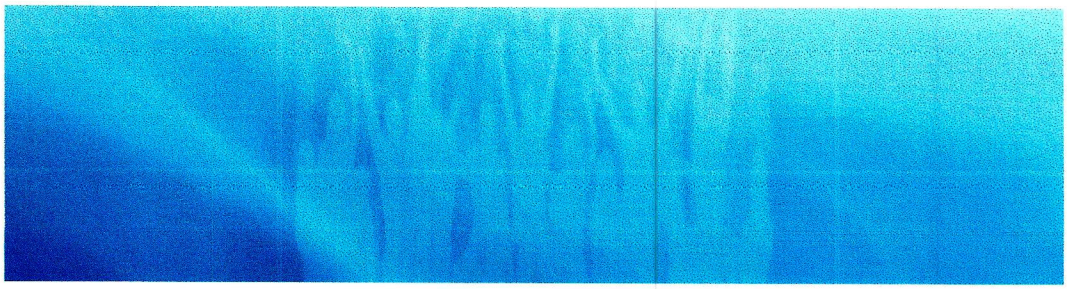

Schull Institute

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Report Concerning Study

Insulin Infusion Therapy on Diabetic Complications, Medications, Quality of Life, Hemoglobin A1C, and Metabolic Functioning: Retrospective Analyses

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Introduction/Background

Diabetes is the seventh cause of death in the U.S. and its estimated total cost is over $240 Billion. The morbidity associated with diabetes is significant with complications of neuropathy, retinopathy, and nephropathy.[1] It is well established through national and international consensus/guidelines that early detection and normalization of blood glucose, blood pressure, and lipids decreases the onset and progression of diabetic complications. While this is the ideal approach and should be practiced with commitment the reality today is that the burden of advanced diabetes complications (e.g., end-stage renal disease, neuropathy, blindness, and amputation) is crippling the healthcare system and results in tremendous suffering of individuals. Unfortunately, when examining these same guidelines and consensus there is a relative void between prevention and treatment. Specifically, how do we manage patients with advanced diabetes complications with clinically significant impact?[2,3]

A Significant Physiological Issue

In the non-diabetic, normal physiological insulin secretion in response to oral carbohydrate consumption occurs in burst secretions that are released in approximately 5- to 7-minute intervals. In contrast, type 2 diabetics lose this characteristic profile and have erratic, flattened, and aberrant insulin secretion profiles. In the case of type 1 diabetics, there is an absolute deficiency of insulin secretion; therefore, no secretion profile is present. While exogenous subcutaneous insulin therapy can be administered to control hyperglycemia, this administration route fails to produce blood levels in the portal vein seen in normal physiological secretion. Having normal physiological concentrations in the portal vein allows for hepatic stimulation resulting in important metabolic cascades and homeostatic reactions. It is well acknowledged that the qualitative and quantitative aspects of normal physiological insulin secretion plays a critical role in the regulation of metabolism such as glucose homeostasis and adenosine triphosphate (ATP) production.[4,5]

Filling the Void & Answering the Questions

The application of exogenous intravenous insulin therapy mimicking a normal secretion profile with physiological concentrations in the portal vein simultaneously with an induced hyperglycemic state may provide improved glucose disposition/utilization, adenosine triphosphate (ATP) production, and mitochondria function. These effects result in decreased progression of diabetic complications and improved quality of life for patients suffering from advanced diabetic complications. Objective measures of metabolic functioning such as resting metabolic ratio (RMR) and respiratory quotient (RQ) can be used to assess how efficiently carbohydrates are being utilized for the primary cellular energy substrate before and after treatment sessions, as well as indicate a lasting improvement in overall carbohydrate metabolism. In addition, the principal indicator of glycemic control for diabetics, Hemoglobin A1c (A1c), is well accepted and established as an objective measure of treatment effect.[6-11]

Table 1: Chronic Intermittent Intravenous Insulin Studies

Author/Study Design	Objective	Subjects	Results	Conclusions
Aoki TT. Grecu EO, et al. 1999 Retrospective, longitudinal, three-center study	To assess the effects of chronic (long-term) intermittent intravenous insulin therapy (CIIIT) on the progression of overt nephropathy in patients with type 1 diabetes mellitus.	31 patients with type 1 DM and overt nephropathy	A1c levels declined significantly from 8.6+/-0.6% to 7.6+/-0.3% (P = 0.0062). Creatinine clearance remained unchanged (from 46.1+/-3.0 mL/min per 1.73 m2 at baseline to 46. +/- 3.9 mL/min per 1.73 m2	The addition of CIIIT to intensive subcutaneous insulin therapy in patients with type 1 DM seems to arrest or appreciably reduce the progression of overt diabetic nephropathy, as well as substantially improve their glycemic control.
Aoki TT. Grecu EO, et al. 1999 Prospective, randomized, open-label, cross-over	To assess the antihypertensive (CIIIT) on blood pressure control (BP) less or equal to 140/90 mmHg.	26 hypertensive IDDM patients with nephropathy	The antihypertensive medication requirements for maintenance of the baseline BP levels decreased significantly (46%; P < 0.0001) and linearly over time (P < 0.0058) during the treatment phase, while remaining essentially unchanged during the control phase.	CIIIT markedly improves BP control, as evidenced by the significantly reduced antihypertensive medication requirements in subjects with IDDM and hypertension, possibly through an improvement in vascular reactivity.
Dailey GE, Boden GH, et al. 2000 Multicenter, prospective, controlled study	To assess the effects of pulsatile intravenous insulin therapy (PIVIT) on the progression of diabetic nephropathy in patients with type 1 diabetes mellitus (DM)	49 type 1 DM patients with nephropathy	The rate of CrCl decline in the treatment group (2.21+/-1.62mL/min/yr) was significantly less than in the control group (7.69+/-1.88 mL/min/yr, P =.0343).	When PIVIT is added to IT in type 1 DM patients with overt nephropathy, it appears to markedly reduce the progression of diabetic nephropathy. The effect appears independent of ACE inhibitor therapy, blood pressure, or glycemic control.

Methods Patient Population/Sampling/Data Management

A retrospective assessment of the clinical impact of intravenous insulin therapy on patient outcomes was conducted with external review of medical records by two independent clinical auditors. Medical records were reviewed by the auditors. Once identifiers were removed, data analysis was performed by an external entity nonprofit organization, The Schull Institute.

Patients were categorized into either Active Infusion Group if they were currently receiving treatments or No Active Infusion Group if they had not had infusions for at least six months. A standardized questionnaire/chart review tool was used to categorize diabetic complications and medication changes for both groups. Diabetic complications were categorized into the number and types of complications for each group. For each medical complication, patients were categorized as improved, same, or worsened. For medications, changes in medications for each diabetic complication were assessed. A quality of life survey was conducted with both the active and inactive patients. Quality of life was assessed as improved, same, or worsened.

In a second analysis, a random sample of patients who were actively receiving therapy was evaluated for treatment effects on A1c and Respiratory Quotient (RQ). This analysis applied a paired t-test for statistical testing and included patients with a pre-treatment A1c and another A1c at least 3 months after treatments had begun. Similarly, the RQ was evaluated for those having a pre-treatment RQ measurement and the RQ measurement prior to the most recent treatment.

Results

Retrospective Assessment of the Clinical and Quality of Life Impact

There were 49 patients in the active treatment group and 11 patients in the inactive group.

Table 2: Demographics

	Active infusion	No Active Infusion
Age	62.6 yrs	68.7 yrs
Years diabetic	12.6 yrs	8.4 yrs
Sex		
Male	73%	64%
Female	27%	36%
Race		
White	81%	90%
Black	7%	10%
Hispanic	7%	0
Asian	5%	0

Table 3: Active Infusion Group Impact on Diabetic Complications and Medications

ACTIVE INFUSION IMPACT ON DIABETIC COMPLICATIONS AND MEDICATIONS							
Baseline Conditions	**Total**	**Clinical condition**			**Medications**		
		Improve	***Same***	***Worsen***	***Increase***	***Same***	***Decrease***
No baseline neuropathy, wound, vision, nephropathy conditions	8	0	8	0	0	6	2 diabetes medications
Single baseline conditions							
Neuropathy	21	20	1	0	0	12	8 diabetes 1 neuropathy
Wound	1	1	0	0	0	1	0
Vision	3	3	0	0	0	2	1 diabetes and blood pressure
Nephropathy	1	1	0	0	0	1	0
Two baseline conditions							
Neuropathy / Wound	5	5 Neuropathy 5 Wound	0	0	1 Increase Diabetes	2	1 Diabetes 1 Sleep Medication
Neuropathy / Vision	5	4 Neuropathy 3 Vision	1 Neuropathy 2 Vision	0	0	2	2 Diabetes 1 Sleep Medication
Neuropathy / Nephropathy	1	1 Nephropathy	1 Neuropathy	0	0	0	1 Diabetes and blood pressure
Wound / Vision	3	2 Wound 3 Vision	1 Wound	0	0	1	2 Diabetes medications
Three baseline conditions							
Neuropathy/ Wound / Vision	1	1 Neuropathy 1 Wound 1 Vision	0	0	0	1	0
TOTAL	49	37	12	0	1	28	20
Percentage		76%	24%	0%	2%	57%	41%

Table 4: No Active Infusion Group Impact on Diabetic Complications and Medications

NO ACTIVE INFUSION IMPACT ON DIABETIC COMPLICATIONS AND MEDICATIONS							
Baseline Conditions	**Total**	**Clinical condition**			**Medications**		
		Improve	***Same***	***Worsen***	***Increase***	***Same***	***Decrease***
No baseline neuropathy, wound, vision, nephropathy conditions	2	0	2	0	0	1	1 Blood pressure
Single baseline conditions							
Neuropathy							
Wound	2	1	1	0	1 Diabetes medication	1	0
Vision							
Nephropathy							
Two baseline conditions							
Neuropathy / Wound	3	1 Wound	1 Wound	1 Wound 3 Neuropathy	1 Neuropathy medication	2	0
Neuropathy / Vision							
Neuropathy / Nephropathy							
Wound / Vision							
Three baseline conditions							
Neuropathy/ Nephropathy/ Vision	1	0	1 Retinopathy	1 Neuropathy 1 Nephropathy	0	1	0
Four baseline conditions							
Neuropathy/ Nephropathy/ Vision/Wound	3	1 Wound 1 Retinopathy 1 Neuropathy 1 Nephropathy	2 Wound 2 Retinopathy 1 Neuropathy 2 Nephropathy	1 Neuropathy	0	3	0
TOTAL	11	3	3	5	2	8	1
Percentage		27%	27%	45%	18%	73%	9%

Table 5: Quality of Life Impact

Active Infusion			
	Increase	Decrease	Same
Physical Activity	72%	0%	28%
Energy	73%	5%	22%
Sleep	31%	0%	69%
Mood	34%	0%	66%
Hair/Finger nail growth	25%	0%	75%
Hypoglycemic/ Hyperglycemic episodes	31%	0%	69%
Weight	24%	12%	64%

No Active Infusion			
	Increase	Decrease	Same
Physical Activity	27%	55%	18%
Energy	18%	45%	36%
Sleep	36%	9%	55%
Mood	0%	18%	82%
Hair/Finger nail growth	30%	10%	60%
Hypoglycemic/ Hyperglycemic episodes	0%	11%	89%
Weight	27%	9%	64%

For table 5: (Increase = Improvement), (Decrease = Worsening), (Same = Same)

In the second analysis the mean A1c/RQ, standard deviation (SD), standard error of mean (SEM), and number (N) of actively treated patients randomly sampled from July 7, 2014, to September 14, 2015, was reported as a pre-post analysis.

Table 5: Pre-Treatment and Post-Treatment Analysis on A1c

	Pre-Treatment	Post-Treatment
Mean A1c	8.76	7.87
SD	1.68	1.13
SEM	0.45	0.30
N	14	14

P > 0.05

Table 6: Pre-Treatment and Post-Treatment Analysis on RQ

	Pre-Treatment	Post-Treatment
Mean RQ	0.82	0.97
SD	0.08	0.05
SEM	0.02	0.01
N	18	18

P < 0.05

Discussion

Retrospective Assessment of the Clinical and Quality of Life Impact

Diabetic Complications: Both groups had significant burden of diabetic complications. In the Active Infusion Group 76% of patients had at least one diabetic complication improved, 24% had no change in diabetic complications, and no patients had a worsening of diabetic complications. In the No Active Infusion Group 27% had at least one diabetic complication improved, 27% had no change in diabetic complications and 45% had progression in diabetic complications.

Medications: Both groups had significant numbers of medications required to manage their diabetic complications. In the Active Infusion Group 2% had an increase in medications, 57% had no change in medications, and 41% had a decrease of at least one medication. In the No Active Infusion Group 18% had an increase in medications, 73% no change in medications, and 9% had a decrease in medications.

Quality of Life: Patients in the Active Infusion group had higher percentages of patients who had improved physical activity, energy, mood, and decrease in hypo or hyperglycemic events as compared to the No Active Infusion group.

Pre-Post Analysis of A1c and RQ

Hemoglobin A1C: Patients demonstrated a reduction of A1C by 0.9 ($p > 0.05$). While this analysis did not reach statistical significance, 63% of the patients had an improvement in A1C.

Respiratory Quotient: Patients had statically significant ($p < 0.05$) normalization of their respiratory quotient.

Conclusions

These internal retrospective analyses showed results consistent with prior published studies using similar approaches.

Preliminary results show promise to consider infusion therapy for diabetic patients with intransigent complications such as neuropathy, poor wound healing, nephropathy, and retinopathy. As patients improve their metabolic functioning and quality of life (e.g. increased energy and decreased neuropathic pain), it is important to monitor for opportunities to decrease medications and to reinforce lifestyle modifications.

While the effects on A1c did not reach statistical significance, the clinical significance is well established with a 44% relative risk reduction in microvascular complications (e.g., neuropathy, nephropathy, retinopathy) for every 1% decrease in A1c.[1,2] Moreover, the effect on carbohydrate metabolism via respiratory quotient demonstrates that the treatment has positive effects on the metabolic functioning of the diabetic patient.

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MISSION STATEMENT
OF THE SCHULL INSTITUTE
(Excerpts)

Founded in March 2000, the Schull Institute grew out of a series of community-based symposia on medical disparities in vulnerable populations. It was created to preserve the lifelong principles and accomplishments Dr. William J. Schull, a distinguished geneticist, epidemiologist, and international scientist. The overarching mission of the Schull Institute is to "address the health care needs of vulnerable populations." The long-term goals of the institute are to promote multidisciplinary community-based training and research within vulnerable populations; to support an exchange of scholars at the national and international levels; to encourage student student altruism and a spirit of community service; provide technical advice to policy makers involved in the establishment of health care and research practices affecting vulnerable populations; and to further academic, community, and industrial collaboration in developing communities and disseminating health care information and technology, locally, nationally and internationally.

The Schull Institute is committed to easing the global crisis in health care by cultivating healthcare professionals whose education encompasses the many determinants of health, and discussions of health issues that affect vulnerable people. Preventing disease is at the heart of Dr. Schull's lifelong efforts in genetics, radiation studies, epidemiology and public health.

In its infancy, the Schull Institute has achieved the following benchmarks:

- Ten funded collaborative research projects with universities and the local government in Japan and the School of Bimedical Informatics at The University of Texas Health Science Center-Houston

- Funded two Scholars; Mentored eight Scholars and three Fellows, Mentoring two Scholars

- Two courses conducted in Informatics and outcomes in Japan

- Collaborative education and research program development in health informatics/ management with nonprofit organizations and graduate schools in Japan and the School of Biomedical Informatics at The University of Texas Health Science Center-Houston

- Successful launch of a demonstration project that engages targeted communities in a collaborative partnership to reduce risk behaviors that increase the probability for heart disease and cardiovascular disease

- Conducted five CME presentations with St. Joseph Medical Center and other medical institutions.

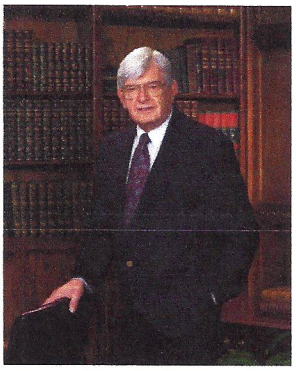
The Institution continues to build on this outstanding record of achievement through our programs: The Scholars Program - This program is dedicated to mentoring the next generation of local, national and international health care providers and scientific leaders. It was designed to preserve the global network crafted by Dr. Schull in his over fifty years of service to the world community to empower health care leaders to combat the problems facing the health care community today.

We are dedicated to developing initiatives to improve healthcare for vulnerable populations here in Houston, Texas, and around the world.

Tax deductible contributions can be made the the Schull Institute, a nonprofit 501(c)(3) foundation by checks in any currency to:

The Schull Institute
PO BOX 131755
Houston, TX 77219-1755

THE MAN BEHIND THE MISSION
William J. Schull, Ph.D.



Dr. Schull has contributed extensively to human genetics and public health for more than five decades, the last three in Houston. Prior to his retirement, he was Ashbel Smith Professor of Academic Medicine at The University of Texas Health Science Center at Houston. He was the Health Science Center's inaugural President's Scholar. He is also the recipient of the Silvio O. Conte Environmental Health Award, and in 1992, he was awarded the Order of the Sacred Treasure Third Class by the Emperor of Japan, the highest honor bestowed on foreign, non-diplomatic individuals.

In addition to authoring more than 400 publications, including 14 books, he has served on numerous editorial boards, as a visiting professor in several universities, and on more than 40 national and international panels. He has worked tirelessly on reports that summarize knowledge on the effect of exposure to ionizing radiation; these reports have guided the United States, the United Nations,and the World Health Organization in formulating policies that affect us all. While these accomplishments speak to a lifetime of sustained scientific productivity, it is only when his research themes are fully examined that one begins to sense

the true depth and breadth of Dr. Schull's contributions to the world community. His research career reveals *three recurring themes*: **First**, a career-long interest in the effects of radiation exposure on the survivors of the atomic bombing of Hiroshima and Nagasaki; **Second**, his focus on the genetics of populations and the epidemiology of chronic disease conditions; **Third**, his continuous interest in the creation and maintenance of research environments in which early career scientists and clinicians are free to flourish.

Dr. Schull's collaborations with South America began in Chile in 1967 when he was joined at the University of Michigan by Dr. Edmundo Covarrubias, the first of several Fogarty International Fellows from Chile to study with Dr. Schull. Subsequently he was invited to Santiago to assist Drs. Covarrubias and José Barzelatto in the analysis of data collected from a study of endemic goiter in the Pehuenche. This association would lead to some twelve additional Chilean scholars who either studied with or conducted research under the guidance of Dr. Schull at the Center for Demographic and Population Genetics of the University of Texas Health Science Center in Houston.

Much of what we currently know regarding the genetic effects of exposure to ionizing radiation is the result of studies initiated by Drs. Schull and James V. Neel and guided by them for more than 50 years. These endeavors have established the risk for cancers following exposure to ionizing radiation, and led to fundamental insights into the effects of the timing of prenatal radiation exposure and subsequent mental retardation. The research involving the critical nature of exposure on the developing embryo particularly demonstrates Dr. Schull's excitement for research and scholarship. He has pursued these studies with the enthusiasm of a graduate student and the wisdom of a senior scientist.

Dr. Schull's research efforts have also concentrated on the genetics of populations and the etiology of common chronic conditions. Initially he pursued these efforts as one of the founding members of the first human genetics department in the country. In 1954 he coauthored one of the first textbooks of human genetics, laying out the foundations and directions of the field. In 1965, with Drs. JV Neel and MW Shaw, Dr. Schull edited a volume on the genetics and epidemiology of chronic disease (Neel, J. V., Shaw, M. W. and Schull, W. J., eds., 1965, *Genetics and the Epidemiology of Chronic Disease.* Washington, D. C.: Government Printing Office). The research directions set out in this conference were at least 10 to 15 years ahead of their time. In 1972, he came to The University of Texas Health Science Center at Houston and founded the Center for Demographic and Population Genetics (CDPG).The latter brought together population geneticists and demographers in a manner that had not been previously achieved. The purpose of the Center was to understand the impact of genetic variation on individuals, families, and populations considering time and geographic distribution. He embarked on a series of genetic studies of New World Native peoples. He led expeditions to the altiplano of Chile to study the Aymará in 1973 and 1974, as well as expeditions to Alaska, Panama, and Bolivia, seeking genetically unique reference populations

(Schull, W. J. and Rothhammer, F., 1977, A multinational Andean genetic and health program: A study of adaptation to the hypoxia of altitude. In: Weiner, J. S., Ed., *Physiological Variation and its Genetic Basis. Soc. Study Human Biology*. Vol. 17. London: Taylor and Francis, pp. 139-169; Schull, W. J. and Rothhammer, F., Eds., 1990, *The Aymará: Strategies in Human Adaptation to a Rigorous Environment*. Kluwer Academic Publishers, The Netherlands; and Barton, S. A., Rothhammer, R., and Schull, W. J., eds., 1997, Patterns of Morbidity in Andean Aboriginal Populations: 8000 Years of Evolution. Santiago, Chile: Amphora Editores). In the late 1970's, Dr. Schull recognized the biological and societal need for understanding chronic disease in the Mexican-American population of Texas. This was long before mandated interest in such groups occurred. He set up a series of continuing studies that have contributed much to our understanding of the genetics and epidemiology of cancer, non-insulin-dependent diabetes, gallbladder disease and cardiovascular risk among Mexican-Americans in South Texas and elsewhere. This work has been fundamental in defining the chronic disease burden disproportionately borne by the Mexican-American population and its unique genetic factors.

Finally, in addition to devotion to his own research interests, Dr. Schull has unselfishly given of his time, energy, and compassion to fostering the careers of young scientists in the U.S., Japan, South America and elsewhere. Without question he is a delight to know. He is insightful, educated in the arts and humanities, enthusiastic and well versed in language and other pursuits. Perhaps evidencing these attributes best, are his recent books titled *Song Among the Ruins* (Harvard Press, 1990) in which he gives his personal observations and reflections on life and change in postwar Japan and *Effects of Atomic Radiation: A Half Century of Research in Hiroshima and Nagasaki* (Wiley, 1995). Here we gain a glimpse of who Dr. Jack Schull is beyond his research contributions.

(Source: http://schullinstitute.com)