, approximately 1,000 units per day in divided doses. While at the NIH, James was examined by clinicians in seven different disciplines/care teams; he estimated that he met with more than 30 specialists. He was repeatedly examined, shared his story multiple times and was invited to share his story at their Grand Rounds. When asked about these experiences he recounted his earlier distrust of doctors and nurses but

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that through this journey he "learned to trust" again, relying on Mary for support.

Upon James' return from the NIH, the authors were able to continue his therapy with U-500 insulin. At the time U-500 had to be ordered through the Health Canada Special Access Program; it was available only in 20 mL vials and had to be administered in a syringe. In the early months of 2009, James reached his peak insulin dose—1800 units/day—administered in four injections—400 units (0.8 mL) before breakfast, 500 units (1.0 mL) before lunch, 500 units before dinner, and 400 units before bedtime. His HbA1c reached a peak of 13.0% around that time, despite the very large doses of insulin. There was frequent communication between the care team at the NIH and the care team in British Columbia.

In July of 2009, James and Mary returned to the NIH for the second and final time. Another round of multiple specialist visits took place and James was administered another two doses of 1,000 mg IV rituximab. His insulin doses were being tapered and his HbA1c had already begun to lower but remained quite high. He was receiving approximately 1,000 units per day of insulin and his HbA1c was 10%. By August of 2009, five months after his first trip to the NIH, James ceased the insulin and had normal blood sugars. His HbA1c normalized a couple of months later.

## The Relapse

In late 2010 into early 2011 there was a steady rise in James' blood glucose despite no obvious changes in diet, exercise or medications. There was a discussion between NIH and the authors as to whether this was "just" his T2DM returning or his severe insulin resistance recurring. The conclusion was that this was a recurrence of his severe insulin resistance, the first such case the NIH had seen with this treatment protocol. On this occasion James was treated with cyclophosphamide and two pulses of dexamethasone. His insulin requirements peaked at "only" 1,100 units/day and he ceased insulin by April 2011. Other than peri-operatively, he has not needed insulin for the subsequent 12 years. At times he was treated with metformin and/or linagliptin with positive glycemic effect.

## Type B Severe Insulin Resistance Syndrome

The syndrome was first described by Flier et al in 1975.[2] The underlying pathophysiology is that of anti-insulin receptor antibodies blocking insulin's ability to dock with the receptor. Patients with this syndrome require massive doses of insulin and suffer dramatic weight loss (in distinction to obesity-related insulin resistance); women will manifest hyperandrogenism,[3] which might be confused with obesity-related polycystic ovarian syndrome (PCOS). Acanthosis nigricans, common in other insulin resistance states, can be widespread.[4] Typically there is an associated rheumatologic illness with a wide range of auto-antibodies. The first descriptive case series from the NIH was published in 2002 and described 24 patients seen over a 28-year period; clearly it is quite rare.[5] In a subsequent treatment-related publication in 2010[1] which cited James' case, 14 patients were described with mixed connective tissue disease and five with systemic lupus erythematosus. The remaining six did not have a clear diagnosis but had positive titers including ANA, extractable nuclear antigen (ENA), and double-stranded DNA (ds-DNA). In addition to James, 12 of the 14 patients were female; 11 were African-American and two were Hispanic. At the time of publication in 2002, all of the patients were in remission; their anti-insulin receptor antibodies were measured in the laboratory of Dr. Robert Semple in the Department of Clinical Biochemistry, Cambridge University (UK). At the time of the NIH publication in 2010, James had among the highest antibody titers.

A subsequent publication in 2018[6] described 22 patients (again including James) treated with rituximab, high-dose pulsed steroids and cyclophosphamide until remission, followed by maintenance therapy with azathioprine. In this, study James' 1,800 units of insulin per day was average in the group. James was one of three patients who had had a relapse before responding to a second treatment course. All of the described and treated patients were alive at the time of the 2018 publication after a median follow-up to 72 months (six years). To date, James is the only Indigenous individual seen by the NIH with this severe insulin resistance syndrome (personal communication, Elaine Cochran to David Miller, April 2023).

The NIH group has authored publications regarding the use of U-500 insulin in patients with insulin resistance.[7] This treatment is typically reserved for patients receiving in excess of 2 units/ kg/day. It is now commercially available in Canada in pre-loaded pen format and manufactured by Eli-Lilly as Entuzity™.

## Conclusion

James required coronary artery bypass grafting in 2014 and recovered well from the procedure. Hemodialysis was initiated in 2022. He last regularly took insulin in 2011.

James' wife Mary passed away in 2015. James lives with some of his children and grandchildren near where he was born and grew up (other than his forced trips to residential schools) on Vancouver Island.

We wanted to tell this story for a few reasons. The first, and most important, was to pay respect to James and the story-telling tradition in which he lives. His distrust of doctors and nurses dating back to his residential school experience could have been a barrier to the excellent treatment he received. With the support of his family and community, this distrust was lessened. The second reason is to raise awareness of this rare, but now treatable, form of diabetes. Finally, James and his British Columbia treatment team have nothing but gratitude and respect for his NIH-based team. What started with an email to the NIH led to this story.

## Correspondence

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## References

1. Malek R, Chong AY, Lupsa BC, et al. Treatment of type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. J Clin Endocrinol Metab. 2010;95(8):3641-3647.
2. Flier JS, Kahn CR, Jarrett DB, et al. Characterization of antibodies to the insulin receptor: a cause of insulin-resistant diabetes in man. J Clin Invest. 1976;58:1442-1449.
3. Brown RJ, Joseph J, Cochran E, et al. Type B insulin resistance masquerading as ovarian hyperthecosis. J Clin Endocrinol Metab. 2017;102(6):1789-1791.
4. Willard DL, Stevenson M, Steenkamp D. Type B insulin resistance syndrome. Curr Opin Endocrinol Diabetes Obes. 2016;23:318-323.
5. Arioglu E, Andewelt A, Diabo C, et al. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. Medicine (Baltimore). 2002;81(2):87-100.
6. Klubo-Gwiezdzinska J, Lange M, Cochran E, at al. Combined immunosuppressive therapy induces remission in patients with severe type B insulin resistance: a prospective cohort study. Diabetes Care. 2018;41(11): 2353-2360.
7. Cochran E, Musso C, Gorden P. The use of U-500 in patients with extreme insulin resistance. Diabetes Care. 2005;28(5):1240-1244.