UTHSCD MEDICAL GRAND ROUNDS

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DIABETIC NEPHROPATHY:
CLINICAL CHARACTERISTICS AND THERAPY

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"I find the great thing in this world is not so much where we stand as in what direction we are moving."

Oliver Wendell Holmes

TABLE OF CONTENTS

INDEX OF FIGURES

INDEX OF TABLES

DIABETIC NEPHROPATHY: CLINICAL CHARACTERISTICS AND THERAPY.

I. INTRODUCTION

Diabetes mellitus is the single most common known etiology of renal disease in the United States. This stems from 2 factors: 1) roughly 2% of the population are known diabetics (with an additional 2% who have "subclinical" disease), 2) renal disease accounts for a large proportion of the morbidity and mortality associated with diabetes. The advent of dialysis and transplantation for management of end-stage renal disease (ESRD) offers the potential for significantly increasing the survival of the many diabetics who develop this complication. Although dialysis and transplantation have been widely available for a number of years, their acceptance for treatment of diabetics has been rather slow but steady. This gradual change in attitude and its ultimate socio-economic impact (increasing genetic population pool, increasing health care costs) has not yet been fully appreciated. As the expected number of diabetics entering dialysis and transplantation programs increases it becomes imperative to discern the relative benefits and risks of both treatment modalities. The purpose of this review is to describe the characteristics of diabetic nephropathy and to assess the current status of management of its most common outcome, end stage renal disease.

II. PATHOLOGY

In 1936, Kimmelstiel and Wilson described an unusual hyaline intercapillary glomerular thickening with nodule formation in the kidneys of 8 patients who presented with hypertension, edema, and albuminuria. Seven of these patients were diabetic (1). The term "diabetic nephropathy" or Kimmelstiel-Wilson disease has since been commonly applied to any diabetic

with renal disease, primarily manifested by proteinuria, edema, hypertension, bacteriuria and azotemia, and often progressing to renal failure. The syndrome we refer to as diabetic nephropathy is probably most often a manifestation of a spectrum of renal disease processes rather than a result of the specific nodular lesion described by Kimmelstiel and Wilson. Thus, "diabetic nephropathy" is a useful clinical term encompassing a group of lesions causing renal disease in diabetes while the term "K-W disease" should be reserved for individuals with proven diabetic nodular glomerulosclerosis.

Table 1

PATHOLOGY

I. Intrinsic

A. Glomerular

1) Diffuse Glomerulosclerosis
- Most frequent - 75%
- Non-specific

2) Nodular Glomerulosclerosis
- Less common - 30-50%
- Always accompanied by diffuse
- K-W lesion: pathognomonic

3) Exudative and capsular drop
- rare

B. Vascular

1) Arteriolosclerosis
   - Almost always present
   - Affects all arterioles
   - More extensive than in any other disease

2) Atherosclerosis
   - Part of diffuse vascular disease
   - May result in renovascular stenosis or thrombosis

3) Atheroemboli
   - Increased risk during catheterization

C. Tubulo-Interstitial

- Lipid vacuolization common in nephrotics
- Tubular atrophy and interstitial fibrosis related to degree of ischemia

II. Extrinsic

A. Infection

1) Bacteruria
2) Cystitis
3) Pyelonephritis
   - All are 2 - 10x more common in diabetics
   - Predisposing factors include:
     Decreased resistance to infection
     Glycosuria
     Vesical dysfunction causes stasis
     Vascular disease compromises renal and vesical circulation

4) Papillary Necrosis
- Represents medullary and papillary infarction
- Most often associated with diabetes
- Often results in irreversible renal failure

B. Vesical Dysfunction

- Universal if peripheral neuropathy present
- Occurs 10 years after onset of diabetes
- Cystometrogram most sensitive test

Glomerular

Diabetic glomerulosclerosis refers to a group of more or less distinc glomerular lesions which generally coexist. The primary pathological rena lesion of diabetes, diffuse glomerulosclerosis, is characteristic but by n means diagnostic of the disease. It consists of a diffuse hyaline thicken ing of the capillary wall and basement membrane as well as an increase i mesangal matrix. Similar changes may be seen in some forms of glomerulo nephritis, particularly membranous glomerulonephropathy (2), and arteriola nephrosclerosis (3). The nodular lesion, on the other hand, is generall agreed to be pathognomonic of the disease (3). In this form there i deposition of eosinophilic nodules, distinct from the basement membrane within the capillaries.

The frequency of the occurance of diabetic glomerulosclerosis (GS) i uncertain, primarily because of differing views regarding pathologica definition of the lesions. Most estimates by light microscopy, however suggest that the diffuse lesion is somewhat more common and that the nodu lar lesion is virtually always accompanied by the diffuse lesion (2,4,5 (Table 2). It has been reported that the lesion can be found on electro microscopy in 100% of diabetics (6).

Table 2

INCIDENCE OF NODULAR AND DIFFUSE GLOMERULOSCLEROTIC LESIONS IN DIABETIC PATIENTS

Source	Percentage with Diffuse Lesion (with and without nodules)	Percentage with Nodular and Diffuse Lesions	Percentage with Diffuse Lesion Only
Autopsy series			
Bell (4)	51	38	13
Biopsy series			
Gellman et al. (2)	77	53	24
Hatch et al. (5)	87	36	51
Mean	72	42	30

Generally, the incidence of the pathologic finding of glomerulosclerosis increases with duration of disease (7). In one autopsy series, the finding of no lesion or diffuse or nodular lesion was associated with the following mean duration of disease, as shown in Table 3.

Table 3

DURATION OF DIABETES AND INCIDENCE OF LESIONS

	Yrs.
No Lesion	7.0
Diffuse GS	11.9
Nodular GS	13.2

The severity of the diffuse form appears to increase with duration c disease, while presence but not severity of the nodular form also corre lates with duration of disease (3). The exudative lesion, also calle "fibrin cap", is found in diabetics with severe vascular disease. It i not specific and seen also in glomerulonephritis and SLE. The capsula drop lesion is a rare lesion, represented as a rounded eosinophilic mass o the inside of Bowman's capsule. It is said to be specific in its earl stages.

Vascular

Vascular lesions are almost universal in diabetes. The most charact eristic renal vascular lesion is hyaline arteriolosclerosis. It is mor severe, more extensive and occurs at an earlier age in diabetes than in th general population. It frequently involves the efferent arterioles as wel as the afferent arterioles. This distinguishes it from non-diabetic arter iolosclerosis which generally involves only the afferent arterioles Atherosclerosis of the main renal artery and its branches may lead to rena artery stenosis sufficient to cause ischemic hypertension. In addition the frequency of atheromatous plaques increases the possibility of embolis and predisposes diabetics to this complication, particularly during cather ization procedures.

Tubulo-Interstitial

Tubular and interstitial changes are common. Tubules exhibit lipi vacuolization and atrophy expecially in nephrotic patients. The inter stituum is often fibrotic. Tubular atrophy and interstitial fibrosis ar related to degree of renal ischemia.

Infection

The diabetic is also predisposed to bacteruria, cystitis, pyelonephri tis, and papillary necrosis, all of which occur 2-10 times more often tha in non-diabetics. Several factors contribute to this predispositio including 1) decreased resistance to infection, 2) glycosuria, which offer

an excellent culture medium, 3) neuropathic bladder, common after 10 years of diabetes, causing obstruction and stagnation of urine flow, and 4) vascular disease, resulting in impaired circulation to the bladder and kidneys.

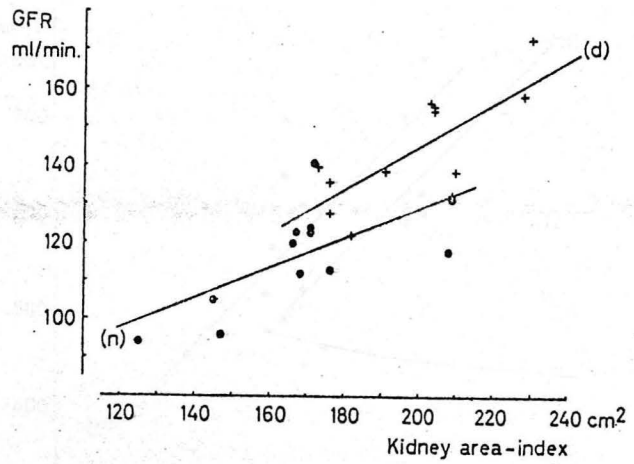
Neuropathic Bladder

Vesical dysfunction is a common finding particularly if peripheral neuropathy is present. It generally begins to occur after about 10 years of diabetes.

Clinico-pathological correlation of either the presence or severity of either lesion and the syndrome of diabetic nephropathy is fair to poor. When the diagnosis of diabetic nephropathy is based on the presence of the classical clinical triad of proteinuria, hypertension and edema, it is often liable to be erroneous. This is so because the population of patients under consideration commonly develop atherosclerosis, congestive heart failure, and bacteriuria, and these complications may frequently elicit the same classical triad. Only two-thirds of diabetics suspected of having glomerulosclerosis on clinical grounds, will exhibit the characteristic pathological lesion. Conversely, only one-third of all diabetics who develop a renal lesion histologically will exhibit the "classical" clinical findings of proteinuria, hypertension and edema (8).

III. EARLY DIABETES

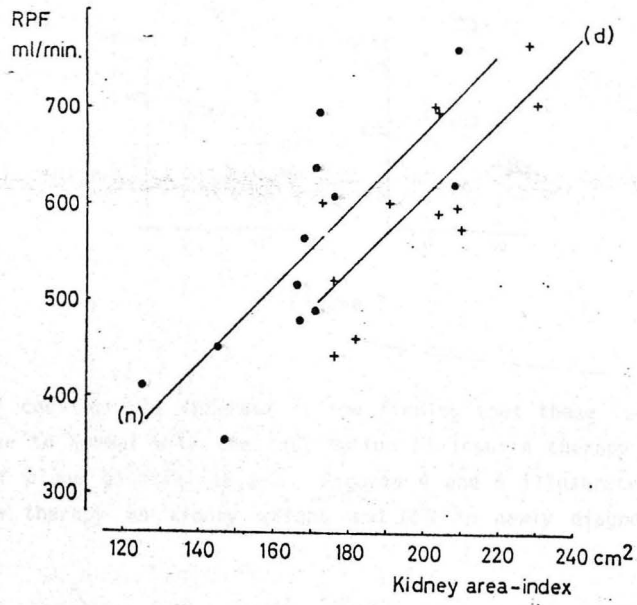
"Pre-clinical" diabetics exhibit renal structural and functional changes unique to this disease. Kidney size is frequently increased in early diabetics (9,10) (Figure 1).



GFR and kidney area-index in 12 normal (•)
and 12 diabetic (+) subjects.
Regression line for normals (n)
——"—— diabetics (d)

Figure 1

Among the explanations proposed are increased blood flow, hypertrophy, an pathological substrate accumulations. None of these hypotheses have bee substantiated. Increased glomerular filtration rate (GFR) (Figure 1) i another well described early phenomenon although the mechanism for thi also remains to be elucidated (10,11,12). Normal glomerular permeabilit to high molecular weight dextran and the absence of albuminuria in thes individuals suggests that alterations in membrane permeability are not th explanation for increased GFR (11,13). The renal plasma flow in earl diabetics is slightly below normal (as shown in Fig. 2) (10) and the fil tration fraction is thus elevated, raising the possibility that thes individuals have increased filtration pressure to explain the increase i GFR.



RPF and kidney area-index in 12 normal (•) and 12 diabetic (+) subjects.
Regression line for normals (n)
—"— diabetics (d)

Figure 2

An interesting possibility has been raised by certain studies utilizing stereological analysis of electron microscopic sections. These studies imply that GFR is increased secondary to an increase in glomerular capillary surface area (14). In addition to increased renal size and GFR, the early diabetic kidney exhibits an increase in the maximum tubular reabsorption of glucose (15), shown in Figure 3.

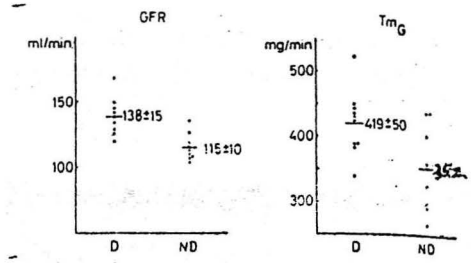


Figure 3

Of considerable interest is the finding that these "super-function decrease to normal with the institution of insulin therapy and normaliza tion of blood glucose (16,17). Figures 4 and 5 illustrate the effect o insulin therapy on kidney weight and GFR in newly diagnosed diabetics

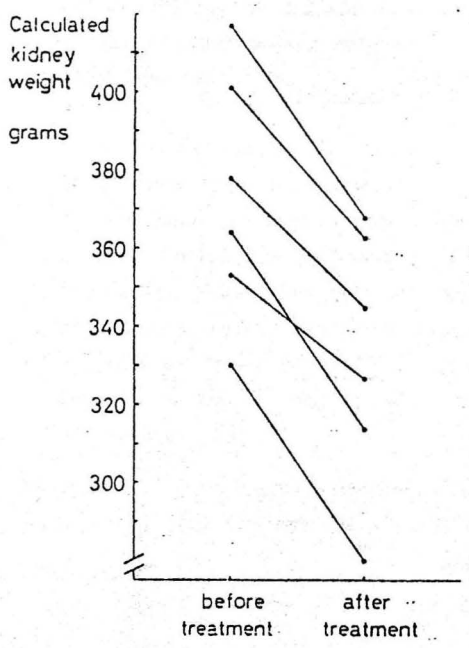


Figure 4

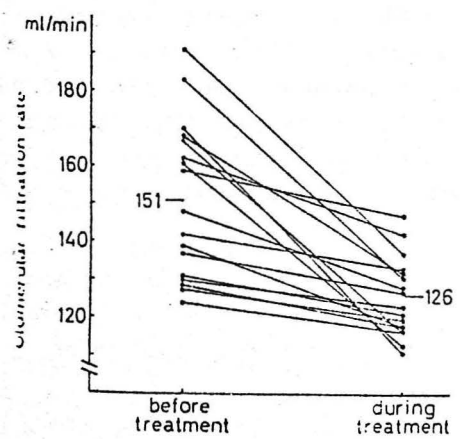


Figure 5

It is tempting to speculate that these various changes result from hyperglycemia and its osmotic effects, although there is no data to support this hypothesis.

IV. NATURAL HISTORY AND CLINICAL CHARACTERISTICS

It is apparent that individuals who develop the disease early in life (to age 20-25) and require insulin - juvenile onset diabetes mellitus (JODM) - are more liable to develop certain complications, including nephropathy, than are those individuals who develop diabetes later in life and who may not require insulin - adult onset diabetes mellitus (AODM). Recognizing that the classification of diabetes based on age of onset may not describe two entirely distinct or homogeneous populations, it is nevertheless useful to analyze and compare some clinical characteristics of two groups of individuals arbitrarily classified as those who have JODM and those who have AODM.

The most common manifestation of diabetic nephropathy is proteinuria. It differs from proteinuria associated with other renal diseases in that the 24 hour urinary albumin excretion does not decrease as the GFR decreases (18). The explanation for this peculiarity is unknown, although increasing glomerular permeability and decreasing tubular reabsorption may both play a role. Proteinuria generally begins after 14 years of diabetes in JODM as shown in Table 4 (19) and its incidence increases with time. Roughly 40-50% of patients with JODM will have proteinuria after 25 years of diabetes (20).

Table 4

PREVALENCES OF ALBUMINURIA AND HYPERTENSION AT KNOWN DURATION OF JUVENILE DIABETES MELLITUS

Duration, yr	Albumin, %	Hypertension, %
0-9	2	1
15-19	18	15
25-29	39	44
35-39	63	70

Data on the prevalence of renal disease in AODM is not well documente because most studies of nephropathy have focused on juvenile diabetes Proteinuria occurs in only 10% of this population and begins to occur afte about 17 years of diabetes (21).

Although proteinuria is a complication of long standing diabetes, i can occur within one month after the onset of clinical glucose intoleranc (22). Moreover, it can occur in the absence of any evidence of metaboli disturbance. Several studies have described diabetics with proteinuria bu no other clinical abnormality. Although these individuals demonstrate diffuse glomerulosclerosis on renal biopsy, the diagnosis of diabetes coul be made only by borderline abnormalities on glucose tolerance testin (23,24). The nephrotic syndrome, per se, is relatively rare and is seen i only 5% of all diabetics (25). When it occurs it is usually associate with advanced renal disease.

It is axiomatic that nephropathy generally parallels retinopathy i progression and that they are usually found together. There are however numerous exceptions to this rule. The absence of retinopathy does no exclude the presence of nephropathy.

The onset of proteinuria heralds the initiation of progressive renal functional impairment. The incidence of hypertension roughly parallels that of proteinuria in JODM (19,20) (Table 4). The long term prognosis is clearly worse after the onset of proteinuria in both JODM and AODM. Over 75% of individuals with JODM and proteinuria will die or at least develop end stage renal disease within 10 years of onset of proteinuria (Table 5) or after 25-30 years of diabetes (20,26) (Figures 6 and 7).

Table 5

MORTALITY IN JUVENILE DIABETIC PATIENTS WITH PROTEINURIA

Year of proteinuria	% azotemia	% death
1	2	0
3	43	17
5	57	48
8	68	77
10	81	77
12	81	88

Figure 6 illustrates the cumulative risk of nephropathy in JODM.

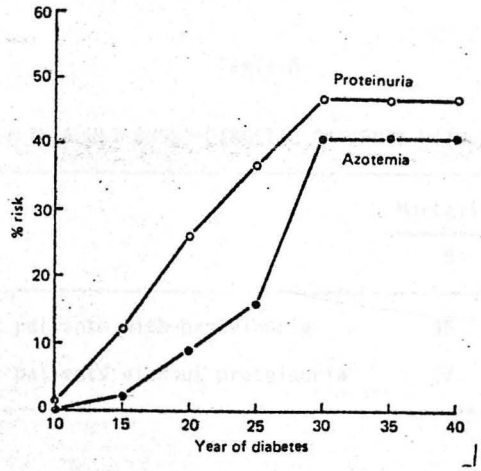


Figure 6

Shown in Figure 7 is the duration of survival of 136 juvenile diabetics who died of renal disease.

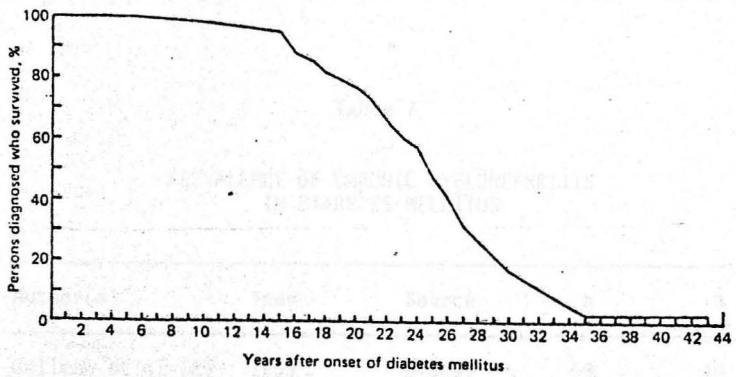


Figure 7

The high mortality associated with proteinuria also appears to be true of adult onset diabetics (27) (Table 6).

Table 6

MORTALITY IN ADULT ONSET DIABETIC PATIENTS WITH PROTEINURIA

	Mortality, % at yr	
	5	10
Diabetic patients with proteinuria	35	72
Diabetic patients without proteinuria	27	54

V. INFECTION AND ACUTE RENAL FAILURE

Among 1,000 consecutive urine analyses at the Joslin Clinic, pyuria of 10 or more white cells was found in 116 (12%) and bacteria in 388 (39%) (28). Acute and chronic pyelonephritis are several fold more common than in the non-diabetic population, for whom the incidence is said to be 1-2% (29).

Table 7

PREVALENCE OF CHRONIC PYELONEPHRITIS
IN DIABETES MELLITUS

Author(s)	Year	Source	N	%
Gellman et al (2)	1959	Biopsy	59	10
Warren et al (29)	1966	Autopsy	351	36

Papillary necrosis in diabetics accounts for 50-80% of all cases described (28). It is responsible for a large proportion of acute renal insufficiency in diabetics. Recently, it has been shown that diabetes is a major risk factor for acute renal failure following administration of x-ray contrast medium (30,31). Additional risk factors, frequently present in diabetics are, 1) hypertension, 2) impaired renal function, 3) advanced age, and 4) dehydration. Use of x-ray contrast in diabetics should be performed only after careful hydration and with the smallest possible volume of dye.

VI. CAUSES OF MORTALITY

As noted above, renal disease in diabetes signifies a poor prognosis. The mortality of diabetics with proteinuria at any given age is at least 50% greater than those without this complication and twice that of non-diabetics of similar age and sex. Survival after the onset of azotemia is not greater than 12-24 months. Mortality due to renal disease accounts for 50% of the deaths in untreated patients with JODM (28) but causes death in only 6% of untreated patients with AODM.

Table 8

CAUSES OF DIABETIC PATIENT MORTALITY

	Patients		Patients diagnosed at age, N			
Causes of death	N	%	<20	(%)	20+	(%)
Renal	615	9	229	(48)	386	(6)
Cardiovascular	4,613	67	132	(28)	4,481	(71)
Other	1,572	23	111	(24)	1,461	(23)
Total	6,800	99	472	(100	6,328	(100)

The most important causes of death in AODM, by far, are complications of macrovascular disease such as coronary disease and stroke. The reason for the preponderance of renal deaths in JODM is not understood but is most probably related to the generally longer duration of disease in these individuals.

It is of interest to note that those individuals who live greater than 30 years after onset of diabetes develop a risk of macrovascular disease approaching that of individuals with AODM (20), as shown in Figure 8.

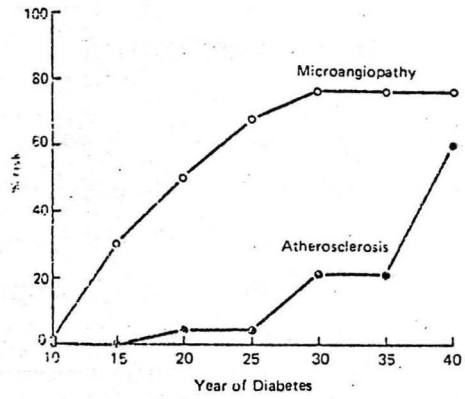


Figure 8

The clinical observation that these individuals differ in some way from those who succumb to microvascular disease has been confirmed by several studies (32,33) describing their clinical characteristics (Table 9). As this table illustrates, only 29% of 73 patients with 40 years duration of JODM had proteinuria and only 8% had azotemia. The factors responsible for their increased longevity remain to be identified.

Table 9

FORTY-YEAR SURVIVORS WITH JUVENILE DIABETES

A. Nephropathy

	Patients	%
No renal involvement	43	58.9
Proteinuria Normotensive:	15	20.5
Hypertensive: + ↑BUN	6	8.2
Hypertension without proteinuria	9	12.3
Totals	73	99.9
Urinary tract infection	12	16.4

B. Cardiac Complications

	Sex			
	M	F	Totals	%
Myocardial infarction	2	10	12	16.4
Angina pectoris	1	2	3	4.1
No involvement	29	29	58	79.4
Totals	32	41	73	99.9

Eighteen patients (24.6 %) had history of cardiac failure.

VII. THERAPY

A. Insulin

Certain groups of diabetologists have, over the years, advocate rigid control of blood glucose to prevent the complications of dia betes, on the assumption that microangiopathy is caused by the meta bolic defect. It has been demonstrated that rigid control of bloo

glucose via continuous subcutaneous insulin infusion decreases urinary albumin loss quantitatively, at least in the short term (34).

Figure 9 illustrates urinary albumin excretion before and after strict glucose control via continuous insulin infusion.

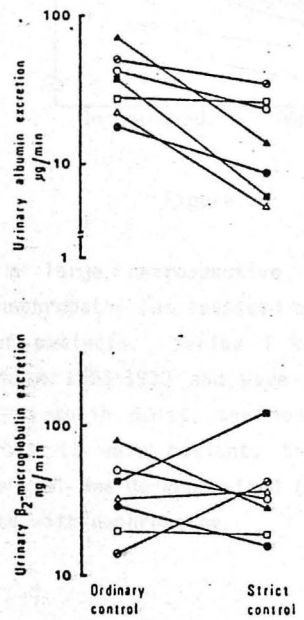


Figure 9

Confirming this is the observation that good control of diabetes by conventional insulin therapy results in decreased urinary albumin excretion (17). Figure 10 shows a decrease in urinary ablumin loss with treatment of poorly controlled diabetes.

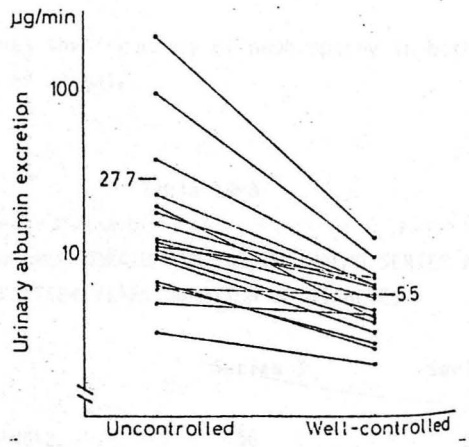


Figure 10

Furthermore, a large retrospective study in Sweden analyzed th frequency of nephropathy (as assessed by qualitative proteinuria) in populations of patients. Series I represents patients who starte treatment between 1922-1935 and were managed with "strict diet" ar multiple daily insulin doses, the goal being normalization of bloc glucose. Series II were patients treated from 1936-1945, in whc blood sugar control was de-emphasized (35). Table 10-A shown result in all patients with nephropathy.

Table 10-A

INCIDENCE OF NEPHROPATHY IN THE TWO MALMO SERIES
INCLUDING LIVING AND FATAL CASES

	Series I	Series II
Duration of diabetes in years	19-35 (24.5)	10-21 (15.9)
Number of patients	56	104
Patients with nephropathy	18 (32%)	56 (54%)

Table 10-B gives the frequency of nephropathy in both groups after the same duration of diabetes.

Table 10-B

INCIDENCE OF NEPHROPATHY IN THE TWO MALMO SERIES AFTER FIFTEEN YEARS DURATION OF DIABETES

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

This study shows that the frequency of nephropathy is strikingly reduced in the group in which treatment was rigidly controlled.

Further evidence in favor of the metabolic theory is the frequency of diffuse glomerulosclerosis in secondary diabetes. On the other hand, a number of studies which purport to demonstrate microangiopathy and glomerulosclerosis in the absence of clinically evident carbohydrate intolerance lend credence to the theory that the genetic locus responsible for the metabolic abnormalities is independent of the locus which determines microangiopathy (23,24). There still seems to be no clear cut answer to this most basic question regarding treatment of diabetes. In support of those who favor strict control one might observe that poorly controlled diabetes has never been shown to increase longevity.

Practically speaking, there is no effective treatment of diabetic nephropathy until the patient reaches end stage renal disease.

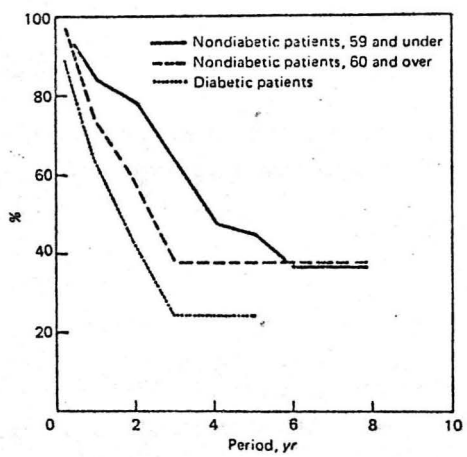
B. Dialysis

Although this modality has been widely available for some time, the initial reaction to its use in diabetics must be described as unenthusiastic at best. Until relatively recently, there appeared to be a general consensus that such an extraordinary means of prolonging life is unrealistic or unjustified in a patient population for which the chances of successful rehabilitation or useful life was deemed to be so unlikely.

1. Early Results

The early results of chronic hemodialysis for diabetics seemed to confirm the worst fears of the skeptics. Initial survival statistics indicated a one year mortality of 60-80% in diabetics compared to 15-20% one year mortality for non-diabetics (36,37,38).

Figure 11 depicts the cumulative survival of 58 diabetic dialysis patients.



Cumulative survival, 1965 through 1973.

Figure 11

Dialysis failed to stem the progression of retinopathy. The effect on neuropathy was unclear. A high incidence of major vascular catastrophies (myocardial infarction, CVA) led some to conclude that dialysis resulted in accelerated atherogenesis. Needless to say, a control group of diabetics who developed terminal renal failure and did not start dialysis was not alive one year later for comparison with those who did. It is of course true that dialyzed diabetics have the metabolic defects of chronic renal failure as well as the cardiovascular effects of hypertension superimposed on the metabolic and vascular complications of diabetes itself. As a result, it is reasonable to conclude that these individuals may undergo progression of their cardiovascular disease at an extremely rapid rate.

However, it is important to realize that the kidney is just another victim of the ravages of diabetes, rather than the culprit. There is thus, no reason to suppose that dialysis can alter any of the metabolic abnormalities or complications of the basic disease.

2. Later Results

As experience with dialysis of diabetics has increased, survival rates improved significantly (39), as illustrated in Figure 12.

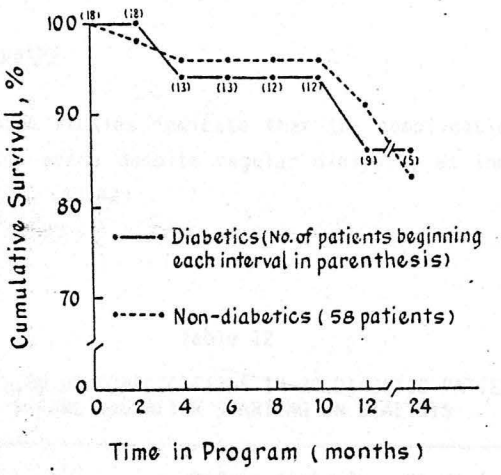


Figure 12

It is important to note that age has a significant effect or one year survival of dialysis patients, as shown in Table 11 (40).

Table 11

EFFECT OF AGE ON SURVIVAL ON DIALYSIS

	No. Patients	Mean Age (yrs)	No. Deaths	1st Yr Mortality (%)
< 45 yrs				
Diabetic	36	33.2	12	23.0
Nondiabetic	78	30.3	4	5.5
45-59 yrs				
Diabetic	21	53.9	7	22.2
Nondiabetic	95	52.5	12	6.3
> 60 yrs				
Diabetic	9	67.6	6	50.0
Nondiabetic	123	67.2	41	26.2

3. Retinopathy

Most studies indicate that the complication of retinopathy proceeds apace despite regular dialysis, as indicated in Tables 12 and 13 (41,42).

Table 12

COMPARISON OF COMPLICATIONS IN 20 DIABETIC PATIENTS BEFORE AND AFTER STARTING ON DIALYSIS

Complications	Before dialysis, no. of patients	On dialysis program, no. of patients
Angina	2	7
Other arterial disease	4	6
Neuropathy	18	Worse in 4
Retinopathy-mild	7	4
Retinopathy-moderate	5	3
Retinopathy-severe	7	12
Blindness	5	10
Infections		15
Uremic complications		6

Table 13

EFFECT OF DIALYSIS ON

CATARACTS AND VISION IN JUVENILE DIABETES MELLITUS (31 PATIENTS)

		Predialysis	Course postdialysis
6	(19.3%)	Bilateral blindness	One patient underwent bilateral enucleation for glaucoma
2	(6.4%)	Unilateral blindness	Unchanged
21	(67.9%)	Advanced diabetic retin opathy, useful vision	Three patients developed unilateral blindness secondary to vitreous hemorrhages
1	(3.2%)	Mild hypertensive retin opathy, excellent vision	Unchanged
1	(3.2%)	No retinopathy	Unchanged
7	(22.2%)	Cataracts	Unchanged

4. Peripheral Neuropathy

Symptoms of neuropathy also seem to progress. The fact that these individuals have a combination of diabetic and uremic neuropathy makes this finding difficult to interpret.

5. Cardiovascular

The effect of 3 times weekly chronic hemodialysis on cardiovascular disease is shown in Table 14 (42).

Table 14

EFFECT OF DIALYSIS ON CARDIOVASCULAR COMPLICATION IN JUVENILE DIABETES MELLITUS (31 PATIENTS)

	Predialysis	Postdialysis
Angina pectoris	6	4
Myocardial infarction	3	5
Congestive heart failure		
Severe	14	9
Minimal	6	0
None	11	22
Hypertension		
>120 diastolic	4	1
>100	10	3
100 or less	17	27
Peripheral vascular disease		
Gangrene/amputation	2	1
Vascular calcification	21	22
Decreased pulses without radiographic VC	2	2
Normal	6	6

There is no significant reduction of angina pectoris or myocardial infarction or peripheral vascular disease. On the other hand, dialysis, by reducing volume overload, markedly decreases the severity of hypertension and congestive heart failure (42).

Coronary artery and cerebrovascular disease remain a major cause of death , as shown in Tables 15 and 16 (38,42).

Table 15

CAUSE OF DEATH IN DIABETIC DIALYSIS PATIENTS

Cardiac	13	(12)[a]
Uremia	5	(1)
Accidental	3	(3)
CVA	2	(2)
Sepsis	2	(0)
Hyperkalemia	1	(1)
Pneumonia and ASHD	1	(1)
	27	(20)

[a]( ) = autopsy

Table 16

CAUSES OF DEATH IN DIABETICS ON REGULAR DIALYSIS

	Juvenile (8/31)	Adult (4/12)
Acute myocardial infarction (MI)	4	1
Pulmonary edema (no MI by autopsy)	1	-
Cardiac arrest (no MI by autopsy)	1	1
Infection (sepsis)	1	-
Suicide	1	-
Pulmonary embolism	-	1
Unknown	-	1

6. Infection

Yet another serious complication is a high incidence of infections frequently involving vascular access and requiring frequent hospitalization. Diabetic patients on dialysis average about 3.5 days per month hospitalization versus 1.8 days per month in nondiabetic patients.

Despite the seemingly endless variety, severity, and frequency of serious problems, a recent study of 289 diabetic dialysis patients shows that 23% are fully rehabilitated and an additional 25% are able to carry on normal daily activity (43). Figure 13 illustrates rehabilitation of diabetics versus nondiabetics on dialysis. The Karnofsky scale used is an index of relative activity quantifying an individual's ability to work and carry on normal activity. In addition, I might note that an informal survey of nephrologists with extensive experience in dialysis of diabetics reveals that an insignificant portion, perhaps 1 or 2%, of diabetics voluntarily withdraw from dialysis. This suggests that virtually all the patients, even though they are not fully rehabilitated, find life on dialysis acceptable.

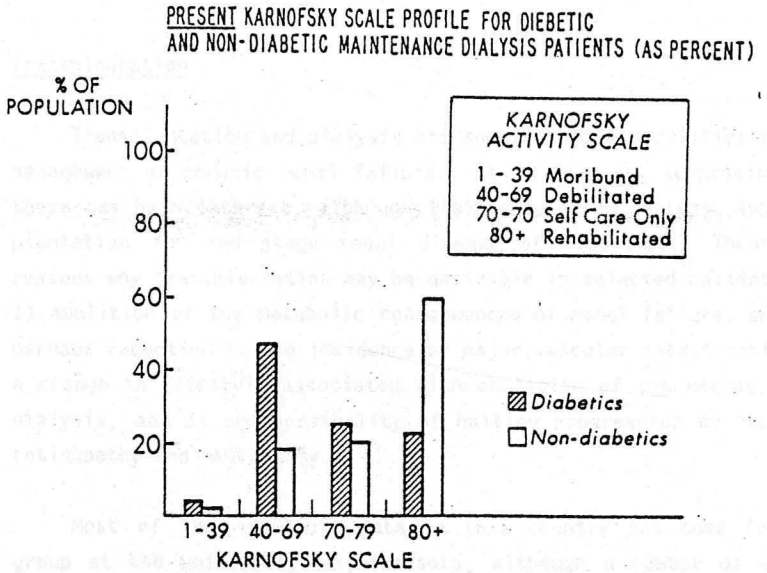


Figure 13

To summarize the results of chronic hemodialysis in diabetic

1. Overall, one, two and three year survival will be approximate 85, 80 and 65%, survival being significantly affected by ag

2. Significant morbidity, including progression of retinopathy a neuropathy, as well as frequent infections and hospitalizatio must be expected.

3. As indicated earlier, patients who do not die of microangiopat and renal disease will have progression of atheroscleros accounting for the bulk of mortality.

4. A significant proportion of dialyzed diabetics do become ful rehabilitated and lead productive lives.

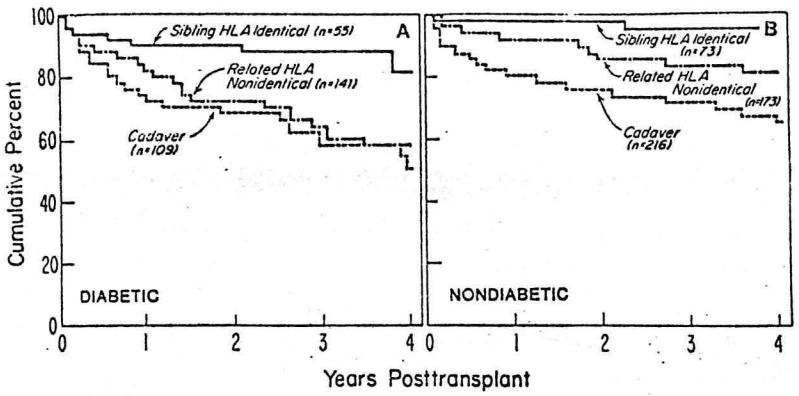
C. Transplantation

Transplantation and dialysis are complementary modalities for the management of chronic renal failure. It is thus not surprising that there has been interest, although limited to a few centers, in transplantation for end stage renal disease of diabetics. Theoretical reasons why transplantation may be desirable in selected patients are, 1) abolition of the metabolic consequences of renal failure, and thus perhaps reduction in the incidence of major vascular catastrophies, 2) a change in lifestyle associated with abolition of the necessity for dialysis, and 3) the possibility of halting progression or improving retinopathy and neuropathy.

Most of the available data in this country has come from the group at the University of Minnesota, although a number of smaller centers are also gradually developing more activity in this area. The vast majority of patients who have been transplanted have JODM. This is probably because most adult onset diabetics are over 55 when they develop ESRD. Most centers arbitrarily use an arbitrary age cut-off of 55 as a criterion for transplant. Thus, transplantation data essentially applies to juvenile onset diabetics.

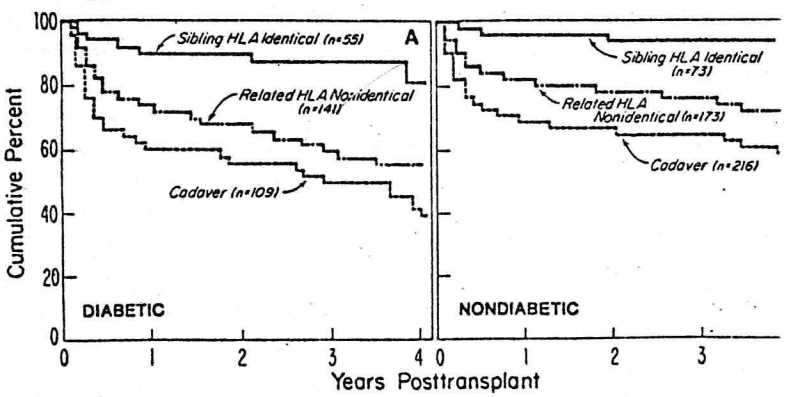
1. Patient and Renal Graft Survival

The general result of transplantation in diabetics in Minnesota has been surprisingly good when compared to results in non-diabetics (44). Figures 14 and 15 illustrate patient and graft survival respectively, according to donor source.



Patient surviv
305 diabetic, A, and
nondiabetic, B, pri
renal allograft recipi
according to donor so

Figure 14



Kidney functional survival in 305 diabetic, A, and 462 nondiabetic, B, primary renal allograft recipients, according to donor source.

Figure 15

Cumulative 2 year patient survivals for HLA identical siblings is 90% in diabetics and 97% in non-diabetics. That for related non-HLA identical patient survival is 73% in diabetics and 86% in non-diabetics, and that for cadavar recipients is 68% in diabetics and 75% in non-diabetics. The graft survivals for diabetics and nondiabetics are similarly comparable as shown in Table 17 (44).

Table 17

PATIENT AND GRAFT FUNCTIONAL SURVIVAL IN 305 DIABETIC AND 462 NONDIABETIC RENAL ALLOGRAFT RECIPIENTS AT TWO YEARS ACCORDING TO DONOR SOURCE

Donor Source	Cumulative Per Cent 2 Year Patient Survival		Cumulative Per Cent 2 Year Graft Survival	
	Di-abetic	Non-diabetic	Di-abetic	Non-diabetic
HLA-identical Sibling	90	97	90	94
Related HLA-donidentical	73	86	67	77
Cadaver	68	75	55	64
Total group	73	83	66	74

The results at other centers are not quite as good as those reported by Minnesota (45,46). Results from two other programs are shown in Table 18.

Table 18

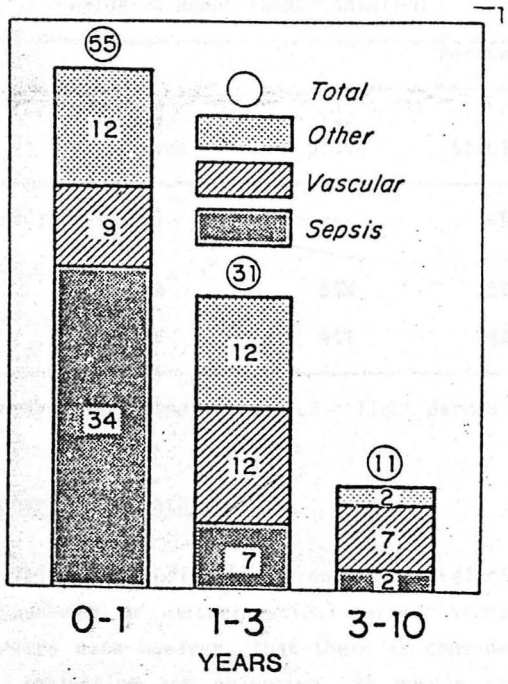
PATIENT AND GRAFT SURVIVAL IN RENAL TRANSPLANTATION OF DIABETICS

	Patient Survival			Graft Survival		
	1 yr	2 yr	3 yr	1 yr	2 yr	3 yr
Mayo (45)						
Living related donor	80	80	80	70	67	67
Cadavar	64	52	59	59	48	48
OSLO (46)						
Living related donor	90	85	65	75	75	60
Cadavar	60	45	35	40	35	30
Mean						
Living related donor	85	83	73	73	71	64
Cadavar	62	49	44	50	41	39

The discrepency between Minnesota and the other centers may b accounted for by the fact that the Minnesota program is essenti ally the largest transplant program in the United States and tha their experience in diabetic transplantation amounts to about t perhaps 50% of all such transplants performed to date or may b due to patient selection. It certainly appears in any event tha transplantation is a viable alternative to dialysis, particularl in individuals who may have a suitable related donor.

The causes of mortality of diabetic transplant recipients i shown in Figure 16. As might be expected, infections account fo

62% of the deaths in the first year, while cardiovascular deaths account for only 16% (44).



Distribution of diabetic recipient deaths by cause, according to the time interval after transplantation.

Figure 16

2. Retinopathy

The influence of transplantation on retinopathy has generally been felt to be favorable, as shown in Table 19 (44).

Table 19

VISUAL STABILITY ONE YEAR POSTTRANSPLANT IN EYES OF DIABETIC RECIPIENTS ACCORDING TO CORRECTED VISUAL ACUITY PRIOR TO RENAL TRANSPLANTATION

Vision Pretransplant	Number of eyes	Per Cent		
		Improve	Stable	Decrease
Good (20/20-20/50)	111	—	92%	8%
Impaired (20/70-20/200-CF)*	29	55%	15%	31%
Poor (HM-LP)*	70	44%	33%	23%

*CF = count fingers, HM = hand motion, LP = light perception.

3. Peripheral Neuropathy

Objective studies (nerve conduction velocity) show no change (improvement or deterioration) after transplantation. Most observers note however, that there is considerable improvement, both subjective and objective, in muscle strength (47). The proposed explanation is that arrest of neuropathy allows collateral re-innervation, whereby intramuscular branches of surviving motor units re-innervate previously denervated motor units resulting in their enlargement. This hypothesis remains to be confirmed.

4. Cardiovascular

A relatively frequent complication of diabetic transplantation is peripheral vascular disease necessitating amputation of a limb (Table 20) (44).

Table 20

PERIPHERAL VASCULAR DISEASE REQUIRING AMPUTATIONS
IN 305 DIABETIC TRANSPLANT RECIPIENTS

Extremity	Number	Incidence
Leg	44	
Foot	3	
Toe	22	
Hand	2	
Finger	29	
Total Patients	45*	14.8

*Twenty-two patients have had multiple amputations (including 11 patients with bilateral BK amputations).

As noted earlier, cardiac and cerebrovascular disease account for 60% of the mortality after the first year. The high rate of cardiac and peripheral vascular complications suggests that transplantation fails to halt the progression of vascular disease.

5. Infection

Other frequent complications following transplantation include, 1) difficulty in controlling blood sugar because of steroid therapy 2) hypertension due to steroid related sodium retention, and 3) a higher incidence of urologic complications than in nondiabetics (48).

As mentioned above, infections cause 60% of deaths in the first post-transplant year. The high risk of infection during

the first year is related to the relatively higher doses of immunosuppression required during this time primarily because rejection crises occur more often and are most severe in the first 3-6 months following transplantation. In the subsequent second and third year, infection accounts for only 20% of deaths, while vascular disease increases to approximately 50-60%.

All transplant recipients are particularly prone to infections; many of them are from uncommon organisms and this is no less true in the diabetic. The etiology of infections in transplant patients is shown in Table 21 (48).

Table 21

ETIOLOGY OF INFECTIONS IN TRANSPLANT PATIENTS

Bacterial	62%
Viral	26%
Fungal	21%
Pneumocystis	5%

Of the unusual organisms, cytomegalovirus, herpes, listeria, cryptococcus, and aspergillus are seen 10-20 times more often than in non-immunosuppressed individuals.

6. Recurrence of Disease

Diabetic glomerulosclerosis is known to recur in normal kidneys transplanted into diabetics. Abnormal thickening of the capillary basement membrane has been reported in the majority of cases examined over one year after transplant (47). In a series of 12 biopsies in diabetic patients, 10 (83%) had arteriolosclerosis at a mean time of 33 months post-transplant. As shown in Table 22, three of 28 (11%) nondiabetics developed this lesion (50).

Table 22

INCIDENCE OF RECURRENT 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 38	0 of 23
P value*	<0.001	<0.0005

*By chi-square test.

In addition, one diabetic developed nodular glomerulosclerosis. These findings do not support the concept that microangiopathy results from a genetic defect independent from that causing carbohydrate intolerance but do suggest that the lesions seen in the kidney result directly the metabolic defect. To date, there have been no reports of recurrent diabetic renal disease adversely affecting renal function, although duration of follow-up and the number of studies are at present inadequate to make any conclusion possible.

7. Patient Selection

In some quarters, this is regarded as a philosophical question. Except for the imposition of age criteria, the Joslin Clinic makes transplantation available to virtually all diabetics (51). Other observers feel that presence and degree of complications, particularly coronary artery disease, are important in selecting patients. A recent study by the Joslin group provides

some insight (52). Twenty-one diabetic patients were studied by coronary angiography and grouped according to absence (Group A) or presence (Group B) of significant coronary artery disease. Table 23 shows the results at 2 year followup.

Table 23

DIALYSIS AND TRANSPLANTATION IN DIABETICS WITH (B) OR WITHOUT (A) CORONARY DISEASE

Group	No. Patients	No. Transplants	Graft Success	Deaths Transplantation	Deaths Dialysis
A	12	12	11	4	0
B	9	4	0	0	5

The overall death rate for those without coronary disease was 33%, that for those with coronary disease 57%. This difference is not statistically significantly because of the small numbers.

Until recently the Minnesota group inadvertantly used stringent patient selection. All potential recipients had bilateral nephrectomy and splenectomy before transplantation. The mortality of this procedure was about 15% and only the survivors of this surgical "stress" test were transplanted. These procedures are no longer routinely performed by this group.

Our general consensus is that complications of diabetes such as retinopathy, neuropathy and peripheral vascular disease are not contraindications to transplantation. The significance of symptomatic coronary artery disease is still uncertain. Severe angina requires pretransplant evaluation and bypass surgery if localized disease is present. Asymptomatic or mildly symptomatic coronary disease is not a contraindication nor is a prior history of CVA without significant sequelae.

To summarize the results of transplantation in diabetics:

1. It offers a reasonably good chance of restoring renal function depending on donor source.

2. The risk of mortality is not substantially greater than in non-diabetics.

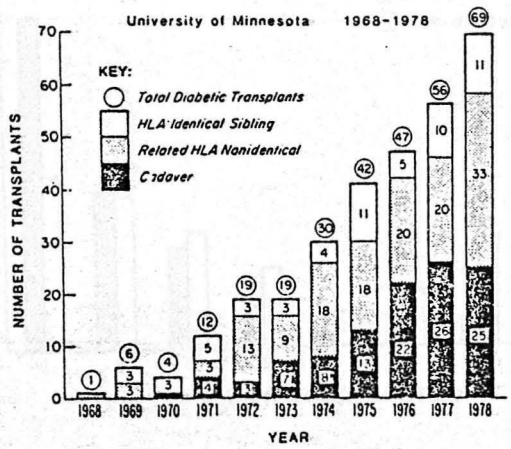
3. Retinopathy and neuropathy may improve or stabilize.

4. It does not alter the pathophysiology of the disease.

5. Life style is altered in a positive manner for those with functioning transplants.

VIII. THE FUTURE

Larger numbers of diabetics are gradually entering end stage renal disease programs as illustrated in Figure 17, which represents the number of diabetics transplanted annually at the University of Minnesota.



Number of primary renal transplants to diabetic recipients by year, University of Minnesota, 1968–1978.

Figure 17

An estimate of the magnitude of the number we can expect can be ascertained from the following. There are roughly 4.5 million diabetics in the United States. Assuming, conservatively, that 12% (53) are JODM, there are roughly 4 million adult onset and 500,000 juvenile diabetics in this country. If 6% of the adult (240,000) and 40% of the juvenile (200,000) onset diabetics develop renal failure over 35 years, there will be an annual incidence of 12,500 cases of end stage renal disease in diabetics.

It is unlikely that more than a fraction of these individuals are presently being dialyzed or transplanted. Figure 18, from the Duke Cooperative Study (43) shows that almost 70% of diabetics have been on dialysis for 2 years or less compared to 45% for nondiabetics. This suggests that they have a much greater death rate than is generally reported or that physicians have been agreeing to initiate dialysis in this group of patients only recently.

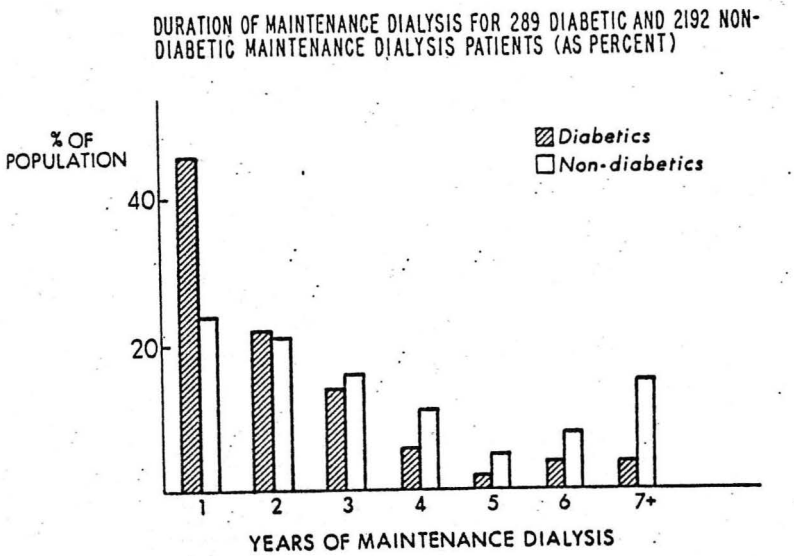


Figure 18

The latter is borne out by the latest figures available from the Social Security Administration of the United States Department of Health Education and Welfare, which show an estimated annual increase in the end stage renal disease program of only 3-4000 persons per year. It is inconceivable that this figure includes the diabetic population, which would add 6000 annually if only half the patients who developed renal failure were considered "candidates" for dialysis or transplantation. In addition, this neglects the fact that the annual increase in persons entering ESRD programing in the early seventies was 5-6000 per year, when only negligible numbers of diabetics were entered, and the annual increase represented only nondiabetic ESRD.

Health care planners and physicians alike must become aware that end stage renal disease in diabetics can be managed successfully. With the passage of time and proper planning we can expect dialysis and transplantation to offer useful productive lives to diabetics stricken with the once uniformly fatal complication of diabetic nephropathy.

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