MEDICINE GRAND ROUNDS

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DIABETES CONTROL AND COMPLICATIONS

UPDATE 1984

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"The Great Tragedy of Science -
The Slaying of a Beautiful
Hypothesis by an Ugly Fact"

T.H. Huxley
Collected Essays

INTRODUCTION

Almost 8 years ago, I reviewed the relationship between the microvascular complications of diabetes and diabetes control. At that time there was considerable evidence that, at least in the experimental diabetes of animals, there was some relationship between antecedent diabetic control and the subsequent development of a characteristic diabetic lesion in their eyes and kidneys. In humans, this relationship was far from clear. There was evidence on both sides of this issue, however I was unable to come to a firm conclusion regarding the matter because at that time it was next to impossible to provide treatment strategies that would result in normal or near normal blood glucose levels for sustained periods of time in most patients with insulin dependent diabetes. Thus, it was impossible to compare diabetic complications in large groups of patients with normal or near normal blood glucose levels to those in whom blood glucose levels were elevated. The recent development of more effective treatment modalities as well as the rapidily expanding use of self monitoring of blood glucose levels has now made it possible to achieve near-normal glycemia for prolonged periods of time.

It is the purpose of this exercise to review the more pertinent older data and to discuss the most recently acquired information in this area, much of which has been accumulated in a prospective fashion.

The Natural History of Diabetes

Table 1 shows the results of two long term studies of the occurrance of vascular complications in patients who have had diabetes for more than 40 years. The incidence of complications in this group of patients is quite low. These patients, who have survived diabetes for more than forty years, may represent a special subset of patients that are different from those we usually see.

Table 1

VASCULAR COMPLICATION IN DIABETES AFTER 40 YEARS

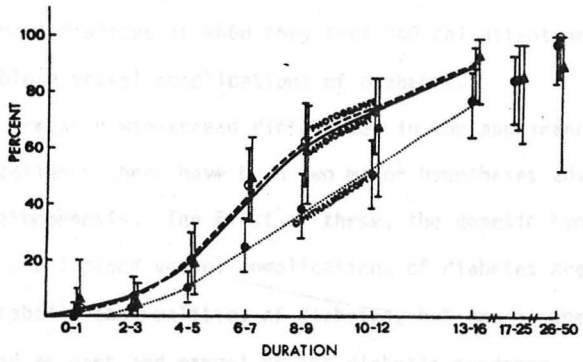
	Boston	London
Patients	73 (31M, 41 F)	92 (32 M, 60 F)
Therapy	Insulin	Insulin
Complications(%)		
Retinopathy	75.3	60.8
Nonproliferative Type	45.0	43.4
Proliferative Type	17.8	10.8
Proliferative Type (blind)	12.3	6.5
Nephropathy	41.0	8.6
Proteinuria only	28.7	6.5
Proteinuria and renal failure	8.2	2.1
Neuropathy	48.0	16.3
Ischemic heart disease	20.5	45.6
Peripheral vascular disease	40.0	44.5

(Oakley, W.G. 1974 and Paz-Guevara, A.T., 1975)

There are other data to suggest that the incidence of the various complication rate is higher than these two long-term studies. Figure 1 shows the data of Palmberg. These data are perhaps the best available in two regards. First and very importantly, they show the increased ascertainment of diabetic retinopathy when fundus photography and/or angiography is used rather than just the ophthalmoscope. They also show that 80-90% of patients after 20 years of diabetes have some form of identifiable retinopathy.

With respct to nephropathy, the data of Kussman, et al are of interest. They are the result of a retrospective analysis of 112 Type I diabetic patients listed in the death registry of the Joslin Clinic between 1962 and 1972 as well as patients diagnosed as having diabetic nephropathy form 1966-1967. It is evident that nephropathy was far more common and more severe in this group of patients that in those patients in the forty year studies.

Figure 1



Prevalence of retinopathy. The prevalence of retinopathy is given for the modalities of (●) ophthalmoscopy, (O), photography (▲) fluorescein angiography, at each duration of disease. (Palmberg et al, 1981)

Table 2

THE DEVELOPMENT OF NEPHROPATHY IN TYPE I DIABETES MELLITUS

No.	Duration of Diabetes Onset of Proteinuria	Time Onset of Proteinuria to Renal Failure	Mortality Overall	Mortality Renal Failure	CVD
Pts	(years)	(years)	%		
112	17.3 ± 6	4.0	53%	59%	36

(Kussman et al, 1976)

What is important to note from all of this, and an issue that I will return to, is that there are a group of patients with typical insulin dependent diabetes mellitus, that despite many years of diabetes, never get the severe complications of the disease. This fortunate subset of patients makes up approximately 20-25% of patients. Also of interest is the fact that there is an

ever smaller group of patients, perhaps 5% of patients who get severe complications of diabetes in the face of only mild elevation of blood glucose and a short duration of diabetes. These are the unfortunate people whose first indication that they have diabetes is when they seek medical attention because of one of the small blood vessel complications of diabetes.

Because there are such widespread differences in the appearance of diabetic complications in patients there have been two major hypotheses advanced regarding their pathogenesis. The first of these, the genetic hyopthesis, suggests that the small blood vessel complications of diabetes are in no way related to the metabolic abnormalities of diabetes, but are in some way genetically predetermined as part and parcel of the diabetic syndrome. Thus, people with diabetes get diabetic complications because they are in some way genetically prediposed to do so. The other hypothesis, the metabolic hypothesis, suggests that the development of diabetic complications in a direct consequence of the hyperglycemia of diabetes. If one could prevent the hyperglycemia of diabetes, then one would not develop diabetic complications. Arguments between the proponents of these two seemingly opposite hypotheses are legion.

My discussion today is an attempt to show the data that both support or refute both of these two hypotheses. Perhaps at the end some conclusion will be forthcoming.

DIABETIC COMPLICATIONS: GENETIC INFLUENCES

The strongest piece of evidence against the hypothesis that diabetic microangiopathy is the consequence of the metabolic abnormalities of the disease and in support of the genetic hypothesis has come from this Department. Siperstein et al, using a simple morphometric method for measuring the basement

membrane thickness of quadriceps muscle capillaries clearly showed (Table 3) that greater than 90% of adults (>19 years of age) with diabetes had an abnormal capillary basement membrane thickness as compared to a group of normoglycemic controls with a negative family history of diabetes.

Table 3

QUADRICEP CAPILLARY BASEMENT MEMBRANE WIDTH
IN NORMAL, DIABETIC AND PREDIABETIC SUBJECTS

Subjects	Average Basement Membrane Width (A)	Prevalence of Basement Membrane Thickening %
Normal (50)	1080 ± 27	8
Diabetic (51)	2403 ± 119	98
Prediabetic (30)	1373 ± 44	53

(Siperstein et al, 1968)

In addition, he showed that of 30 genetic prediabetic (offspring) of two overt diabetics) adults, whose glucose tolerance was normal, 53% had thickened capillary basement membranes as compared to the control group. In these studies there was no correlation between the severity or duration of the diabetes and the thickness of the basement membrane. Mean capillary basement membrane thickness in 29 "mild" diabetics treated with diet and/or tolbutamide was 2410 ± 167 A° whereas in 22 "severe" diabetics requiring insulin therapy it was 2395 ± 173 A°. There was also no differences seen in basement membrane thickness when the patients were divided into those whose disease began before or after age 21. There was also no correlation between the width of the basement membrane and

the duration of the disease. Lastly, he showed in 8 patients with "secondary" diabetes due to chronic pancreatitis, some of whom had long standing fasting hyperglycemia, that only one patient (20%) had a thickened basement membrane.

These data have been criticized over the years for many reasons and I wish not to spend any time on this controversy. Suffice it to say, although there has been considerable disagreement over the precise prevalence of the lesion of a thickened skeletal muscle capillary basement membrane in human diabetes as well as its relationship to the age of the subject or to the duration of the diabetes, yet a thickened basement membrane in skeletal muscle capillaries from diabetic patients is a finding confirmed on many occasions.

Finally, a bit more evidence with respect to a genetic factor being operative in the development of diabetic microvascular disease comes from Marks, et al. They measured skeletal muscle capillary basement membrane thickness in 38 unaffected parents (i.e. with normal oral glucose tolerance tests) of children with insulin dependent diabetes mellitus and found a striking relationship between the presence of the antigen HLA-DR4 and the thickness of the skeletal muscle capillary basement membrane.

Table 4

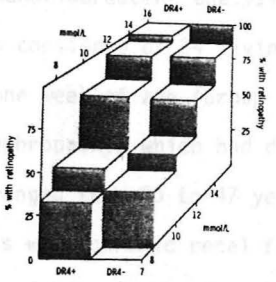
CORRELATION BETWEEN BASEMENT MEMBRANE THICKNESS (BMT) AND HLA-DR4

HLA Phenotype of Parents	Mean BMT (A^{o})	Number BMT > 2000	Number BMT < 2000
HLA-DR4 Positive	2026 ± 350*	12	8**
HLA-DR4 Negative	1642 ± 373	2	6
Normal Subjects	1628 ± 218	8	10

*$p < .001$, t-test (DR4 pos. vs. neg.)
**$p < .005$, fisher test (DR4 pos. vs. neg.)
(Marks, et al, 1981)

Dornan et al, in a very interesting study, compared the incidence of retinopathy in a group of 127 insulin-dependent diabetic patients in relationship to the HLA haplotype. Interestingly, they found that HLA-DR4 was present in 70% of patients with background or proliferative retinopathy and in only 54% with no retinopathy. They also found the retinopathy tended to be more common in patients with "poor diabetic control" (Figure 2). The combination of poor diabetic control and HLA-DR4 increased the odds ratio of having retinopathy to 33.3%. They concluded that genetically determined factors appear to influence susceptibility to retinopathy. This relationship between HLA-DR4 and a seemingly increased susceptability to retinopathy has not been confirmed by other investigators, however.

Figure 2



Patients with and without HLA-DR4 have been divided into five groups by mean blood glucose (<8.0, 8.0-9.9 10.0-11.9, 12.0-13.9 and ≥ 14.0 mmol/L). Within each group the proportion of patients with background or proliferative retinopathy is shown as a percentage (Dornan et al, 1982)

DIABETIC COMPLICATIONS: METABOLIC INFLUENCES

When one discusses the metabolic influences on the development of diabetic microvascular disease one should consider the answer to the following important questions.

THE IMPORTANT QUESTIONS

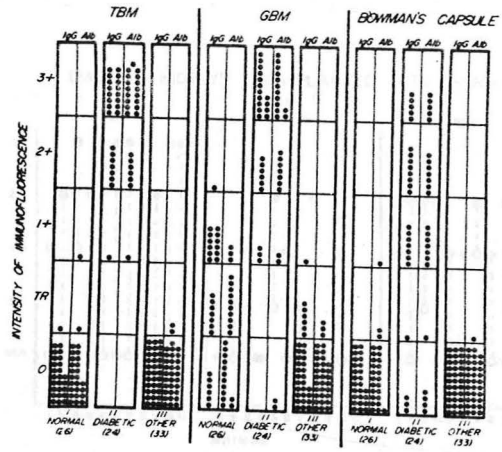
If we control hyperglycemia in diabetes, can we:

1. Prevent the development of diabetic complications?
2. Reverse established diabetic complications?
3. Slow the progression of established diabetic complications?

I plan to discuss this issue in two ways. First I plan to go over pertinent animal data, then move on to the data in humans with diabetes.

Studies using immunohistochemical techniques have added considerable information with regard to renal lesions in diabetes. Miller and Mauer carried out a comprehensive immunofluorescent analysis on renal tissue from three groups of patients. One group consisted of 24 living normal renal allograft donors and two infants less than one week of age (Group 1). Group II included included 24 patients with severe nephropathy, which had diabetes mellitus for 16 to 30 years duration. Their ages ranged from 20 to 47 years. The last group (Group III) consisted of 33 patients with chronic renal failure of diverse eitology other than diabetes. Their ages ranged from 5 to 63 years. Renal sections from patients with diabetes were easily distinguished from those of the other patients and normals by the intense linear staining of extracellular membranes. The most specific reaction was the presence of IgG and albumin lining the tubular basement membrane. Note in Figure 3 the relative specificity of the immunofluorescence in the renal sections from patients with diabetes. Save for some minimal staining of the glomerular basement membrane from the normal kidneys there is practically no overlap among these three groups.

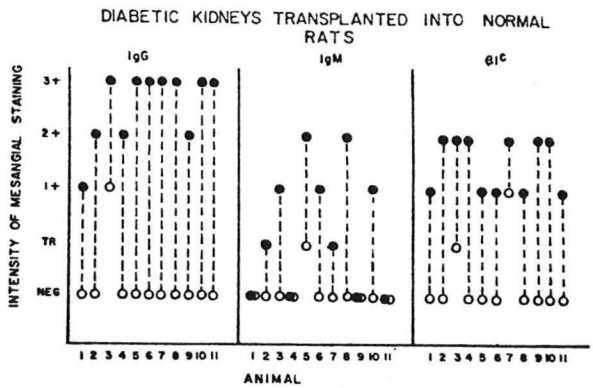
Figure 3



Immunofluorescence for IgG and albumin in tubular basement membranes (TBM), glomerular basement membranes (GBM) and Bowman's capsule in kidneys from normal subjects, and patients with chronic renal failure due to diabetic nephropathy and other renal diseases. (Miller et al 1976)

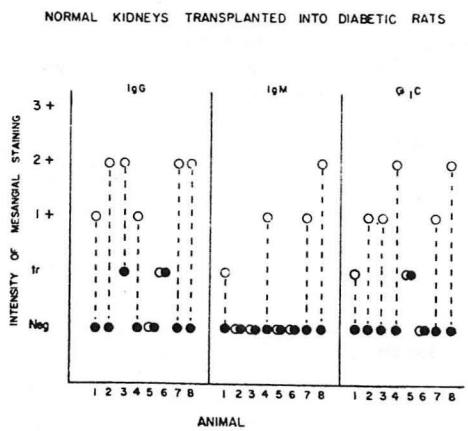
In experimental diabetes in rats, there are exciting data with regard to the role of hyperglycemia and diabetes. First of all similar changes with respect to the immunofluorescent staining for rat IgG and complement C_3 occur after 4-6 months of hyperglycemia. If kidneys from diabetic rats are transplanted into normal rats the characteristic immunofluorescent lesion disappears in 2 months, (Figure 4) and if kidneys from nondiabetic rats are transplanted into diabetic rats the lesion appears after 2 months (Figure 5).

Figure 4



Results of immunofluorescent microscopy studies of kidneys transplanted from diabetic rats into normal recipients; biopsies before transplantation,(●), biopsies 2 months after transplantation, (0). (Lee et al, 1974)

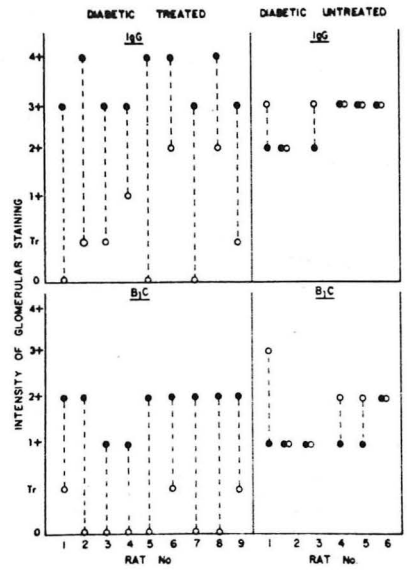
Figure 5



Results of immunofluorescent microscopy studies of kidneys transplanted from normal rats into diabetic recipients; biopsies before transplantation, (●), biopsies 2 months after transplantation, (0). (Lee et al, 1974)

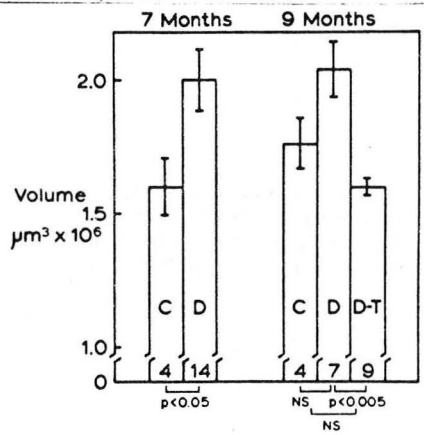
Finally, if diabetic rats are made normoglycemic by islet cell transplantation, there is regression of the immunofluorescent changes (Figure 6) as well as a reduction in the glomerular volume (Figure 7) as well as a reduction in the precentage of the mesangial volume occupied by the matrix component. (Figure 8)

Figure 6



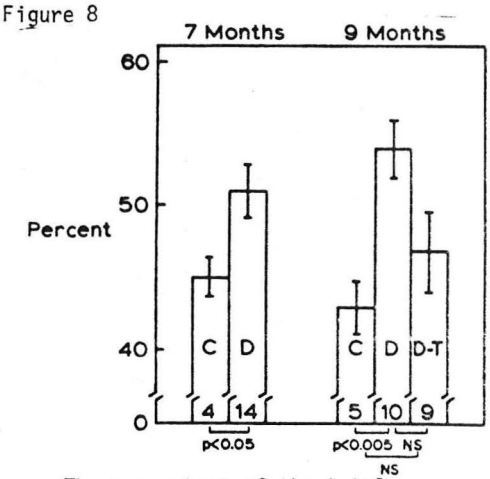
Results of immunofluorescent microscopy studies with staining for rat IgG and B_1C; biopsies before transplantation; (●), biopsies 3 months after transplantation, (0). (Mauer et al, 1974)

Figure 7



Glomerular volumes at the time of and 2 mo after islet transplantation (intraportal distribution of neonatal pancreatic tissue after 7 mo of diabetes C-control, D-diabetic, D-T-diabetic transplanted. (Steffes et al, 1980)

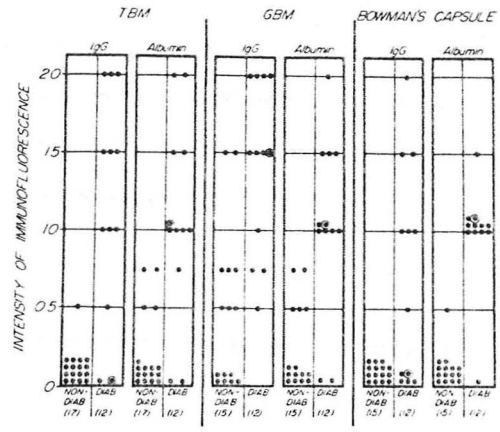
Figure 8



The percentage of the total mesangial volume occupied by the matrix component at the time of and at 2 mo after islet transplants. (Steffes et al, 1980)

In humans, experiments of a similar nature have given results remarkably the same as those obtained in the experimental diabetes of animals. Mauer et al, examined kidney tissue obtained from 12 diabetic and 17 non-diabetic patients from 2 to 12 years after renal transplantation. The frequency and intesity of IgG and albumin staining of the tubular and glomerular basement membrane and Bowman's capsule was significantly greater in the diabetic than in the non-diabetic patients. Except for some staining of the glomerular basement membranes in the non-diabetic kidneys, there was practically no overlap between the two groups (Figure 9).

Figure 9



Immunofluorescense for IgG and albumin in tubular basement membrane (IBM), glomerular basement membranes (GBM) and Bowman's capsule of kidneys transplanted into diabetic and non-diabetic patients. (Mauer et al, 1976)

Although 9 of the 12 diabetic patients received their kidney from a living-related donor, no immunofluorescence was observed in 7 kidneys studied at the time of their transplantation into diabetic recipients.

This same group studied renal-transplant tissue from 12 diabetic and 28 non-diabetic patients who had a renal graft for at least 2 years. Ten of the 12 kidneys studied from diabetic patients showed arteriolar hyalinosis and in 6 of the 10, the hyaline change involve both the afferent and efferent limb of the glomerular arterioles. One diabetic patient developed typical nodular glomerulosclerosis 35 months after transplantation. Three of the 28 kidneys studied from the non-diabetic transplant recipients had hyaline vascular changes. These occured only in rare vessels and did not appear until five years post transplantation and never involved both afferent and efferent arterioles. None of the blood vessel changes were present in the kidneys tranplanted into the diabetic recipients at the time of transplantation although 10 of the 12 received living related donor grafts.

Table 5

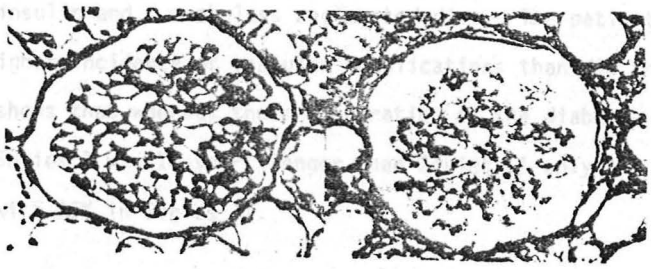
INCIDENCE OF LESIONS OF ARTERIOLAR HYALINE

GROUP	PATIENTS WITH HYALINE DEPOSITS	
	2-10 Yr After Transplantation	2-5 Yr After Transplantation
Diabetic	10 of 12	10 of 12
Nondiabetic	3 of 28	0 of 23
P value*	<0.001	<0.0005

*By chi-square test (Mauer et al, 1976)

There is another interesting human counterpart to some of the studies discribed above in animals. Kidneys from a 37 year old man with a 17 year history of insulin dependent diabetes were offered for transplantation following his becoming comatose and brain dead. His urine was positive for both glucose and protein. All other laboratory tests were unremarkable. At donor nephrectomy both kidneys were grossly normal. After some difficulty placing the organs, they were finally accepted by a transplant center in Kuwait. Both kidneys were successfully transplanted into two male recipients whose chronic renal failure was due to polycystic kidney disease. After transplantation both kidneys functioned well with standard immunosuppression. At the time of transplantation both kidneys showed features of established glomerulosclerosis and an increase the mesangial matrix and a thickening of the glomerular capillary basement membranes. Renal biopsy specimens taken 7 months after transplantation showed complete resolution of the light microscopic abnormalities (Figure 10) and both patients had no proteinuria after an additional 7 months of followup.

Figure 10



Biopsy specimen seven months after transplantation showing (left) widely open glomerular capillaries with almost normal basement membrane and mesangium (PASx400) and (right) almost normal glomerular architecture (methenamine silverx400) (Abouna et al, 1983)

CLINICAL TRIALS

If the metabolic abnormalities of diabetes are in some way responsible in a cause and effect way for the development of microangiopathy then it should be possible to demonstrate that correction of these metabolic abnormalities prevents and/or delays the development of these vascular complications. What follows is a description of clinical trials, whose data bear upon these issues. The first two of these studies are retrospective and thus suffer from all the problems associated with retrospective analysis. Also, there is the problem of the appropriate assessment of overall diabetes control. Most often no objective data are available to judge diabetes control.

The Malmo Study

Johnsson reviewed all diabetic patients in Malmo, Sweden whose diabetes was diagnosed between 1922 and 1945 and who were less than 40 years of age at the onset of their disease. They were divided into two groups. Series I consisted of 56 patients diagnosed from 1922 to 1935. All these patients were initially treated with strict diet control and multiple daily injections of insulin in an attempt to keep the urine free of glucose. Series II consisted of 104 patients whose disease was diagnosed from 1935 to 1945. These patients were treated with long acting insulin and a much less regimented diet. The patients in Series II had a much higher incidence of vascular complications than did those of Series I.

Table 6 shows that whereas the mean duration of the diabetes for those patients in Series I was 10 years longer than Series II only 32% had nephropathy as compared with 56% in Series II.

Table 6

INCIDENCE OF NEPHROPATHY - MALMO STUDY

	Series I	Series II
Number of patients	56	104
Duration of diabetes	24.5 years	15.9 years
Patients with Nephropathy	18 (32%)	56 (54%)

(Johnsson 1960)

The difference is even more striking when one looks at the incidence of nephropathy in patients who have had this disease for more than 15 years. (Table 7)

Table 7

INCIDENCE OF NEPHROPATHY IN MALMO STUDY
AFTER 15 YEARS DURATION OF DIABETES

	Series I	Series II
Number of Patients	56	57
Patients with nephropathy	5 (9%)	35 (61%)

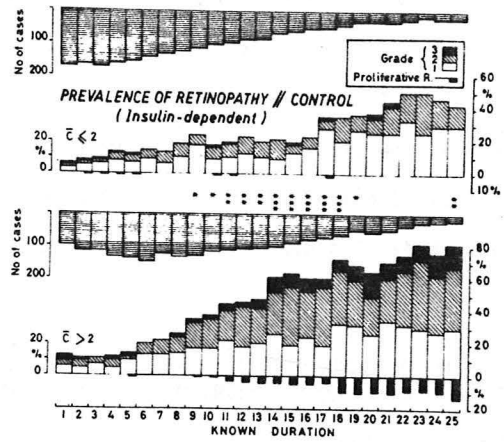
(Johnsson, 1960)

Only 9% of patients in Series I had nephropathy as compared to 61% of Series II. Similar striking differences were seen between the groups when the incidence of retinopathy was compared. Hypoglycemia was far more common in Series I patients, reflecting attempts to achieve normoglycemia and the use of multiple daily insulin injections.

The Belgium Study

This is perhaps the largest study of its kind. Dr. Pirart has followed 4,398 patients with diabetes from 1947, of which 2,795 patients were followed since the initial diagnosis of their diabetes. Despite the obvious limitation of this study, that of the inability to accurately access long term diabetes control, Dr. Pirart's data suggest a strong relationship between the level of diabetic control and the development of diabetic complications. These data can be seen in Figure 11, that demonstrates the prevalence of retinopathy as related to the level of diabetic control over the years of followup. It is clear, the higher the level of diabetic control the greater the prevalence of diabetic retinopathy. Of note however is the fact almost 30% of Dr. Pirart's patients, despite many years of poor diabetes control, had essentially no diabetic retinopathy.

Figure 11



Ascending curves for different grades of retinopathy as a function of duration in severe diabetes with good (top) or with poor cummulative glycemic control (bottom). (Pirart, 1978).

The Job Study

The study by Job et al, as outlined in Table 8 was designed in a prospective fashion. Diabetic patients were randomly assigned to either a single insulin injection injection group or a multiple (three times daily) insulin injection group. Both groups were followed for a mean duration of three years. The progression of retinopathy was evaluated by fluorescien angiography and funduscopic examination. They reported a significantly greater increase in the number of microaneurysms in the single injection group as compared to the multiple injection group. Unfortunately, this study suffers from an important defect which makes the results difficult to evaluate. Of those 21 patients whose data were analyzed from the single injection group, only 16 received one daily insulin injection for the entire period of the study; the other 5 were

changed either to 2 or 3 injections per day after the study began. In the multiple injection group only 5 of the 21 patients analyzed had 3 insulin injections daily for the entire period of the study. The others either initially accepted only 2 injections (4 patients) or some only 1 (4 patients). Nine of the 13 who originally accepted 3 injections daily were reduced to 2 injections after 1 year. The small number of patients initially studied coupled with the many crossovers in the protocol probably make this study invalid.

Table 8

COMPARISON OF THE INCREASE IN THE NUMBER OF MICROANEURYSMS BETWEEN THE TWO GROUPS (Means ± S.E.M.)

		Single Injection Group	Multiple Injection Group	P Values
Number of Microaneurysms	-At Baseline	12.7 ± 3.5	9.0 ± 3.3	N.S.
	-At The Last Examination	33.0 ± 7.9	15.2 ± 4.9	<0.05
	-Difference	20.3 ± 4.9	6.2 ± 2.5	<0.02
Mean Yearly Increase in the Number of Microaneurysms		7.2 ± 1.9	1.8 ± 0.7	<0.01 <0.02*
Mean Yearly Increase in the Square Root of the Number of Microaneurysms		0.85 ± 0.16	0.24 ± 0.13	<0.01

*Nonparametric test. As the variance of the mean yearly increase in the number of microcneurysms differed between the two groups, they were also compared by a nonparametric test (Mann and Whitney) and the square-root transformation, which equalized the variances. (Job et al, 1976)

Controlled Prospective Trials

As elluded to earlier, the past several years have brought great advances in the treatment of insulin dependent diabetes mellitus. Included in these advances are the use of innovative treatment stratagies that include multiple

insulin dosage programs, portable insulin infusion devices, and the increased use of the self monitoring of blood glucose. As a result of these advances it has been possible to design appropriate prospective studies to evaluate more fully in humans the relationship between diabetic control and complications. The following is the results of some of these studies.

The Steno Study

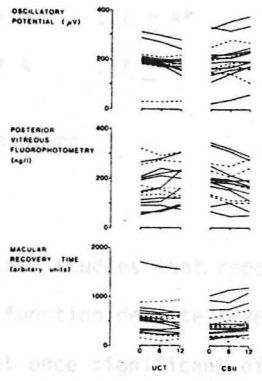
In this study 30 insulin dependent diabetic patients with background retinopathy were given random assignment to either conventional treatment (UCT) (2 daily injections of insulin) or treatment with continuous subcutaneous insulin infusion (CSII) and followed prospectively for now more than 2 years. Retinal examinations were done at 6 month intervals. Mean blood glucose levels and stable hemglobin $A1_C$ values were significantly lower in the CSII treatment group than the UCT treatment group. Retinal morphology deteriorated during the first year in both groups but there were no significant differences between the two. However, the frequency of deterioration was highest in the CSII group, especially among the patients with the best glycemic control. Retinal function (oscillatory potential, macular recovery time, and posterior vitreous fluorophotometry) improved significantly with CSII treatment and deteriorated significantly with conventional treatment. Changes in retinal function were most pronounced in patients with the best and the poorest diabetic control. Table 9 shows the results of stero fundus photographs reveal that despite the apparent, although not statistically significant deterioration of retinopathy after the first year of the study, there appears to have been a leveling off after 2 years of followup. There are now several studies reported now that have shown a tendency toward an acceleration of diabetic retinopathy in patients treated intensively. The mecahnism by which this hopefully reversable deterioration occurs is unknown.

TABLE 9

STENO STUDY
FUNDUS PHOTOGRAPHS

	1 Year		2 Years	
	CT	CSII	CT	CSII
Improved	3	3	2	7
No Change	7	2	2	2
Worse	5	10	10	6

Figure 12



Oscillatory potential posterior vitreous fluorophotometry, and mascular recovery time for UCT and CSII patients. In the UCT panel solid lines indicate the ten poorest regulated patients and in the CSII panel solid lines indicate the ten best regulated patients. In both panels broken lines represent intermediately regulated patients. Each line represents the measurement for one patient at 0, 6, and 12 months. Shaded area indicates normal range (mean ±2SD)(Lauritzen et al, 1983)

In this same study, the effect of diabetic control on glomerular filtration rate and urinary albumin excretion rate was also evaluated. They showed that glomerular filtration rate can be reduced and frequently normalized with prolonged metabolic control, but this does not occur in patients on conventional treatment whose diabetes control is stable though unimproved. There were no effects on urinary albumin excretion with either treatment (Table 10).

Table 10

STENO STUDY
RENAL FUNCTION STUDIES

	Glomerular Filtration Rate (ml/min x 1.73m^2)			Urinary Albumin Excretion Rate µg/min		
	0	1 Year	2 Years	0	1 Year	2 Years
CSII	131 ± 5**	117 ± 5	111 ± 4*	36 ± 9	43 ± 14	79 ± 43
CT	114 ± 4	112 ± 4	112 ± 5	62 ± 18	195 ± 8	267 ± 98*

* = $p<0.05$ 2 years vs baseline
** = $p<0.05$ CSII vs CT

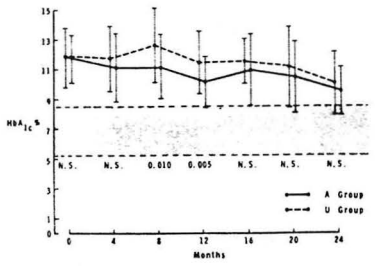
There are several other studies that report similar results, i.e, little or no improvement in renal function despite several years of improved diabetes control. It appears that once significant diabetic renal disease develops improved diabetic control does not cause a reversal or even a slowing of the rate of progression. It is of importance to mention here that aggressive management of patient's hypertension has been shown to be beneficial in terms of slowing the progression of diabetic renal disease.

The British Study

In this study conducted at diabetic clinics at Oxford and Alyesbury, 174 insulin-dependent diabetic patients with background retinopathy were randomized to continue with usual diabetic care (Group U) or to a more intensive program

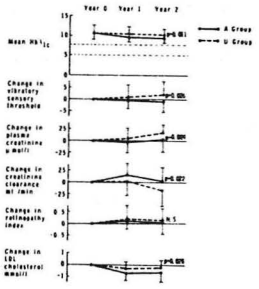
(Group A) using Ultralente insulin as basal cover and soluable insulin before meals. In addition, Group A attended the Clinic more frequently, received closer dietary supervision, and were taught self blood glucose monitoring. Group A had a singificantly lower mean glycosylated hemoglobin level during the study, althought the mean levels also fell in Group U towards the end of year 2. (Figure 13). Renal and sensory nerve function were significantly better preserved in Group A than in Group U (Figure 14). The rate of progression of retinopathy was similar in both groups. They concluded that a modest improvement in diabetic control obtrainable in most clinics is associated with a reduction in the progression of diabetic tissue damage.

Figure 13



Mean HbA_{1c} levels (± 1 SD) in each group. Shaded area = normal range. NS= not significant (Holman et al, 1983)

Figure 14



Changes from entry (year 0) to year 1 and to year 2. With the exception of HbA_{1c} for which values are given at entry and the mean of all values (excluding entry) over year 1 and over 2 years (Holman et al, 1983)

The New Haven Study

In this study 30 eyes of 15 Type I diabetic pateints were evaluated prospectively before and after 11-23 months (mean 18.1 months) of pump treatment. In each patient plasma glucose and total glycosylated hemoglobin levels fell to normal or near normal levels. The 10 eyes without diabetic retinopathy at entry remained without. Four of 20 eyes with diabetic retinopathy at entry advanced by modified Early Treatment Diabetic Reinopathy Study (ETDRS) classification, including one eye that progressed from background to proliferative diabetic retinopathy. No eyes with diabetic retinopathy improved their modified ETDRS classification. One eye progressed to blindness; no other eye lost vision. Six eyes had laser treatment prior to insulin pump treatment; four of these and two more required laser during pump treatment. Two eyes had vitreous hemorrhages prior to pump treatment; one of these and four others hemorrhaged during pump treatment. No eyes with diabetic retinopathy showed regression of microvascular changes. The data suggested to the authors that prolonged restoration of near normal glucose metabolism with the insulin pump does not reverse established diabetic retinopathy.

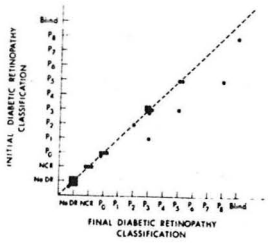
Table 11

SUMMARY DIABETIC RETINOPATHY CLASSIFICATION
(30 EYES OF 15 PATIENTS)

	Entry	Current
No DR	10	10
BDR	9	8
PDR	11	12
Total Eyes	30	30

(Pulkin et al, 1982)

Figure 15



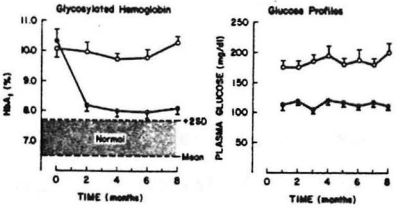
A scatter diagram plotting the initial modified ETDRS classification of each eye on the ordinate with the final modified ETDRS classification on the abscissa. Dots falling on the 45° line represent no change; those below the line represent a progression of retinopathy. (Pulkin et al, 1982)

The Kroc Study

This is a prospective multicenter trial whose data has been recently reported. In this study patients with nonproliferative diabetic retinopathy and absent C-peptide were randomly assigned to pump (n=35) or conventional therapy (n=35). Subsequently, glycemic control and retinopathy (fundus photography and fluoroscein angiography) were periodically assessed over 8 months. At the start of the study, age duration of diabetes, insulin dose, glycemic control, and the degree of retinopathy were similar in the 2 groups. After randomization, mean blood glucose (175 $\pm$ 9 mg/dl) and glycosylated hemoglobin levels (10.0 $\pm$ 0.3%) remained elevated in the conventional treatment group, but fell to near normal values (117 $\pm$ 6 mg/dl, 8.1 $\pm$ 0.3% respectively) during the entire period of pump treatment ($p<0.001$ vs. conventional treatment group) (Figure 16). The frequency of biochemical hypoglycemia was similar in both studies, but ketoacidosis occured only with pump therapy. The level of retinopathy assessed from pho-

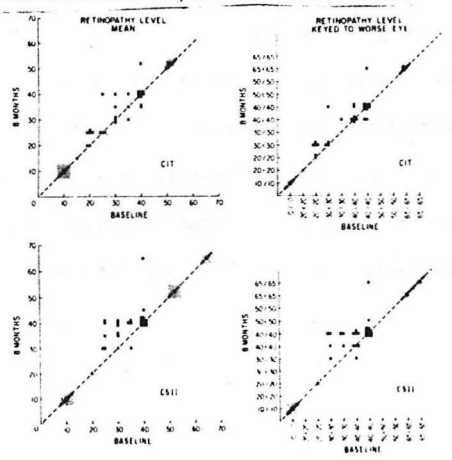
tographs progressed in both groups. Continous subcutaneous insulin infusion was associated with slightly more deterioration in diabetic retinopathy as compared to the conventionally treated group, mainly because of the appearance of soft exudates and intraretinal microvascular abnormalities (Figure 17). In contrast, elevated albumin excretion rates fell during continuous insulin infusion but not conventional treatment (Figure 18). The conclusion from this study is that a nearly normal blood glucose level for 8 months does not retard progression of and in may initially worsen, established retinopathy. They suggested the need for longer trials, particularly directed toward primary prevention.

Figure 16



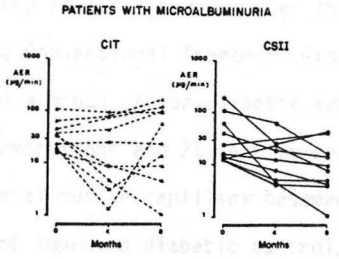
Home assessments of glycemic control in patients randomly assigned to continuous subcutaneous insulin infusion(●) or unchanged conventional injection treatment(o)

Figure 17



Retinopathy levels at baseline and at 8 months in individual patients assigned to CSII or CT

Figure 18



Changes in albumin-excretion rate in the 10 patients in each treatment group with supra-normal baseline values (exceeding 12 μg per minute) (Kroc Study Group, 1984)

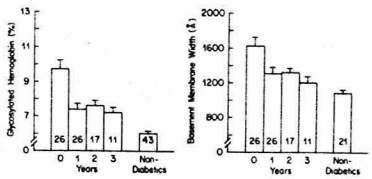
The Dallas Study

We save the best for last! Over the past several years we have been engaged in a prospective non-randomized trial of the effect of an experimental treatment program on diabetic complications in insulin dependent diabetic patients (C-peptide negative). This treatment program includes aggressive dietary instruction, self blood glucose monitoring, and continuous subcutaneous insulin infusion delivered via a portable insulin infusion device. Data from this group of patients have been compared to a similar group of Type I diabetic patients who preferred to continue with their more conventional diabetes treatment rather than accept entry into our experimental treatment program. Over the years we have shown a considerable advantage of the experimental treatment program over conventional treatment with respect to many metabolic parameters such as plasma glucagon profiles, lipid and lipoprotein levels and motor nerve conduction velocities.

We have also measured skeletal muscle capillary basement membrane width in 51 of these patients in whom observations have been made from 1 to 3 years. Of these 51 patients 26 accepted our offer to enter the Experimental Treatment Group and 25 were in the Conventional Treatment Group. Data from diabetic patients was compared to a group of non-diabetic subjects, 43 of whom had glycosylated hemoglobin determinations and 21 that agreed to undergo a muscle biopsy for measurement of skeletal muscle capillary basement membrane width.

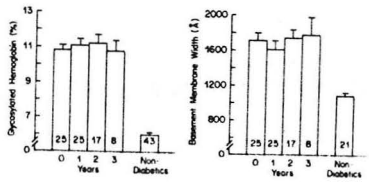
During the 3 years of improved diabetic control, that is reflected by a decrease in glycosylated hemoglobin levels, using an experimental treatment program consisting of rigid dietary control, self blood glucose monitoring and continuous subcutaneous insulin infusion there is a significant reduction in skeletal muscle capillary basement membrane width (Figure 19). This reduction is not evident in the group of diabetic patients treated with a more conventional program who showed a stable though unimproved level of diabetic control (Figure 20). If capillaries in skeletal muscle are reflective of those in retinal and/or renal tissue, then meticulous diabetic control for prolonged periods might be beneficial with respect to the microvascular complications of diabetes.

Figure 19



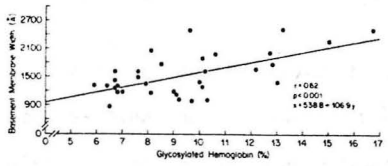
Quadriceps capillary basement membrane width and glycosylated hemoglobin levels in Type I diabetic patients in the Experimental Treatment Group. Values in nondiabetics are included for reference. (Raskin et al, 1983)

Figure 20



Quadriceps capillary basement membrane width and glycosylated hemoglobin levels in Type I diabetic patients in the Conventional Treatment Group. Values in nondiabetics are included for reference. (Raskin et al, 1983)

Figure 21



The relationship between capillary basement membrane width and glycosylated hemoglobin values in Type I diabetic patients after 2 years of treatment. (Raskin et al, 1983).

In addition we have recently evaluated our data on the progression of diabetic retinopathy in 57 of our patients in this trial 33 of whom were in the Experimental Treatment Group and 24 patients that were in the Conventional Treatment Group. The group characteristics are listed in Tables 12 and 13.

Table 12

PATIENT POPULATION
EXPERIMENTAL TREATMENT GROUP

N:	33
AGE:	27.6 ± 2.6 years
DURATION:	13.8 ± 1.2 years
SEX:	12 males, 21 females
FOLLOWUP:	30.7 ± 2.9 months

Table 13

PATIENT POPULATION
CONVENTIONAL TREATMENT GROUP

N :	24
AGE:	27.1 ± 1.7 years
DURATION:	11.9 ± 1.3 years
SEX:	3 males, 21 females
FOLLOWUP:	33.5 ± 3.7 months

All patients were evaluated ophthalmologically at entry and at regular six month intervals. Each examination included best corrected visual acuity, molility, slit lamp evaluation, and direct and indirect ophthalmoscopy performed after dilation of the pupils. Seven field fund photography and fluorescien angiography were obtained at each visit using a Zeiss Fundus Camera that had a field view of 30^{o}.

A standard grading system was utilized to categorize the retinopathy of each eye of each patient on each visit. We used the Puklin modification of the ETDRS grading scheme (Table 14) which creates an additional category (Grade ?) for very minimal retinopathy. We studied the fluorescien angiograms in conjunction with the color photographs to determine areas of neovascularization, intraretinal microvascular abnormalities (IRMA), and macular edema. Using the modified ETDRS grading system each eye at each particular point in time was further categorized by indexing the worst eye and describing the better eye according to a system advocated by Klein, et al. The order of progression within retinopathy categories was thus (1,1) (2,<2) (2,2) (3,<3) (3,3) etc. A patient was considered worse if the eyes changed by 2 or more of these final categories over time.

Table 14

MODIFIED ETDRS GRADING OF DIABETIC RETINOPATHY (AFTER PUKLIN)

Group 1 No diabetic retinopathy

Group 2 The presence of very mild BDR insufficient to be classified as group 3. Specifically, the presence of microaneurysms or red dots >125 in diameter without macular edema or hard exudates standard photograph 3 and without macular edema on fluorescein angiography.

Group 3 BDR insufficient to be classified as group 4. Specifically, at least 1 microaneurysm or red dot >125 in diameter plus macular edema represented by either a thickened retina or hard exudates ≥ standard photograph 3 or with evidence of macular edema on fluorescein angiography.

Group 4 Evidence of any one of the following in any one of seven standard fields: hemorrhages and microaneurysms ≥ standard photography 2A, soft exudates, venous beading, or intraretinal microvascular abnormalities (IRMA).

Group 5 Various combinations of hemorrhages and microaneurysms, soft exudates, venous beading, and IRMA in more than one standard field.

Group 6 Flat NVE (neovascularization elsewhere) present; NVD (neovascularization on the disc or within 1 disc diameter of the disc) absent.

Group 7 Flat NVD present: NVD absent.

Group 8 Flat NVD and NVE present.

Group 9 The same as group 6-8 with regard to NVD and NVE, but at least one plane of the neovascularization must be elevated above the surface of the retina by at least 1/4 disc diameter, but not by more than 1 disc diameter.

Group 10 The same as groups 6-8 with regard to the NVD and NVE, but the neovacularization must be elevated in at least one place by more than 1 disc diameter off the retinal plane.

The results of the modified ETDRS grading are shown in Table 15. There was a significant relationship between the control of diabetes and the progression of diabetic retinopathy as defined by the categories better, stable or worse ($p = 0.037$ by log-likelihood chi-square). That is to say that the diabetic retinopathy in the Experimental Treatment Group showed significantly less deterioration over time, i.e., more were either stable or improved, than did the diabetic retinopathy in the Conventional Treatment Group, where more tended to get worse. Thus, in our study there appears to be some advantage in terms of a slowing of the progression of diabetic retinopathy in our patients treated with portable insulin infusion pumps. The precise reasons why our data differ from the others described above is not entirely clear, but the somewhat longer duration of follow-up and the fact that all our patients (both treatment groups) tended to have very early diabetic retinopathy are two explanations that seem readily apparent.

Table 15

THE EFFECT OF DIABETIC CONTROL ON
THE PROGRESSION OF RETINOPATHY

MODIFIED ETDRS GRADING

	CONVENTIONAL TREATMENT GROUP	EXPERIMENTAL** TREATMENT GROUP
BETTER*	0	4
STABLE	18	26
WORSE*	6	3

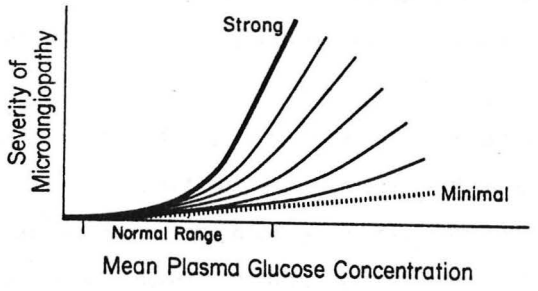
*defined as a change in 2 or more categories when both eyes were taken together

** $p < 0.05$ Experimental Rx vs Conventional Rx (log-likelihood chi-square)

CONCLUSIONS

What are the overall conclusions to be drawn from the data presented. Which of the two hypotheses of the etiology of the microvascular complications of diabetes was the better supported? Given all the facts, I find it difficult to come to a single answer. Alternatively, I would like to submit that the small blood vessel complications of diabetes are related to both genetic and metabolic influences. Figure 22 is my attempt to diagram my thoughts regarding the interrelationship between genetic and metabolic factors in the development of diabetic complications.

Figure 22



INFLUENCE OF GENETIC PREDISPOSITION ON THE SEVERITY OF DIABETIC MICROANGIOPATHY

In perhaps 20-25% of diabetic patients the genetic predisposition to develop diabetic complications is very low. Thus, no matter how severe the metabolic abnormality, i.e., how much hyperglycemia the patients have over the lifetime of their illness, they rarely develop significant complications. If we could identify this subset of patients at the beginning of their disease our treatment recommendations would be simple. Keep them free of symptoms and avoid both hypoglycemia and severe hyperglycemia and ketoacidosis. These people would not

need expensive intensive diabetes management that results in a higher impact on people's lifestyle. In another 5% of patients the genetic predisposition to the development of diabetic complications is so great that even a slight degree of hyperglycemia results in severe microvascular complications. Unfortunately, given our present treatment techniques, we may be unable to completely normalize the blood glucose level sufficiently well enough to help this group of patients. Finally, we have the large bulk of diabetic patients who have varying degrees of the genetic predisposition to develop the microvascular complications. I think that in this group improved diabetic control, that results in a lowering of the overall blood glucose level, might reduce the severity of the microvascular complications.

All of this remains, I feel, to be proven. For although the data seems to support my synthesis it is not yet a proven fact. My prejudice is that in those patients for whom we can do some good by intensive diabetes treatment with resulting long-term near-normal or normal glycemia we must consider this as preventive in nature. I think we will eventually prove that all we can do is prevent diabetic complications from occuring but that once significant diabetic complications occur no degree of normoglycemia will cause a reversal.

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