THE DIABETES CONTROL AND COMPLICATIONS TRIAL:

IMPLICATIONS FOR THE TREATMENT OF DIABETES MELLITUS

"Metabolic Control Matters!"

Philip Raskin, M.D.

MEDICAL GRAND ROUNDS

AUGUST 4, 1994

On January 20, 1977 I gave my first Medical Grand Rounds at UT Southwestern entitled "Diabetic Microangiopathy Revisited". I remember that occasion quite well for several reasons. First of all, as it was my first experience with this exercise, I was terrified. In fact, I spent an entire six months doing nothing else (except going to Diabetes Clinic on Wednesday mornings) but working on the protocol and presentation. The second reason that my first Grand Rounds is indelibly etched in my memory, is that my conclusion that metabolic control might matter was contrary to our local dogma. The Division of Endocrinology and Metabolism at this institution, at that time, had very strong feelings about the relationship of blood glucose control to the subsequent development of the microvascular complications of diabetes. The dogma here was that diabetic control had little to do with complications. My conclusion from that presentation was that there was some rudimentary evidence to the contrary in experimental diabetes in animals, but very little in human diabetes. However, I did leave the impression that I believed the general feeling about the relationship of diabetic control to complications might be in error. As I concluded, at that time, I considered it "a travesty that more than 50 years after the discovery of insulin that this very important question (regarding the relationship between control and complications) remained unanswered. There were several reasons why this was the case. First of all, the proper clinical experiment had yet to be conducted. What was needed was a long-term prospective study in which patients are randomly assigned to either a "tight" or "loose" control treatment group. The duration of this study should be decades rather than years as clearly many of the complications of this disease take decades to develop." Moreover, I also noted that given the technology available at that

time to manage diabetes, it was "impossible to completely restore the diabetic patient's blood glucose to normal levels during the entire day". That lack of effective technology persisted for almost another decade.

In 1983, the Clinical experiment that I proposed in 1977, was finally initiated. The NIDDK upon the urging of the National Diabetes Advisory Board, initiated the Diabetes Control and Complications Trial, better known as the DCCT. This clinical experiment was a 9 year long, multi-centered trial designed to finally decide what the relationship was between antecedent diabetic control and diabetic complications. This discussion will focus on the details of this landmark study and its implications for the management of diabetic patients.

The DCCT was a large 29 multicenter North American trial that included 1441 insulin dependent diabetic individuals. These individuals were randomly assigned to two treatment groups and followed from 3 to 9 years. The average follow-up period was 6.5 years. Actually, the DCCT was two studies in one. There was a "Primary Intervention Trial" consisting of one half of the patients in the Trial. These people had diabetes for less than 5 years and had no diabetic retinopathy (based on stereo fundus photographs) and had an albumin excretion rate of less than 40 mg per 24, hours at study entry. These individuals would be used to answer the question of whether or not diabetic complications could be prevented. The other half of the patients in the study participated in a "Secondary Intervention Trial". These individuals had diabetes for 1 to 15 years prior

to entering the study and had to have at least one microaneurysm, but no more than moderate non-proliferative retinopathy. They could have an albumin excretion rate as high as 200 mg per 24 hours. These individuals would be used to ascertain whether or not diabetic complications could be reversed or their progression slowed.

This study compared the effects of two treatment strategies, a conventional treatment and an intensive diabetes treatment program on the development and progression of diabetic complications. The conventional treatment goals included clinical well being, the absence of symptoms of hypoglycemia and hyperglycemia and the maintenance of ideal body weight. Insulin was given once or twice per day. In most circumstances this was a combination of intermediate and short acting insulin twice daily. Hemoglobin A1c was measured quarterly but it was not reported to the clinic unless it exceeded a value of 13.1%, when management was altered to lower it. Women in the conventional treatment group, who were pregnant or desired to become pregnant, were changed to intensive therapy until the completion of their pregnancy. The intensive treatment had the same clinical goals, but in addition patients were obliged to strive for a treatment goal of blood glucose values in the range of individuals without diabetes and a HbA1c value less than 6.05% which was the upper limit for nondiabetic individuals in the DCCT HbA1c assay.

In order to accomplish these intensive treatment goals, insulin was administered by multiple injections three or four times daily or with the use of an insulin pump. Blood glucose was monitored a minimum of four times per day and insulin doses were adjusted

based on meal content and anticipated exercise. Intensive treatment subjects were seen at least monthly and often more frequently.

Data collection and patient follow-up were incredibly complete, with end of study data being collected on 99% of study subjects.

DCCT STUDY QUESTIONS

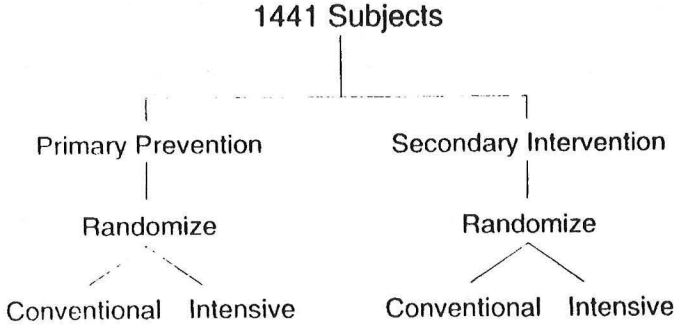
Primary Intervention

Will intensive therapy prevent the development and subsequent progression of retinopathy?

Secondary Intervention

Will intensive therapy affect the progression of retinopathy?

RANDOMIZATION



CONVENTIONAL THERAPY

Intended to Mimic Conventional Care

- **Clinical Goals: No Symptoms of Hyperglycemia or Hypoglycemia**
- **1 or 2 Injections Per Day**
- **Daily Self Monitoring**
- **Quarterly HbA1c**
- **Pregnant Women Treated Intensively**
- **Diet and Exercise Education**
- **Quarterly Visits**

INTENSIVE THERAPY GOALS

- Same Clinical Goals as Conventional Treatment

PLUS

- Maintain Blood Glucose as close to Nondiabetic Range as Possible

Pre-Meal	Post-Meal	3 AM
70-120 mg/dl	<180	> 65

- Hemoglobin A1c <6.05%

INTENSIVE THERAPY METHODS

- 3 or 4 Daily Injections or Insulin Pump
- 4 or more Blood Glucose Tests Daily
- Hospitalization for Initiation of Therapy
- Frequent Dietary Instruction to Help Achieve Goals
- Monthly Clinic Visits

COMPLETENESS OF FOLLOW UP

1422 Subjects (99%) Completed Study
19 Subjects (1%) Failed to Complete Study
11 Deaths
8 Dropouts

RETINOPATHY SCALE

Steps	Level of Retinopathy	Eligibility
1	No Retinopathy	Primary Prevention
2	Microaneurysms one eye	Secondary Intervention
3	Microaneurysms both eyes	Secondary Intervention
4-5	Mild NPDR	Secondary Intervention
6-9	Moderate NPDR	Secondary Intervention
10-13	Severe NPDR	
14-15	Mild PDR	
16-17	Moderate PDR	
18-25	High risk PDR and worse	

RESULTS OF INTERVENTION ON DIABETIC RETINOPATHY

MEASURES OF OPHTHALMIC OUTCOME

Test	Frequency
Stereo Fundus Photos	6 Months
Eye Examination	Yearly

Figure 1.

CUMULATIVE INCIDENCE OF THE DEVELOPMENT OF AT LEAST ONE MICROANEURYSM IN THE PRIMARY PREVENTION COHORT OF IDDM PATIENTS RECEIVING CONVENTIONAL OR INTENSIVE THERAPY IN THE DCCT

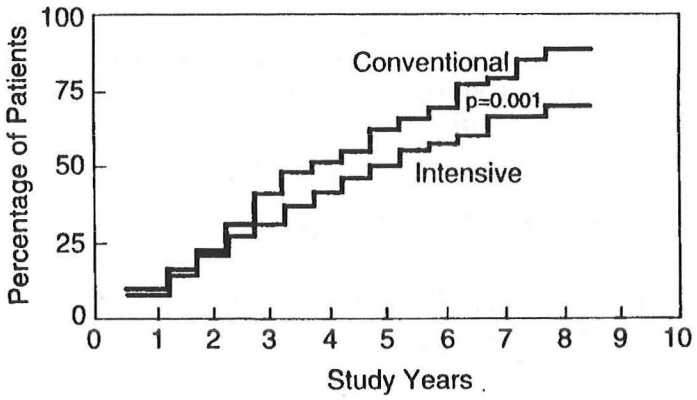


Figure 2.

CUMULATIVE INCIDENCE OF A SUSTAINED CHANGE IN RETINOPATHY IN THE PRIMARY COHORT OF IDDM PATIENTS RECEIVING CONVENTIONAL OR INTENSIVE THERAPY IN THE DCCT

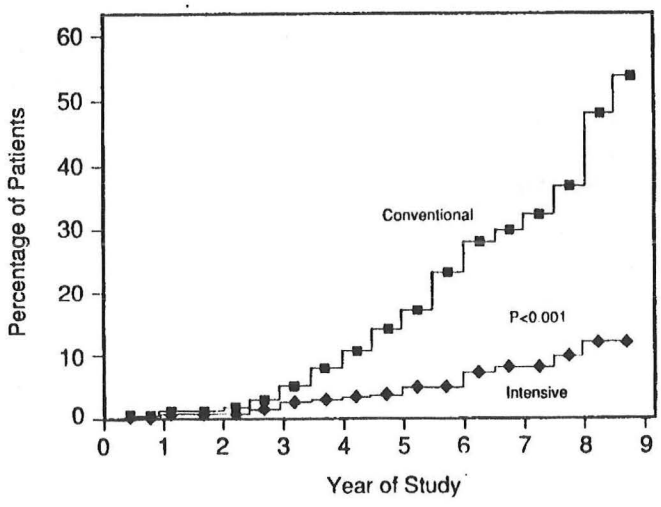
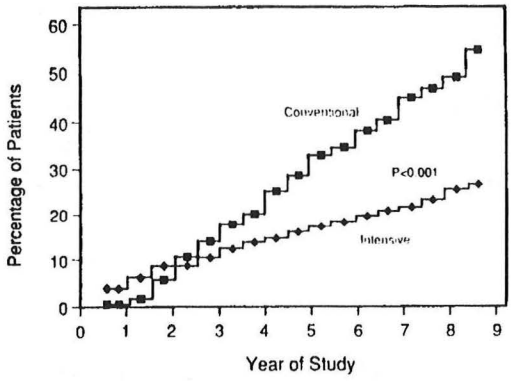


Figure 3.

CUMULATIVE INCIDENCE OF A SUSTAINED CHANGE IN RETINOPATHY IN THE SECONDARY COHORT OF IDDM PATIENTS RECEIVING CONVENTIONAL OR INTENSIVE THERAPY IN THE DCCT



RISK REDUCTION WITH INTENSIVE THERAPY

PRIMARY PREVENTION

OUTCOME	RISK REDUCTION
1 Microaneurysm	27%
3-Step Progression	60%
Sustained 3-Step	76%

RISK REDUCTION WITH INTENSIVE THERAPY SECONDARY INTERVENTION

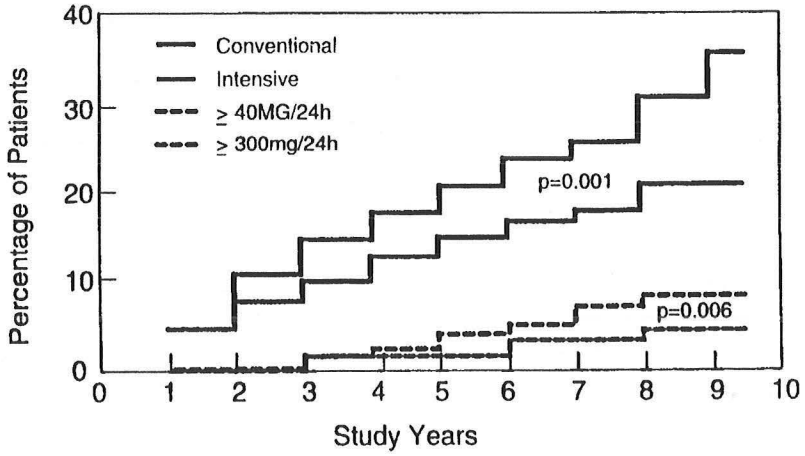
OUTCOME	RISK REDUCTION
Sustained 3-Step	54%
Proliferative or Severe NPDR	46%
Laser Therapy	54%
Macular Edema	22%

RESULTS OF INTERVENTION ON DIABETIC NEPHROPATHY

MEASURES OF NEPHROPATHY

Test	Frequency
Albumin Excretion Rate	Yearly
Serum Creatinine	Yearly
Creatinine Clearance	Yearly
^{125}Iothalamate Clearance	3 Y, End

Figure 4. CUMULATIVE INCIDENCE OF MICROALBUMINURIA AND ALBUMINURIA IN THE COMBINED COHORTS OF IDDM PATIENTS RECEIVING EITHER INTENSIVE OR CONVENTIONAL THERAPY IN THE DCCT



RISK REDUCTION WITH INTENSIVE THERAPY COMBINED COHORT

Outome	Risk Reduction
AER > 40 MG/24 H	35%
AER > 300 MG/24 H	56%

RESULTS OF INTERVENTION ON DIABETIC NEUROPATHY

MEASURES OF NEUROPATHY

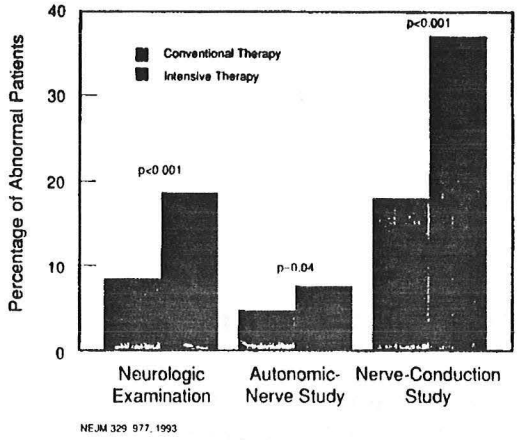
TEST	FREQUENCY
History & Exam	Y 5, End
Neurophysiologic Battery	Y 5, End
Autonomic Battery	Biennial

DEFINITION OF CLINICAL NEUROPATHY

Peripheral Sensorimotor Polyneuropathy
Plus
Abnormal Nerve Conduction in ≥ 2 Nerves
or
Abnormal Autonomic Function

Figure 5

EFFECTS OF INTENSIVE AND CONVENTIONAL THERAPY ON NEUROLOGICAL PARAMETERS AT FIVE YEARS IN THE DCCT



PREVALENCE OF CLINICAL NEUROPATHY

	5 Years	Risk Reduction
Primary Prevention	-	-
Conventional	10%	
Intensive	3%	70%

EFFECTS OF INTERVENTION ON MACROVASCULAR DISEASE

MEASURES OF MACROVASCULAR DISEASE AND RISK FACTORS

Test	Frequency
History/Exam	Quarterly
Blood Pressure	
Weight	
Pulses	
Fasting Lipids	Yearly
Electrocardiogram	Biennial

INCIDENCE OF CARDIAC RISK FACTORS

Combined Cohort-Cases Per 100 Pt-Yrs

	Intensive	Conventional	Risk Reduction
Hypertension	1.8	1.9	NS
Triglycerides >500 mg/dl	0.04	0.09	NS
LDL-CHOL >160 mg/dl	1.1	1.7	35%

ANALYTIC DEFINITIONS OF MACROVASCULAR EVENTS

Cardiac:	Death from CAD, Sudden Death, MI, CAD requiring surgery or confirmed angina
Cerebral:	Fatal or non-fatal stroke
Peripheral:	Amputation, PVD requiring surgery, or confirmed claudication

MAJOR MACROVASCULAR EVENTS

Combined Cohort

	Intensive	Conventional
Cardiac	3	14
Cerebral	0	0
Peripheral	18	24
Total	21	38

MAJOR MACROVASCULAR EVENTS

Combined Cohort
Episodes Per 100 Pt-Yrs

	Intensive	Conventional	Risk Reduction
Cardiac	0.06	0.3	80%
Peripheral	0.39	0.51	24%
Combined	0.86	1.47	44%

ADVERSE EVENTS

There were some adverse effects of intensive diabetes treatment. On the downside, intensive diabetes treatment was associated with about a ten pound great increase in weight over the duration of the study and a three fold greater risk of the development of severe hypoglycemic.

COMBINED COHORT

Cases Per 100 Pt-Yrs

	Intensive	Conventional	Risk Ratio
Weight Gain (>120% IBW)	11	7	1.6
Catheter Infections	12	0	0
Ketoacidosis	2	2	NS

ADVERSE EVENTS

Severe Hypoglycemia
Treatment requires assistance.
Includes: Coma and seizure, episodes treated with IV dextrose or glucagon, or episodes requiring administration of oral carbohydrate by another.

SEVERE HYPOGLYCEMIA

COMBINED COHORT
Episodes Per 100 Pt-Yrs

	Intensive	Conventional	Risk Ratio
Severe	**62**	**19**	**3.3**
Coma/Seizure	**16**	**5**	**3.0**
ER/Hospital	**9**	**4**	**2.3**
Deaths	**0**	**0**	**0**

FIGURE 6

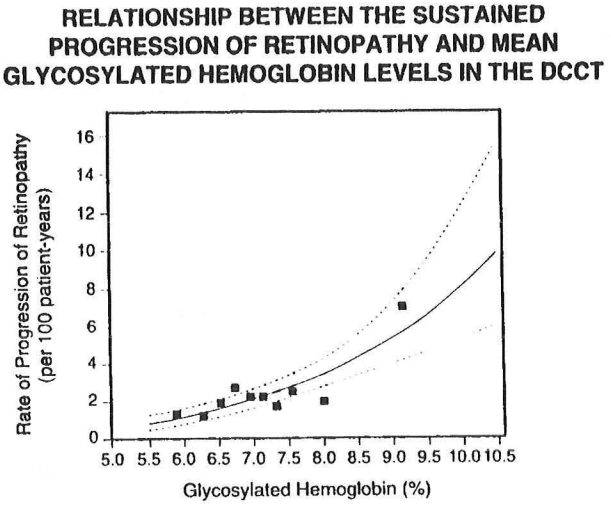
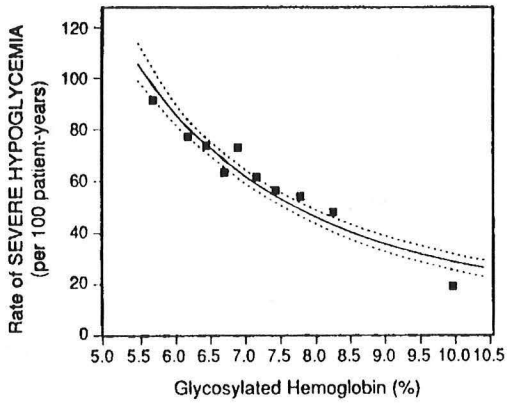


FIGURE 7

RELATIONSHIP BETWEEN THE RATE OF SEVERE HYPOGLYCEMIA AND MEAN GLYCOSYLATED HEMOGLOBIN LEVELS IN THE DCCT



Based on these data, the DCCT Research group recommended that intensive diabetes treatment be instituted in most individuals with insulin dependent diabetes mellitus. Since the study did not include diabetic individuals less than age 13 or those with severe diabetic complications or other severe medical problems, the decision to implement intensive diabetes treatment must be individualized by attempting to assess the risk benefit ratio for each patient. Finally, although individuals with non-insulin dependent diabetes were not studied, it was suggested that the results of this study could be extrapolated to persons with non-insulin dependent diabetes, as well.

What do the results of the DCCT mean to the million of individuals in the world with diabetes? I think it means that the level of diabetes control must be improved in everybody with diabetes. We now know that normoglycemia will delay the development and slow the progression the long term complications of diabetes. Our treatment goal is clear. It is blood glucose levels and a glycosylated hemoglobin value that are identical to those in individuals without diabetes. However, we may not be able to achieve our goal

in every patient. Even within the DCCT clinics who presumably had among the most experienced intensive diabetes treatment teams in the world, the goal was achieved in only a minority of patients. Given the tools we have for intensive treatment, it is often impossible to achieve normoglycemia. Then there is the ever present risk of hypoglycemia. The three fold increase in the risk of severe hypoglycemia must be carefully balanced against the 50% reduction in the risk of development and progression of complications. In many individuals the risk benefit ratio is unfavorable. Despite my concerns that by changing our treatment goals we may be doing more harm than good, let me be clear - I believe very strongly that all individuals with diabetes should be reevaluated with respect to their glycemic goals and treatment regimen. Treatment changes should be instituted where ever it is appropriate from a risk benefit perspective with the goal of achieving normoglycemia. No longer will I be personally satisfied with near-normoglycemia if my patient can do better and avoid serious hypoglycemia. Neither should the diabetic individual or their physician.

Intensive diabetes treatment is very complex and requires a treatment team consisting of well educated and experienced nurses, dietitians and mental health professionals. For example, in our DCCT clinic at the University of Texas Southwestern Medical Center at Dallas, the Master's prepared Clinical Nurse Specialist (Suzanne Strowig) Master's trained Dietician (Susan Cercone) and Ph.D. level Mental Health Professional (Monica Basco) have more than thirty years combined experience in the intensive diabetes management. This type of expertise is not available everywhere. It is also important to point out that one should not equate intensive diabetes treatment within insulin. Too

many people think intensive diabetes treatment is the use of multiple insulin injections or the use of an insulin pump. *Intensive diabetes treatment has little to do with insulin!* Although it is usually impossible to achieve normoglycemia without using an insulin pump or multiple injections of insulin, the use of these two insulin delivery strategies without intensive behavioral and psychological intervention is useless. Intensive diabetes treatment is mostly "life style management"; thus the need for the multi-disciplinary diabetes team.

Finally, intensive diabetes treatment is two to four times more expensive than standard treatment. I hope those in Government who are responsible for the fiscal decisions for health care, will take note of the results of the DCCT and make sure that there will always be appropriate funding for the care of individuals with diabetes.

In conclusion, I feel that the majority of individuals with insulin dependent diabetes should be treated with an intensive therapy with the goal of achieving blood glucose and glycated hemoglobin levels in the range of individuals without diabetes. I also believe that these data can be extrapolated to all individuals with diabetes. It is incumbent on the health care profession to help our patients implement appropriate medical and behavior changes to achieve these goals.

BIBLIOGRAPHY

1. Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, Sandvik L: The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. Arch Ophthalmol 106:1242-6, 1988.

2. Chase HP, Jackson WE, Hoops SL, Cokerham RS, Archer PG, O'Brein D: Glucose control and the renal and retinal complications of insulin-dependent diabetes. JAMA 261:1155-60, 1989.

3. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Asgenaes O: Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. BMJ 290:811-5, 1985.

4. DCCT Research Group: The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase. Diabetes 35:530-45, 1986.

5. DCCT Research Group: Feasibility of centralized measurements of glycated hemoglobin in the Diabetes Control and Complications Trial: a multicenter study. Clin Chem 33:2267-71, 1987.

6. DCCT Research Group: Implementation of a multicomponent process to obtain informed consent in the Diabetes Control and Complications Trial. Controlled Clin Trials 10:83-96, 1989.

7. DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 90:450-9, 1991.

8. Deckert T, Poulsen JE, Larsen M: Prognosis of diabetics with diabetes onset before the age of thrity-one. Diabetologia 14:363-77, 1978.

9. Dorman JS, Laporte RE, Kuller LH, et al.: The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: mortality study: mortality results. Diabetes 33:271-6, 1984.

10. Early Treatment Diabetic Retinopathy Study Research Group: Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report no. 12. Ophthalmology 98:823-33, 1991.

11. Engerman R, Bloodworth JM Jr, Nelson S: Relationship of microvascular disease in diabetes to metabolic control. Diabetes 26:760-9, 1977.

12. Engerman RL, Kern TS: Progression of incipient diabetic retinopathy during good glycemic controll. Diabetes 36:808-12, 1987.

13. Greene DA, et al: Effeccts of insulin and dietary myoinositol on impaired peripheral nerve conduction velocity in acute streptozotocin diabetes. J ClinInvest 55:1326, 1975.

14. Idem. Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care 10:1-9, 1987.

15. Idem. Color photography vs fluorescein angiography in the detection of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 105:1344-51, 1987.

16. Idem. Factors in development of diabetic neuropathy: baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). Diabetes 37:476-81, 1988.

17. Idem. Reliability and validity of a diabetes quality-of-life measure for the Diabetes Control and Complications Trial (DCCT). Diabetes Care 11:725-32, 1988.

18. Idem. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 260:2864-71, 1988.

19. Idem. DCCT protocol. Spingfield, Va: Department of Commerce, National Techinical Information Service, 1988. (Puclication no. 88-116462-AS).

20. Idem. Diabetes Control and Complications Trial (DCCT): update. Diabetes Care 13:427-33, 1990.

21. Idem. DCCT protocol. Spingfield, Va: Department of Commerce, National Techinical Information Service, 1993. (Puclication no. 93-183382).

22. Job D, et al: Effect of multiple daily insulin injection on the cause of retinopathy. Diabetes 2:463, 1976.

23. Johnson S: Retinopathy and nephropathy in diabetes mellitus: COmparison of the effect of two forms of treatment. Diabetes 9:1, 1960.

24. Kilo C, Vogler N, Williamson JR: Muscle capillary basement membrane changes related to aging and diabetes mellitus. Diabetes 21:881, 1972.

25. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 102:520-6, 1984.

26. Knowles HC, et al: The course of juvenile diabetes treated with unmeasured diet. Diabetes 14:239, 1965.

27. Kroc Collaborative Study Group: Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trail. New Engl J Med 311:365-72, 1984.

28. Laritzen T, Frost-Larsen K, Larsen HW, Deckert T: Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neurolpathy. Diabetes 34:Suppl:74-9, 1985

29. Laritzen T, Frost-Larsen K, Larsen HW, Deckert T: Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin dependent diabetics. Lancet 1:200-4, 1983.

30. Lee CS, et al: Renal transsplantations in diabetes mellitus in rats. J Exp Med 139:793, 1974.

31. Mauer SM, et al: Studies of the rate of regression of the glomerular lesions in diabetic rats treated with pancreatic islet transplantation. Diabetes 24:280, 1975.

32. Mauer SM, et al: Immunopathology of renal extracellular membranes in kidneys transplanted into patients with diabetes mellitus. Diabetes 25:709, 1976.

33. Raskin P: Diabetes Microangiopathy Revisited. Medical Grand Rounds, UT Southwestern Medical Center. January 20, 1977.

34. Raskin P: The DCCT -Finally. J. Diabetes and its Comp. 7:214-15, 1993.

35. Reichard P, Nilsson B-Y, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 329:304-9, 1993.

36. Siebert C, Clark DM Jr.: Operational and policy considerations of data monitoring in clinical trials: the diabetes Control and Complications Trial experience. Controlled Clin Trials 14:30-44, 1993.

37. Siperstein MD, et al: Studies of muscle capillary basement membranes in normal subjects diabetic and prediabetic patients. J Clin Invest 47:1973, 1968.

38. Winegrad AI, Greene DA: Diabetic polyneuropathy: The importance of insulin deficiency, hyperglycemia on alterations in myoinositol metabolism in its pathogenesis. N Eng J Med 295:1416, 1975.