Review Articles

The Treatment of Diabetic Kidney Disease

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Key words: Diabetic glomerulosclerosis, dialysis, kidney transplantation, conservative treatment, diabetes mellitus, diabetic complications.

The purpose of this review is to consider treatment available at present for patients suffering from kidney failure due to diabetes. Most attention has been paid so far to the relief of patients in the final stages of the disorder. For a number of reasons, the principal one being the long-drawn-out nature of the disease, there have been almost no controlled studies of treatment at any stage. As a result, it is hard to avoid emphasis on personal experience and subjective evaluation. Also, there is a clear obligation to look ahead to simpler and cheaper methods of treatment, or indeed of prevention, than those in present use.

Renal failure in the diabetic is a serious problem: if one uses the incidence rate of 1,000 new cases of childhood diabetes per year from the United Kingdom [1], and the expectation that half of them will develop serious nephropathy [2, 3], then at least one death per 100,000 population is to be expected per year from this cause in countries similar to the U.S.A. and Great Britain. In addition, there is evidence to expect nephropathy as a contributing factor in the deaths of at least 25% of maturity-onset diabetic patients.

The estimate of 3,200 deaths a year from diabetic nephropathy offered by Knowles [2] for the U.S.A. is quite consistent with the above and may indeed be too low. It will be useful to keep it in mind when present efforts to keep these patients alive are considered.

1. The Clinical Picture of Diabetic Nephropathy and Its Underlying Causes

The clinical course of advanced kidney disease in diabetes has become almost monotonously familiar in the last 30 years, once it was recognized as an entity (compare Fishberg, 1939 [4] and Fishberg, 1954 [5]).

The stereotype is documented in retrospective figures from the Joslin Clinic [6]: proteinuria recognized after about 17 years of juvenile-onset diabetes; mild azotaemia and hypertension noted two years later; death three years after that, in uraemia or fluid overload. None of these features is unique to diabetic kidney disease, but the sequence is so characteristic in an individual with long-standing diabetes that any other diagnosis is unlikely.

The lesions that one expects to find with the light microscope in the kidneys of such patients have also become familiar: hyalinisation of both afferent and efferent glomerular arterioles [7, 8]; thickening of the mesangial stalks of the glomeruli and of the basement membrane of peripheral glomerular capillaries, and glomerular nodules [9, 10]. The basement membrane of Bowman's capsule and of tubules are also thickened [10]. These and other changes form a picture which is generally accepted as characteristic of the diabetic kidney, although some features – including the nodule – may be missing in samples from a given patient, and sometimes all are obliterated by end-stage changes.

Although both the typical clinical picture and the typical (light) microscopic picture seem clear, the precise relationship of the elements of one to those of the other has not been established. Proteinuria seems to be due to leaky glomeruli rather than to impaired tubular reabsorption of protein [11]. Azotaemia and hypertension presumably result from partial or com-

plete obliteration or ischaemia of individual nephrons – but this says very little about detailed mechanisms, especially those peculiar to diabetes.

Equally fundamental is the question of the relationship between the diabetic state and the development of kidney damage in the first place. Impressive evidence supports the interpretation that the diabetic state in some direct way injures the kidney; much of it comes from animal experiments [12]. On the other hand, a large proportion of youth-onset diabetics, about 50%, may live with diabetes for 30 or more years without developing nephropathy [2, 3]. Hence, it seems necessary to assume that susceptibility to diabetic kidney injury is not uniform, and that as many as half the population may be resistant.

Significant progress is also being made in identifying much earlier changes in kidney function in diabetes. These may accelerate glomerulosclerosis in concert with, or as part of, the “diabetic state”. There is evidence that altered glomerular dynamics [13, 14, 15], systemic hypertension [16] and decreased renal mass *per se* [17] may speed up damage to the kidney. Bacterial infection of kidney parenchyma, and retention of urine in the bladder due to neuropathy, have been accepted in clinical medicine as important contributors to diabetic kidney damage, although rigorous proof has been scanty.

2. Prevention or Reversal of Diabetic Kidney Disease

Although the current attention of physicians is mainly directed to providing a substitute for the function of the hopelessly damaged diabetic kidney, there is obvious need to develop better methods for preventing or reversing the underlying renal lesion(s).

Control of the diabetic state is the logical place to begin but evidence of benefit to the human kidney from diabetic control has been very scanty. In a clinical trial of treatments for nonketotic diabetes, the University Group Diabetes Program, it was reported that no benefit with respect to the incidence of renal disease could be attributed to treatment with either of two oral agents, tolbutamide and phenoformin [18, 19]. The most recent paper from this study, reporting twelve years of treatment with insulin, again found no benefit with respect to survival or most causes of morbidity in comparison to the course of patients treated with placebo and dietary advice [20]. However, there was a suggestion of benefit with regard to renal disease: more subjects developed an elevated serum creatinine level in the placebo group than in the two insulin-treated groups (see Table 4, page 40). It remains for further analysis to confirm

and extend this finding and to look for a possible relationship between glucose control over time and risk of nephropathy in insulin-independent diabetes.

A similar prospective, randomized study of the effects of treatment on renal disease in “juvenile” insulin-dependent (Type I) diabetes would be even more difficult to perform and to justify than the U.G.D.P. study and indeed has not been undertaken. We must be satisfied with the remarkable single case reported by Gliedman and others [21], one of the very few examples of successful restoration of insulin secretion for a prolonged period after pancreas transplantation. In this patient, at four years the longest reported effective pancreas transplant, characteristic arteriolar hyalinisation was lacking in the kidney simultaneously grafted with the pancreas. In contrast, 85% of kidneys biopsied two to four years after transplantation of kidney alone [22] have shown this arteriolar change.

Logic, and the meagre evidence just noted, seem to be on the side of careful metabolic control whenever possible. Moreover, an important series of papers from Denmark has shown that decrease of hyperglycaemia toward normal in early, “uncomplicated” insulin-requiring diabetes may reverse the abnormalities which seem to be related to altered kidney dynamics: increased kidney size, slightly increased albumin excretion, and increased glomerular filtration rate and filtration fraction [23, 24, 25]. Of course, the relationship of these reversible disturbances to the late, serious stages of glomerulosclerosis is as yet unknown.

Self-testing of blood glucose at home and open-loop insulin delivery can yield short-term improvements in diabetic control which are remarkable [26, 27]. The question now becomes: can such intensity of treatment be maintained over the many years of life now granted to the diabetic patient?

Pituitary ablation was reported by Ireland and others [28] to be followed by “significant reduction” in glomerular capillary basement membrane thickness, but no reversal of arteriolar lesions. Careful measurements were presented of biopsies before and one to two years after pituitary ablation, in five subjects with moderately advanced kidney disease. Setting aside one case considered to have incomplete pituitary ablation, it is noteworthy that the remaining four cases failed to show an increase in thickness on the second biopsy, although only one case showed unequivocally thinner measurements. What the study lacks are control observations on similar patients, such as paired biopsies over the same time interval without pituitary intervention. Without these, the results can only be suggestive. Regrettably, many

patients have shown progression of glomerulosclerosis to end-stage despite pituitary ablation [29]. The benefit, if it exists, must be partial.

Adrenocortical steroids or ACTH were tried in cases of diabetic kidney disease in the period 1950–1960, following observation of the striking response to these drugs of many children with nephrotic syndrome. Among many reports of their use in a variety of kidney diseases there were scattered experiences with diabetic glomerulosclerosis. The report of Danowski and others [30] was typical: three advanced cases were treated with ACTH or cortisone for one to three months. Judgement of benefit was based entirely on clinical response, and this was poor.

It is difficult to find any mention of this treatment after 1960, and there seem to have been no systematic or prospective trials. It was perhaps a matter of the wrong timing for a dramatic new treatment, appearing when recognition of diabetic glomerulosclerosis as an entity was just beginning and only advanced cases were recognized. Physicians were deterred by the powerful hyperglycaemic action of the new drugs, and the first anecdotal trials were discouraging. More recent knowledge of the collagen-like nature of basement membrane supplies at least a superficial rationale for a trial of steroids much earlier in the course of the disease, but current clinical and experimental interest lies elsewhere.

Urinary tract infection must be mentioned as a potentially treatable cause of renal damage in diabetes, although its importance in this regard, and more particularly the long-term value of treatment, do not seem to have been clearly demonstrated. Kass [31] found evidence lacking for benefit in respect to *any* preventive programmes in urinary infection. Unremitting search for urinary bacterial infection, with or without symptoms; vigorous and prolonged antibiotic treatment for infection when it is found; and vigilance in finding and relieving the urinary retention which is often present – all are rational, sensible measures in the long-term care of the diabetic patient. A prospective and extended clinical trial would be difficult but valuable indeed if prevention of kidney damage could be demonstrated.

Benefit to the kidney through treatment of hypertension. Mogensen [24] has reported improvement in kidney function i.e. increased glomerular filtration rate (GFR), by treatment of hypertension in patients with diabetic kidney disease. The intention is to alter the internal dynamics of the glomerulus and to prevent acceleration of the glomerular damage. Improvement in GFR of course does not necessarily

mean reversal of such damage. Further reports on this approach, and especially its effect on kidney morphology, should be of great value.

Anticoagulant treatment has not been systematically or widely tried since the early report of Engelberg [32], and it appears to be controversial in other kinds of kidney disease [33]. Nonetheless, two recent preliminary reports raise the possibility that drugs altering platelet function might have value in diabetic nephropathy: the sulphonylurea gliclazide [34], and dipyridamole combined with clofibrate [35].

Kazandjian, Riveline, and Lagrue [34] reported a significant decrease in the mean protein loss of 16 patients with mild proteinuria, from 1.01 to 0.58 g/24 h after an average of 18 months on gliclazide. In six patients with greater losses (> 3 g/day), the average proteinuria did not change (from 4.8 to 6.3 g/24 h). No control patients were reported, and since only mean values were given, it is not possible to judge if the decreased proteinuria was accounted for mostly by a few patients with worsening GFR which by itself could lessen protein excretion. Mean serum creatinine did not rise, however, and there remains a suggestion of benefit attributable to the drug. The report of Astrug [35] was not available for examination. Given the total lack of any direct treatment for diabetic glomerulosclerosis, these suggestions are worth pursuing.

3. Medical Treatment for Relief of Symptoms

Preventive treatment for glomerulosclerosis remains rudimentary. Fortunately, a number of relatively simple and inexpensive measures are available for the relief of the major symptoms of kidney disease, once they appear. They have been overshadowed, in fact, by the more dramatic but more costly advantages of dialysis or transplantation.

The principles of medical management of uraemia have recently been well reviewed by Walser [36]. Their application to diabetic patients does not differ in essential from that to non-diabetics. There are some details, however which are important for the diabetic patient.

Modification of dietary protein to 40 g/day or less (for an adult) has long been a familiar measure for the relief of uraemic symptoms. The demonstration by Giovanetti [37] and Giordano [38] of the benefit of limiting non-essential amino acids in the diet proved to be a major advance on traditional treatment. To be fully effective, however, their approach requires the provision of a generous number of calories a day of palatable food, almost all of which is carbohydrate or fat.

Not surprisingly, it is very difficult for patients with longstanding diabetes to adjust themselves to the large amount of carbohydrates which is unavoidable in such diets. Many patients with childhood-onset diabetes have struggled for many years with the discipline of carbohydrate restriction. It is deeply disturbing to them if they are abruptly told that it is "all right" to eat concentrated sweets and desserts.

Yet, a high carbohydrate intake, even if concentrated monosaccharides and disaccharides are included, does not necessarily mean loss of diabetic control with gross hyperglycaemia. Providing several doses of insulin each day may achieve a glycaemic control which is at least as good as that on a conventional diet. The key is the abatement of nausea and the return of a good appetite; if the patient can reliably eat four or more high carbohydrate feedings spread evenly throughout the day, the adjustment of insulin dosage may be relatively simple.

Insulin dosage must be continued with care, however, regardless of carbohydrate intake: most uraemic diabetics are ketosis-prone, insulinopenic patients who readily shift toward protein catabolism and gluconeogenesis in the absence of insulin. This would seem especially undesirable in uraemic patients.

Current attention seems to be directed to patients already committed to dialysis, which sharply increases losses of amino acids and protein. The practice now is to encourage a generous intake of protein of "high biological value", i. e. rich in essential amino acids, such as a potato-egg diet with amino acid supplements, and plenty of calories by the use of energy supplements containing fat and honey or sugar. Reporting experience with such a regimen, Kluthe et al. [39] suggest 1.2 g protein and 35 Kcal daily/kg body weight for dialysis patients.

The special needs of the diabetic patient, and the best diet for uraemic patients before dialysis is necessary, seem to be neglected subjects at present. Two papers offer some promise, however. Noreé and Bergström [40] offer convincing evidence of the benefit of essential amino acid supplementation (including histidine) in non-diabetic uraemia, delaying dialysis by many months. Walser [41] reports keeping two diabetic subjects (out of a total of 7 severe uraemics) "active and well" for three to six months with use of ketoacid analogues of five amino acids together with four amino acids. The ketoacids appear to have a special effect in decreasing nitrogen turnover.

These are impressive and important results. Such regimens, of course, take more than the usual patience on the part of everyone concerned, including the dietician and the physician. When the regimen is

fully accepted by the patient, the results can be rewarding and seem to suppress uraemic symptoms for many months or even years.

Fluid overload. This term conveniently indicates that the cause of fluid retention in patients with advanced renal disease is often not clear. In diabetic patients especially, the likelihood of co-existing heart disease is increased. Fortunately, salt and water retention responds about as well to medical treatment whether it is of cardiac or renal origin.

The treatment of choice is the use of diuretic drugs. We have found it difficult to assess the benefits of digitalis preparations and use them rarely. In cases of moderate severity, and especially if the patient is already committed to insulin treatment, the thiazide drugs (chlorothiazide and hydrochlorothiazide) and chlorthalidone are helpful and seem to have no effect on insulin requirement. In the patient who is treated by diet or an oral agent, on the other hand, the thiazides may cause exacerbation of the hyperglycaemia. In such patients the choice must be made between starting insulin treatment or choosing another diuretic.

With massive or refractory fluid retention, especially if pulmonary congestion has developed, a more potent diuretic is necessary. Our current choice is furosemide (frusemide), and we use it generously, sometimes in doses as high as 1,000 mg/day. The only undesirable side effects seem to come simply from too vigorous a renal response, with symptoms of plasma volume depletion.

A word of caution should be recorded about possible deafness due to furosemide. Although experience suggests that deafness from furosemide is less likely than from ethacrynic acid [42], some animal studies [43] have shown that furosemide also damages the ear. The uraemic diabetic patient may already be blind or nearly so. Deafness and blindness at the same time is a supreme tragedy which a patient already suffering from a complex illness may be unable to bear. We have not personally observed any clearcut example of deafness due to furosemide in a uraemic patient, but it might have been contributory in some patients.

Hypertension demands vigorous treatment for its own sake, and fortunately, there are many kinds of treatment available. Fortunately, also, the course of hypertension with diabetic nephropathy rarely follows an accelerated or malignant course. Presumably, however, it is an aggravating factor for coronary heart disease and stroke.

We have found the drugs conventionally used in other forms of hypertension equally effective for the

diabetic patient: diuretics (with the reservations mentioned above), alpha-methyl DOPA, hydralazine, and propranolol. Occasionally clonidine and minipress may be needed as alternative or additional treatment, but this is unusual.

The diabetic patient is unusual in showing marked susceptibility to postural hypertension; one often deals with a patient whose blood pressure is too high lying down and too low standing up. We regularly advise patients to raise the heads of their beds permanently, so that they are never horizontal, day or night. This seems to relieve some of the symptoms of postural dizziness. Other simple measures (elastic stockings, regular walks) may also relieve this troublesome symptom. The physician's main effort, however, is in careful regulation of antihypertensive drugs and in encouraging compliance.

4. Substitution or Replacement for Loss of Kidney Function: Dialysis

The course of diabetic kidney disease may stretch out over many years, but once kidney function (creatinine clearance) has fallen below 20 percent of normal, in the non-stressed patient, the likelihood of symptoms of uraemia or of fluid overload developing is very great, and the benefits of management by drugs and diet are less striking. Experience in the last decade makes clear that the two principal means of sustaining life – dialysis and kidney transplantation – both have much to offer to the patient with diabetes.

History of dialysis. Chronic *haemodialysis* for diabetic patients initially gave very discouraging results [44]. The 50% survival time ($T_{1/2}$) was only about one year. The major cause of death was coronary heart disease and myocardial infarction; there was also a discouraging frequency of progression to blindness, mostly due to vitreous haemorrhage associated with proliferative retinopathy [45].

There has been much comment about the special problems of dialysis in the diabetic patient. Some of this may be due to autonomic neuropathy, making the patient especially vulnerable to drastic shifts in blood pressure regulation when plasma volume changes abruptly during haemodialysis. Presumably, such shifts in blood pressure may contribute to death from myocardial infarction.

Certainly the diabetic patient is in an especially difficult situation when his kidney disease has reached a stage of chronic low urine output, making fluid overload an ever-present risk. Thirst related to a high blood glucose concentration is often severe. It

Table 1. Recent survival figures for diabetic patients on chronic hemodialysis (Selected reports)

<i>Dialysis centre</i>	Number of patients	Mean age, in years (Range)	Survival
Hennepin County Medical Center, Minneapolis [48]	60	40 (23–59)	73% – 1st year
Veterans Administration Hospital, Minneapolis [49]	18	48 (40–58)	86% – 1st year
Joslin & Lahey Clinics – New England Deaconess Hospital, Boston [50]	27	46	82% – 1st year 74% – 2nd year
Hôpital de La Pitié, Paris [51]	31		72% – 1st year

is difficult for such patients to “cooperate” with a regimen including drastic restriction of drinking.

The reported rapid progression of retinopathy on chronic haemodialysis is difficult to evaluate. It has been attributed to the necessary use of anticoagulation during dialysis – but the evidence that systemic use of anticoagulants has anything to do with bleeding in the eye is not strong. In fact, at one time heparin was advocated as a possible treatment for proliferative retinopathy [46]. Arterial hypertension, abrupt shifts in plasma volume, and some persisting chemical aspect of uraemia – all might be factors favouring vitreous bleeding.

Fortunately, recent experience with survival in chronically dialyzed diabetic patients is considerably better.

Although some groups in the United States continue to report discouraging results [47], others have reported sharp improvements in survival since 1972 (Table 1). Two centres in Minneapolis with contrasting patient populations have both reported first-year survivals for diabetics of over 70%: the regional dialysis centre, based at Hennepin County Medical Center [48] and the Minneapolis Veterans Hospital [49]; so also have the Joslin Clinic in Boston [50], and the Nephrology Service at the Hôpital de La Pitié in Paris [51]. Some of this experience is included in the impressive results reported in the 13th Report of the European Dialysis and Transplant Association [52].

An instructive point emerges when the large number of diabetic cases now reported in world experience – 1,421 were known to us as of late 1978 – are analyzed. The cumulative survival curve (Fig. 1) shows that a constant proportion of about

Fig. 1. World survival experience for patients with diabetic kidney disease, reported up to January 1979. Patients treated by chronic haemodialysis are indicated by the heavy line and by kidney transplantation by the thin lines. Data compiled by Kjellstrand. Δ = Cadaver, $\circ$ = Related, $\circ$ — $\circ$ and Δ — Δ = Survival, $\circ$ ---- $\circ$ and Δ ---- Δ = Function, $\bullet$ — $\bullet$ = Dialysis

one-fifth of the survivors is lost each year, for at least the first four years. An overall 50% survival time ($T_{1/2}$) of three years is now found.

In the experience at Hennepin County Hospital [48], the early cause of death on dialysis (less than 18 months) remains cardiovascular disease. Later, the problem of dialysis dementia becomes important as a cause of death.

The reasons for the improvement are as yet unclear. Greater skill and experience in the conduct of dialysis in patients with unstable vascular systems may be important. However, greater experience in the management of diabetes in such patients may also be a factor: frequent blood glucose selfmonitoring at home with improved methods has provided great symptomatic relief from thirst in patients on dialysis.

The survival of diabetic patients seems to be improving and may be approaching that for non-diabetics. There may also be a better outlook for vision now than in earlier experience [53]. This apparent improvement could result from increased use of new treatments for retinopathy, such as photocoagulation, although precise data are not yet available.

There is a return of interest in chronic *peritoneal* dialysis as an alternative to haemodialysis for renal failure of all causes, resulting in part from improved devices and techniques [54, 55]. Diabetic patients in particular might benefit, since blood vessel access for haemodialysis is often difficult for them. The first report for diabetics [56] included 15 patients from

four centres. The results in these high-risk patients were mixed: symptoms were relieved, but 10 of the 15 died in 6 to 22 months (five from a perforated viscus, peritonitis, or peritoneal haemorrhage).

Results do appear to be improving, however with greater experience. A later report from one of the four centres indicates survival for 7 out of 12 diabetics on peritoneal dialysis for more than a year, with no greater frequency of peritonitis or other peritoneal complications than in non-diabetics [57]. Currently, the 1-year survival for diabetic patients on chronic intermittent peritoneal dialysis at Toronto Western Hospital is 44% (31 patients) [58]. Further, a non-randomized comparison at the Mayo Clinic between 14 diabetic patients on peritoneal dialysis against 43 on haemodialysis showed the same survival for both groups of about 50% at one year [59]. Both groups report that progression of retinopathy was less, and general well-being was better, for the peritoneal group than for diabetics on chronic haemodialysis.

Although the numbers of patients are as yet small for firm judgment on retinopathy, such results are worthy of notice. Chronic peritoneal dialysis may be especially appropriate for any for whom haemodialysis is impractical or unsafe.

5. Kidney Transplantation

History of kidney transplantation for diabetics. The first reports of successful kidney transplantation for renal disease of any kind came from Paris [60] and Boston [61]. Development of effective immunosuppressive treatment (with corticosteroid and azathioprine or similar drugs) made possible transplants between persons not closely related. A register of human kidney transplantation world experience has been published annually from 1963 to 1977 [62]. Transplantation by disease category has been reported since 1971, and diabetes is first mentioned in 1972. In that year, the 9th Registry [63] reported that 19 out of 5,432 transplants in cumulative world experience were performed for diabetic kidney disease. In the 12th Registry (1975) [64] there were 198 diabetics out of a total of 15,921.

Why was this experience so small, and so slow in coming? Diabetic patients were considered too risky, (a) because of the possibility of recurrence of diabetic glomerulosclerosis in the transplanted kidney, (b) because of possibly increased risks conferred by immunosuppression in diabetic patients and (c) because of concurrent or future vascular disease in other organs than the kidney. It was assumed that transplanting kidneys into diabetic patients would waste effort, money, and kidneys.

Fig. 2a-d. Survival of 301 diabetic patients receiving kidney transplants at the University of Minnesota Hospitals, 1969–1979, compared with non-diabetic patients of the same age range transplanted on the same service during the same years. Panel **a** shows cumulative survival for all patients. The other panels show subgroups according to donors of the kidneys; **b** living HLA-identical siblings; **c** living non HLA-identical relatives; **d** cadavers. In all the comparisons the survival of the diabetic recipients is somewhat poorer, although for the HLA-identical living donors the difference is small and the results are the best of any of the groups. Adapted from Najarian and others [69]

In our own unit, the barriers against transplantation for diabetics were broken down by the proposal to transplant the pancreas as an endocrine organ. In 1966, it was ethically acceptable to offer, as an experiment, simultaneous pancreas and kidney transplants to patients dying of diabetic glomerulosclerosis, even though there was then strong prejudice against accepting them for chronic haemodialysis or for kidney transplantation alone [65].

There is irony in the course of events since then: a simple, safe and effective method of endocrine pancreas transplantation seems still to be beyond reach. In contrast, transplantation of one kidney alone, as primary treatment for diabetic glomerulosclerosis, has almost reached the state of standard treatment, assuming that kidney transplantation is an acceptable procedure in the first place.

A systematic trial of kidney transplantation alone for the diabetic patients began at the University of Minnesota in 1969, and in two other centres in the United States (Mayo Clinic and Joslin Clinic) at about the same time. It was clear in following the first five patients at Minnesota for the first year that the results were much better with respect to patient survival than with the double pancreas-plus-kidney procedure, and the latter was stopped.

In 1974, our five year experience with 63 diabetic

patients, matched with 63 non-diabetic kidney transplant recipients was reported [66]. This tentatively favourable report was confirmed by the Mayo group [67]. In 1977, we reported a 6½ year experience with 132 patients [68], and recently our ten year experience with 305 patients [69]. Currently about two patients out of five presenting themselves to us for kidney transplantation have diabetic renal disease. It may be useful to compare our current results and practices with those described in 1974.

Survival. Two points stood out from the 1974 experience, and they are confirmed by our current experience (Fig. 2).

The first is that while the overall survival of diabetic recipients is not quite as good as that of non-diabetic patients, the two are not too disparate, and both are good enough to be satisfying. The 50% survival time ($T_{1/2}$) for all the diabetic cases is greater than five years (Fig. 2a). This remains better than the survival on chronic dialysis, even at the recent improved $T_{1/2}$ of about three years.

Second, for the diabetic cases, as for the non-diabetics, the source of the kidney is the major factor in survival. Once the kidney is transplanted the chances of patient survival are considerably better if the kidney has come from a living, closely related-

donor than if it came from an unrelated cadaver donor, even if that donor is a so called "beating heart" accident victim sustained by artificial devices. The reasons for the difference, which appear to be sustained and real, are not obvious. The increased mortality in the cadaver cases were attributed by us in 1974 to late infections and cardiovascular events, mostly myocardial infarctions, occurring six months or more after transplantation, rather than to increased frequency of rejection episodes as might be expected. However, as a matter of policy, unrelated-donor recipients on our service are kept on consistently higher doses of corticosteroid (Prednisone 0.3–0.4 mg/kg) than related-donor recipients (0.15–0.2 mg/kg).

Added to the post-transplant mortality is the equally important mortality while the patient is waiting for a cadaver donor. This was especially true before 1974, when the practice was to remove both kidneys and the spleen before transplantation. During this medically and psychologically difficult period, deaths from fluid overload and from coronary disease were frequent. Since 1974 patients have been accepted for transplant with less advanced uraemia and fewer symptoms, but the waiting period and its difficulties are still much less for the patient with an electively-scheduled transplantation from a living donor.

Our cumulative experience is now great enough to allow a look at the effect of donor-to-recipient matching and tissue typing. HLA matching at the A and B loci and cytotoxic cross-matching have been carried out since 1969. The results shown in Figure 2 (b, c, d) suggest strongly that for diabetic patients as for non-diabetics, HLA compatibility makes a difference in the likelihood of survival for the diabetic patient. This is especially true for recipients over 40 years of age.

The large experiences reported by other centres are consistent with the University of Minnesota results. The Mayo Clinic reports excellent survival for 61 diabetic patients in its most recent publication [70]: 80% survival through four years for all living-donor kidney recipients, including the outstandingly good four-year survival of nearly 90% for 24 sibling-to-sibling recipients. Cadaver recipients are less favoured, but there is a sharp difference in survival for those getting kidneys from donors given massive immunosuppression just before donation (about 80% at four years) and those getting kidneys from untreated donors (about 20% at four years). If such a striking effect of donor pretreatment persists in future experience, it will mean a major advantage for diabetic recipients.

At Joslin Clinic, experience with 22 diabetic recipients [50] shows very similar trends: two-year sur-

vival of 77% with living donors and less than half that (36%) with cadaver donors.

The first large European report appeared in late 1978 [71]. It gives survival data on 146 diabetic patients transplanted in eight Scandinavian hospitals. It agrees with the American experience in several noteworthy respects: while only one-sixth of the patients received grafts from living donors, those 25 subjects had an excellent survival of about 85% at two years. The 121 subjects receiving cadaver kidneys showed, as in the U.S., a much less satisfactory survival of about 45% at two years. The major difference between the Scandinavian and Minneapolis experiences lies in the effect of certain risk factors on survival (see below).

We have summed up the world experience with diabetic patients up to the end of 1978, amounting to 629 patients, including 240 of our own (Fig. 1). In agreement with the individual reports, the cumulated three-year survival after related-donor grafting is a satisfying 75%. For cadaver kidneys, it is only about 50%, about the same as for dialysis. An important point of difference between dialysis and transplant survival emerges: while the death rate for the former is steady, for transplant recipients the first tumultuous 6 to 12 months carry the greatest risk. The $T_{1/2}$ for that early period is about two years for related graft recipients and one year for cadaver graft recipients. The slopes of the survival curves then change, so that for related recipients $T_{1/2}$ becomes about 12 years and for cadaver recipients about four and one-half years. So far, no second inflection point in this survival curve is apparent.

The major *cause of death* for transplanted diabetic patients, as for dialyzed diabetics, is cardiovascular disease, mainly myocardial infarction [69, 70, 71]. It is more common than for transplanted non-diabetics. Infection is an additional major risk for transplanted patients, diabetic or non-diabetic: bacterial, mycotic, or viral. These risks primarily apply in the first year after transplant, and to cadaver recipients. The preponderance of cadaver-kidney recipients in the Scandinavian series seems the likeliest explanation for the apparent difference in prognosis for poor-risk patients (blind, heart disease) in the Scandinavian and the Minneapolis series. For the cadaver recipients, obvious vascular disease at the time of transplant may be an intolerable burden. For the living-donor recipients, who weight the Minneapolis experience heavily, it may be tolerable, since base-line cardiovascular disease does not seem to predict outcome [66].

It seems likely, in any case, that virtually all uraemic diabetic patients have advanced coronary disease, at least by angiography [72].

Fig. 3. Sections from needle biopsy of a kidney transplanted 8 years before from a healthy man to his HLA-identical diabetic brother. PAS stain. The lower power view on the left shows a moderate amount of mesangial thickening; no nodules were seen. However, about a quarter of the glomeruli in the biopsy were hyalinized. The higher power view on the left of one glomerulus is selected to show hyalinization of afferent and efferent arterioles (arrows). Arrow A shows what is probably the afferent arteriole. (Photographs by courtesy of Dr. Richard Sibley.)

Surgical complications. The obvious area of problems for the diabetic group is the increased frequency of complications with the ureter of the transplanted kidney, and the bladder of the recipient. These problems are roughly twice as frequent as in our non-diabetic experience. Possible explanations include a slower rate of vascularization of the ureter after transplant, distention of the lower urinary tract due to autonomic bladder neuropathy, plus the huge urine volume (sometimes 10 to 15 l/day) which is common in the first 28 to 96 h after the transplant.

Measures used since 1974 to combat these problems include prolonged chronic catheter drainage of the bladder in all diabetic recipients (4 to 5 days rather than 1 to 2), and more intensive efforts at control of hyperglycaemia in the immediate post-transplantation period.

State of the kidney after transplantation. Great interest attaches to the fate of the kidney transplanted abruptly from a non-diabetic into a diabetic milieu.

The striking change by light microscopy is hyalinisation of both afferent and efferent glomerular arterioles, in biopsies taken two to four years after transplantation [22]. Similar lesions have been observed in non-diabetic recipients only rarely and after a much longer period. This arteriolar change, which morphologically is characteristic of and nearly specific for diabetes, is generally described in long-standing diabetes and would be unexpected in two to four years of ordinary spontaneous diabetes, although precise prospective studies on this point are

lacking. Animal studies suggest a remarkable additive effect on kidney morphology [17] and mass [73] of diabetes and unilateral nephrectomy. Since the transplanted kidney is in effect a single kidney, there may indeed be an acceleration of the typical diabetic arteriolar change in the transplanted kidney.

One naturally might expect the entire picture of diabetic glomerular sclerosis to be unfolding in these kidneys, but so far this has not been the case. Although immunofluorescent studies do indeed show deposition of immunoglobulin in both glomerular and tubular basement membrane in patterns identical with that seen in spontaneous diabetes [74], the Kimmelstiel-Wilson nodule, which remains the most widely accepted morphologic expression of diabetes in the kidney, remains conspicuous by its absence from more than 50 biopsies taken as long as eight years after transplantation. Instead, the one eight-year biopsy so far available shows marked arteriolar change, some mesangial thickening, and total hyaline obliteration of some glomeruli suggesting a non-specific ischaemic effect (Fig. 3). Also, electron microscopic measurements of glomerular basement membrane thickness, while they do reveal consistent thickening of basement membranes after transplantation, do not show an increase over the rate of thickening in the non-diabetic case material so far available.

Fortunately for the patients, the *function* of the transplanted kidneys is not correlated with the development of arteriolar hyalinisation. Serial measurements of creatinine clearance in the first 70 dia-

Fig. 4. Typical finger lesions from two diabetic patients one year **a** and three years **b, c** after kidney transplantation. One arm of the patient on the right had been used for dialysis access, the other had not

betic transplant patients show that in general, kidney function remains quite stable for at least eight years. This means essentially normal function for most subjects, but even when rejection episodes occur early in the post-transplant course of the patient and are associated with reduced function, there has been no progressive subsequent deterioration.

Thus, there appears to be an accelerated development of the arteriolar lesion, but with an arrest of the process of glomerulosclerosis at that stage for as long as eight years after transplantation. The inference may be drawn that while the arteriolar change is characteristics of diabetes, it is not necessarily an inseparable component of the glomerulosclerotic process.

Progression of non-fatal vascular lesions associated with diabetes. The early course of *retinopathy* and *neuropathy* was described in 1974 [75]. The experience then was surprisingly favourable, and in general, it has been confirmed by longer follow-up, and by the Mayo [70] and Scandinavian [71] reports.

In 1972, the initial impression was gained that many patients were progressing rapidly toward blindness at the time of transplantation, but that vision seemed to stabilize in the year following transplantation [76]. This impression has now been confirmed by systematic prospective observation of the first 77 diabetic patients with standardized ophthalmological methods [77]. Whether treated by photocoagulation or not, most of the eyes with active proliferative retinopathy settle into a quiescent involutional stage after transplantation. Although a few eyes have gone on to blindness anyway, the visual acuity of the patients as a group has indeed remained stable for as long as nine years.

Some caution should be expressed about the fate of the eye with involutional proliferative disease. Such eyes are distinctly abnormal in relation to colour vision [78], and are subject to slow attrition of visual acuity, perhaps on the basis of advancing ischaemia. However, abrupt loss of vision from massive haemorrhage rarely occurs.

Similarly, the early impression of stabilization of peripheral neuropathy [75] has been sustained by further clinical observation. Muscle weakness, including foot drop and quadriceps weakness, regularly improves slowly and steadily over the first year to 18 months after transplantation, strongly suggesting that much of the loss of strength has been due either to uraemic nerve damage or to general inanition, rather than to diabetic nerve damage. After this initial improvement, peripheral nerve sensory and motor function remains stable clinically; motor and sensory nerve conduction velocity remain abnormal but stable.

It has not been possible to measure systematically the manifestations of visceral autonomic neuropathy. However, symptoms usually improve after reversal of uraemia by transplanation. Gastric stasis and diarrhoea get better promptly. Postural hypotension and delayed bladder emptying are sometimes troublesome immediately after transplantation, but those also improve later.

In contrast, a serious problem is the loss of toes, legs, and fingers from ischaemia or infection. About one patient in five has had at least one amputation. Expecially puzzling is gangrene or ulceration of fingers. This was at first attributed to a "steal" of blood from the fingers through the arterial-venous fistula created in the forearm for dialysis in preparation for transplantation [79], but it has also occasionally

occurred in hands where no fistula or shunt has been placed (Fig. 4).

Rehabilitation of the diabetic patient after transplantation and "quality of life". A detailed review of initial experience at the University of Minnesota [80] indicated that a return to reasonably normal life was possible for a considerable number of diabetic patients, although the chances were not as good as for the non-diabetic transplant recipient. More detailed information is now available after six to eight years of follow-up [81, 82]. Table 2 shows that about 70% of diabetic patients who survive for four to five years after transplantation maintain for most of that time a state of well-being at least as good as that which they experienced six months or more before final kidney failure and transplantation. Thus half the patients receiving a kidney transplant on our service not only survived but returned to a life of good quality. The others died, or else were significantly disabled by blindness, loss of limbs, depression, or a combination of these.

Management of diabetes. The vast majority of patients treated on our service and elsewhere for diabetic kidney failure have juvenile-onset insulin-dependent Type I diabetes. There are major shifts in their response to insulin, but overall they remain an insulin-sensitive, somewhat unstable group of patients throughout the course of their transplantation experience.

Most of the patients go through four stages in their insulin regimens: (1) diminishing insulin need as uraemia develops, especially obvious in the nephrectomized patient who can be strikingly insulin-sensitive; (2) an abrupt shift to markedly increased insulin requirement and sluggish response to insulin at the time of transplantation, largely accounted for by the beginning of corticosteroid immunosuppressive treatment; (3) a post-operative adjustment period of approximately six to nine months, during which insulin requirement may rise further even though corticosteroid therapy is being reduced (perhaps as a result of hypertrophy of the transplanted kidney); and (4) finally, a stable period of indefinite duration usually reached by the first anniversary after the transplant in which the general diabetic response is much like that before kidney disease became manifest.

On our own service the principles of management have been standardized and simplified as much as possible. A continuous insulin infusion has proven to be very convenient during the first 72 to 96 h after transplantation, when the rate of change of insulin dosage is especially great. A syringe pump is used

Table 2. Rehabilitation status of 120 diabetics surviving (out of 175 patients) 1 to 7 years after kidney transplant at the University of Minnesota

<i>Active</i>	92 Patients (77%)
Working	44
Homemaker	25
Student	7
Avocation	16
<i>Inactive</i>	28 Patients (23%)
Physically disabled	24
No motivation	4

with a capacity of 30 or 40 ml and an insulin concentration of 1 unit/ml. For the first two to four days, until the patient can eat reliably, glucose is supplied IV at the rate of 100 to 150 g/24 h, in a concentration suitable for the patient's fluid requirements. The insulin infusion rate commonly is 4–8 u/h (range 1 to 12), with adjustments every four to six hours according to intermittent plasma glucose measurements. The immediate goal is a plasma glucose level between 8 and 16 mmol/l (150 and 300 mg/dl) – a goal attained perhaps 50% of the time.

As soon as the patient is eating consistently, SC insulin is resumed. We prefer twice-a-day injections, usually of a combination of intermediate (isophane or lente) and soluble insulin. The twice-daily injection scheme is sufficiently flexible to allow for frequent changes in insulin requirement over the first six months. There is usually a marked increase in appetite and food intake after transplantation, and it seems appropriate to encourage a generous intake of calories and protein for restoration of depleted tissues. Physical activity commonly increases a great deal. Also, the occasional rejection episode is customarily treated with a temporary sharp increase in corticosteroids requiring abrupt parallel change in insulin dose.

For all these reasons, the adjustment of insulin dosage is commonly closely monitored by blood glucose measurements several times a week at first and then at more widely-spaced intervals for six to twelve months. Blood glucose levels are emphasized because some patients seem to show a low renal threshold for glucose in the transplanted kidney.

Diabetic management is closely monitored in the central transplantation follow-up clinic for approximately six months. After this time, every effort is made to restore management of the diabetes to the patient and the primary physician.

The regimen described here aims at only approximate glucose control. At the least the goal of avoiding serious hypoglycaemia or ketoacidosis during a period of complicated medical and surgical manage-

ment has been achieved. To this extent it appears to be successful, as carried out by the combined efforts of the surgical team with consultation by the endocrine service and with close follow-up by the specialized nursing team.

The kidney donor. The living related donor offers clear advantages to the recipient, probably greater for the diabetic patient than for the non-diabetic.

What are the risks to the living donor? The general risks have been tabulated for the Minnesota experience by Spanos [83]. Two hundred and eighty-seven healthy donors experienced a total complication rate of 28%, which is by no account a trivial figure. However, most of the complications were minor chest or lower urinary tract problems (mostly infection) without prolonged consequences. The only serious complications were pulmonary embolus in one donor and deep vein thrombophlebitis in another, both resolving on treatment. There were no deaths.

Where siblings or parents donate to a diabetic subject, the possibility of diabetes in the donor is a necessary concern. Mild glucose intolerance was indeed present in a few relatives accepted for donation, but for most, the standard glucose tolerance test was normal (Fajans-Conn criteria). Follow-up tests five years later have shown no deterioration in glucose tolerance or kidney function in 26 donors. So far, the risk to the donor, both general and diabetes-related, seems acceptably small.

Cost. The cost in dollars of kidney transplantation is great, although it is less per life-year than that of chronic haemodialysis [84].

In our own centre, the cost for a transplantation admission for a diabetic patient with a living donor and the smoothest possible course was \$20,000 U.S. for a three week stay in 1972. This is probably an absolute minimum figure. Current figures are in the range of \$30,000 to \$45,000 for the transplantation itself, not including later admission for rejection or other complications.

It is extremely difficult to say whether this cost is "justified" or not. In a sense, all organ transplantation is a national luxury – a luxury which seems justifiable only if basic medical care is already available to most of the public.

Recipient selection. We and other groups (Joslin Clinic, Mayo Clinic) have found it increasingly difficult to define with precision the "suitable" candidate for kidney transplantation for diabetic renal disease. The most obvious possible contra-indications would include the following: blindness; advanced

heart disease; advanced peripheral and visceral neuropathy; a difficult social or psychological situation.

In practice, despite the complexities of life with diabetes and a kidney transplant, no one of these problems by itself has proved to be an insuperable barrier to decent life after transplantation. It has been especially difficult to estimate the prognosis for life where coronary heart disease is assumed to be present. In current practice, we consider a diabetic patient eligible for transplantation on the basis of chronic renal failure when creatinine clearance falls below 5% of normal, or when serum creatinine level has remained steadily elevated at 0.5 to 0.7 mmol/l (6 to 8 mg/dl) for six months or more in the absence of apparently reversible illness. If fluid overload has been a problem, or if retinopathy is rapidly advancing, transplantation may be considered at an even earlier stage. If hypertension is severe, bilateral nephrectomy may be considered; otherwise this is no longer done. Splenectomy is still carried out, but this is under re-evaluation. No one of the contra-indications mentioned above eliminates the patient by itself, but if two or more are present, we are less eager to offer transplantation.

6. Concluding Comments

Before end-stage. Preventive treatment for diabetic glomerulosclerosis is still in its infancy – more than forty years after Kimmelstiel and Wilson's paper. If the key lies in prolonged vigorous control of diabetic metabolism, then simple, cheap and attractive ways of accomplishing that must be provided. Alternative approaches such as finding a drug to halt or reverse the kidney lesion, should also be pursued vigorously.

Palliative measures for the early symptomatic stage are of mixed variety: hypertension and fluid overload respond well to many drugs, but dietary measures, although they have been well established for their value in delaying uraemic symptoms, are largely neglected for the diabetic with developing uraemia. There is room for exploration of their value.

When to transplant? When our own systematic experience with diabetic patients began (1969), it was customary to transplant only when uraemic symptoms were obvious and serum creatinine was grossly elevated (0.9 mmol/l or 10 mg/dl). Bilateral nephrectomy, a somewhat hazardous procedure, was customary. Retinal photocoagulation was not widely used, and rapid loss of vision from bleeding into the eyes appeared to happen often in the months just preceding transplant.

Now we customarily advise transplantation about a year earlier in the presumed course of the nephropathy, when serum creatinine is 0.5 to 0.7 mmol/l (6 to 8 mg/dl) and symptoms of uraemia may be mild or absent; pretransplantation nephrectomy has been stopped. The main reason for the change is the desire to prevent blindness, since vitreous haemorrhage seems less likely after transplantation.

Nevertheless, the course of nephropathy is sometimes very protracted [85], transplantation at any time carries its own risks, and infection, including serious viral infection, is now the major one. Also, photocoagulation of the retina is now well established as preventive treatment for blindness in its own right [86], and is almost universally available in the US.

The question can be raised: should we wait longer before transplanting? This deserves consideration, perhaps by observing a small pilot group of patients on the best possible conservative programme with especially careful attention to the eyes.

Transplantation versus dialysis. Since publication of the Scandinavian transplantation experience [71], there have been at least four letters to Lancet [87] debating the relative merits of transplantation and chronic haemodialysis for diabetic patients. Most of the authors, like ourselves, are experienced in one technique or the other, but not both.

There are, however, two publications reporting experience with both techniques by a single group, with assignment of cases to one treatment or the other from a single pool of patients, not randomly, to be sure, but on the judgment of a committee. At the University of Nebraska [88] both survival and quality of life were better for the transplanted patients (1976). At the Joslin-Lahey Clinics [70] (1978) survival is now equal for both groups, but quality of life is considered superior for those surviving after transplantation.

Our present judgment is that transplantation from a living donor, ideally an HLA-identical sibling, offers the best chance for decent life for as long as ten years. Fortunately, chronic haemodialysis and also peritoneal dialysis offer acceptable alternatives for survival, if transplantation is not possible.

Together these methods make possible a holding action for perhaps the next 20 years, until a truly direct attack on the underlying lesion of diabetic glomerulosclerosis is possible.

Acknowledgements. The transplantation experience from the University of Minnesota summarized here is entirely from the service of Professor John Najarian. It is a pleasure to thank him for un-

ing help in the study of the Minnesota patients. Many other colleagues have contributed to their care and have also provided valuable references. The previous reviews of Thomsen [89] and Watkins, Parsons and Bewick [90] were valuable in preparing this paper.

Sincere thanks are due to Candace Johnson and Carol Connolly for preparation of the manuscript.

Support for our studies came from the General Clinical Research Centers Program (RR-400) of the Division of Research Resources, National Institutes of Health and from the Bush Foundation, St. Paul, Minnesota.

References

1. Bloom, A., Hayes, T., Gamble, D.: Register of newly diagnosed diabetic children. *Br. Med. J.* **1975** *III*, 580–583
2. Knowles, H. C.: Magnitude of the renal failure problem in diabetics. *Kidney Int.* [Suppl. 1] **6**, 2–7 (1974)
3. Deckert, T., Poulsen, J., Larsen, M.: Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. *Diabetologia* **14**, 363–370 (1978)
4. Fishberg, A.: Hypertension and nephritis. Fourth edition, pp. 348–350. Philadelphia: Lea & Febiger 1939
5. Fishberg, A.: Hypertension and nephritis. Fifth edition, pp. 501–514. Philadelphia: Lea & Febiger 1954
6. Kussman, M., Goldstein, H., Gleason, R.: The clinical course of diabetic nephropathy. *J.A.M.A.* **236**, 1861–1863 (1976)
7. Bell, E. T.: Renal diseases, pp. 376–378. Philadelphia: Lea & Febiger 1946
8. Lendrum, A. C., Sidders, W., Fraser, D.: Renal hyaline: a study of amyloidosis and diabetic fibrinous vasculosis with new staining methods. *J. Clin. Pathol.* **25**, 373–396 (1972)
9. Kimmelstiel, P., Wilson, C.: Intercapillary lesions in the glomeruli of the kidney. *Am. J. Pathol.* **12**, 83–98 (1936)
10. Kimmelstiel, P.: Diabetic glomerulosclerosis. In: Structural basis of renal disease. Becker, E. (Ed.), pp. 462–504. New York: Hoeber-Harper & Row 1968
11. Viberti, G. C., Jarrett, R. J., McCartney, M., Keen, H.: Increased glomerular permeability to albumin induced by exercise in diabetic subjects. *Diabetologia* **14**, 293–300 (1978)
12. Mauer, S. M., Sutherland, D., Steffes, M.: Pancreatic islet transplantation. Effects on the glomerular lesions of experimental diabetes in the rat. *Diabetes* **23**, 748–753 (1974)
13. Ditzel, J., Schwartz, M.: Abnormally increased glomerular filtration rate in short-term insulin treated diabetic subjects. *Diabetes* **16**, 264–267 (1967)
14. Mogensen, C. E.: Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. *Scand. J. Clin. Lab. Invest.* **28**, 91–100 (1971)
15. Azar, S.: Increased glomerular capillary pressure (PGC) in pancreatectomized rats with short-term diabetes (Abstract). *Clin. Res.* **26**, 725A (1978)
16. Berkman, J., Rifkin, H.: Unilateral nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson): Report of a case. *Metabolism* **22**, 715–722 (1973)
17. Steffes, M., Brown, D., Mauer, S.: Diabetic glomerulopathy following unilateral nephrectomy in the rat. *Diabetes* **27**, 35–41 (1978)
18. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* [Suppl. 2] **19**, 785–830 (1970)
19. University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. IV. A preliminary report on phenformin results. *J.A.M.A.* **217**, 777–784 (1971)

20. University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patient with adult-onset diabetes. VII. Mortality and selected non-fatal events with insulin treatment. *J.A.M.A.* **240**, 37–42 (1978)
21. Gliedman, M., Tellis, V., Soberman, R., Rifkin, H., Veith, F.: Long-term effects of pancreatic transplant function in patients with advanced juvenile-onset diabetes. *Diabetes Care* **1**, 9 (1978)
22. Mauer, S. M., Barbosa, J., Vernier, R., Kjellstrand, C., Buselmeier, T., Simmons, R., Najarian, J., Goetz, F.: Development of diabetic vascular lesions in normal kidneys transplanted into patients with diabetes mellitus. *N. Engl. J. Med.* **295**, 916–920 (1976)
23. Mogensen, G., Andersen, M.: Increased kidney size and glomerular filtration rate in untreated juvenile diabetics: Normalization by insulin treatment. *Diabetologia* **11**, 221–224 (1975)
24. Mogensen, C.: Renal function changes in diabetes. *Diabetes* **25**, 872–879 (1976)
25. Parving, H., Noer, I., Deckert, T., Evrin, P., Nielsen, S., Lyngsøe, J., Mogensen, C., Rørth, M., Svendsen, R., Trap-Jensen, J., Lassen, N.: The effect of metabolic regulation on microvascular permeability to small and large molecules in short-term juvenile diabetics. *Diabetologia* **12**, 161–166 (1976)
26. Walford, S., Allison, S., Gale, E., Tattersall, R.: Self-monitoring of blood glucose. Improvement of diabetic control. *Lancet* **1978 I**, 732–735
27. Pickup, J., Keen, H., Parsons, J., Alberti, K. G. M. M.: Continuous subcutaneous insulin infusion: an approach to achieving normoglycemia. *Br. Med. J.* **1978 I**, 204–207
28. Ireland, J., Patnaik, B., Duncan, L.: Effect of pituitary ablation on the renal arteriolar and glomerular lesions in diabetes. *Diabetes* **16**, 632–642 (1967)
29. Goetz, F., Kennedy, B. J., Peyton, W., Chou, S.: Pituitary surgery for severe diabetic retinopathy. *Univ. Minn. Med. Bull.* **33**, 389–400 (1962)
30. Danowski, T., Mateer, F., Puntereri, A.: ACTH or adrenocortical steroid therapy of proteinuria in adolescents and in adults. *Am. J. Med. Sci.* **237**, 545–558 (1959)
31. Kass, E.: Horatio at the orifice: the significance of bacteriuria (Maxwell Finland lecture). *J. Infect. Dis.* **138**, 546–557 (1978)
32. Engelberg, H., Gofman, J., Jones, H.: Serum lipids and lipoproteins in diabetic glomerulosclerosis. Preliminary observations of the effect of heparin upon the disease. *Diabetes* **1**, 425–433 (1952)
33. Kincaid-Smith, P.: The kidney: A clinico-pathological study, passim. Oxford: Blackwell 1975
34. Kazandjian, M., Riveline, B., Lagrue, G.: La microangiopathie diabétique. Étude en milieu néphrologique au cours de traitements à long terme per le gliclazide. *Gaz. Med. France* **83**, 1911–1919 (1976)
35. Astrug, A.: Diabetic nephropathy, M.D. Thesis (abstract). University of Sofia 1976
36. Walser, M.: The conservative management of the uremic patient. In: *The kidney*. Brenner, B., Rector, F. (Eds.), pp. 1613–1642. Philadelphia: Saunders 1976
37. Giovannetti, S., Maggiore, Q.: A low-nitrogen diet with proteins of high biological value for severe chronic uremia. *Lancet* **1964 I**, 1000–1003
38. Giordano, C.: Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. *J. Lab. Clin. Med.* **62**, 231 (1963)
39. Kluthe, R., Lüttgen, F., Capetianu, T., Heinze, V., Katz, N., Südhoff, A.: Protein requirements in maintenance hemodialysis. *Am. J. Clin. Nutr.* **31**, 1812–1820 (1978)
40. Noreé, L., Bergström, J.: Treatment of chronic uremic patients with protein-poor diet and oral supply of essential amino acids. II. Clinical results of long-term treatment. *Clin. Nephrol.* **3**, 195–203 (1975)
41. Walser, M.: Ketoacids in the treatment of uremia. *Clin. Nephrol.* **3**, 180–186 (1975)
- 42(a). Quick, C., Duvall, A.: Early changes in the cochlear duct from ethacrynic acid: an electron microscopic evaluation. *Laryngoscope* **80**, 954–965 (1970)
- 42(b). Pillay, V., Schwartz, F., Aimi, K., Kark, R.: Transient and permanent deafness following treatment with ethacrynic acid in renal failure. *Lancet* **1969 I**, 77–79
43. Mathog, R., Thomas, W., Hudson, W.: Ototoxicity of new and potent diuretics. A preliminary study. *Arch. Otolaryngol.* **92**, 7–13 (1970)
44. Ghavarian, M., Gutch, C., Kopp, K., Kolff, W.: The sad truth about hemodialysis in diabetic nephropathy. *J.A.M.A.* **222**, 1386–1389 (1972)
45. White, N., Snowden, S., Parsons, V., Sheldon, J., Bewick, M.: The management of terminal renal failure in diabetic patients by regular dialysis. *Nephron* **11**, 261–275 (1973)
46. Harris, J.: Personal communication (1970)
47. Goldstein, D., Massry, S.: Diabetic nephropathy. Clinical course and effect of hemodialysis. *Nephron* **20**, 286–296 (1978)
48. Comty, C., Kjellsen, D., Shapiro, F.: A reassessment of the prognosis of diabetic patients treated by chronic hemodialysis (CHD). *Trans. Am. Soc. Artif. Intern. Organs* **22**, 404–410 (1976)
49. Ma, K., Masler, D., Brown, D.: Hemodialysis in diabetic patients with chronic renal failure. *Ann. Intern. Med.* **83**, 215–217 (1975)
50. Totten, M., Izenstein, B., Gleason, R., Takacs, F., Libertino, J., D'elia, J.: Chronic renal failure in diabetes: survival with hemodialysis vs. transplantation. *J. Dial.* **2**, 17–32 (1978)
51. Jacobs, C., Rottembourg, J., Frantz, P., Slama, G., Legrain, M.: Le traitement de l'insuffisance rénale terminale du diabétique insulinodépendant. In: *Actualités Néphrologiques de L'Hôpital Necker*. Hamburger, J., Crosnier, J., Funck-Brentano, J. (Eds.), p. 77. Paris: Flammarion 1978
52. Slifkin, R., Neff, M., Baez, A., Gupta, S., Mattoo, N., Haimow, M.: Maintenance dialysis in diabetic patients. In: *Dial. Transpl. Neph. Proc. 13th Cong. EDTA*, Hamburg, pp. 377–384. London: Pitman 1976
53. Rao, K., Sutherland, D., Kjellstrand, C., Najarian, J., Shapiro, F.: Comparative results between dialysis and transplantation in diabetic patients. *Trans. Am. Soc. Artif. Intern. Organs* **23**, 427–432 (1977)
54. Tenckhoff, H., Blagg, C., Curtis, K., Hickman, R.: Chronic peritoneal dialysis. *Proc. Eur. Dialysis Transplant Assoc.* **10**, 333–371 (1973)
55. Tenckhoff, H.: Peritoneal dialysis today: a new look. *Nephron* **12**, 420–436 (1974)
56. Blumenkrantz, M., Shapiro, D., Mimura, N., Oreopoulos, D., Friedler, R., Levin, S., Tenckhoff, H., Coburn, J.: Maintenance peritoneal dialysis as an alternative in the patient with diabetes mellitus and end-stage uremia. *Kidney Int. [Suppl.]* **6**, 108–114 (1974)
57. Rubin, J., Oreopoulos, D., Gordon Blair, R., Chisholm, L., Meema, H., DeVeber, G.: Chronic peritoneal dialysis in the management of diabetics with terminal renal failure. *Nephron* **19**, 265–270 (1977)
58. Oreopoulos, D.: Personal communication (1979)
59. Mitchell, J., Frohnert, P., Kurtz, S., Anderson, C.: Chronic peritoneal dialysis in juvenile-onset diabetes mellitus. A comparison with hemodialysis. *Mayo Clin. Proc.* **53**, 775–781 (1978)
60. Michon, L., Hamburger, J., Oeconomos, N., Delinotte, P.,

- Richet, G., Vaysse, J., Antoine, B.: Une tentative de transplantation rénale chez l'homme. Aspects médicaux et biologiques. *Presse Méd.* **61**, 1419–1423 (1953)
61. Hume, D., Merrill, J., Miller, B., Thorn, G.: Experiences with renal homotransplantation in the human: report of nine cases. *J. Clin. Invest.* **34**, 327–382 (1955)
 62. Advisory Committee to the Renal Transplant Registry: The 13th report of the human renal transplant registry. *Transplant. Proc.* **9**, 9–26 (1977)
 63. Advisory Committee to the Renal Transplant Registry: Ninth report of the human renal transplant registry. *J.A.M.A.* **220**, 253–260 (1972)
 64. Advisory Committee to the ACS/NIH Renal Transplant Registry: 12th report of the human renal transplant registry. *J.A.M.A.* **233**, 787–796 (1975)
 65. Kelly, W., Lillehei, R., Merkel, F., Idezuki, Y., Goetz, F.: Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* **61**, 827–837 (1967)
 66. Kjellstrand, C., Shideman, J., Simmons, R., Buselmeier, T., von Hartitzsch, B., Goetz, F., Najarian, J.: Renal transplantation in insulin-dependent diabetic patients. *Kidney Int.* [Suppl. 1] **6**, 15–20 (1974)
 67. Zincke, H., Woods, J., Palumbo, P., Leary, F., Johnson, W.: Renal transplantation in patients with insulin-dependent diabetes mellitus. *J.A.M.A.* **237**, 1101–1103 (1977)
 68. Najarian, J., Sutherland, D., Simmons, R., Howard, R., Kjellstrand, C., Mauer, S., Kennedy, W., Ramsay, R., Barbosa, J., Goetz, F.: Kidney transplantation for the uremic diabetic patient. *Surg. Gynecol. Obstet.* **144**, 682–690 (1977)
 69. Najarian, J., Sutherland, D., Simmons, R., Howard, R., Kjellstrand, C., Ramsay, R., Goetz, F., Fryd, D., Sommer, B.: Ten year experience with renal transplantation in juvenile onset diabetics. *Ann. Surg.* (in press)
 70. Zincke, H., Woods, J., Sterioff, S., Johnson, W., Palumbo, P., Mitchell, J., Frohnert, P., Anderson, C., Service, F., Leary, F.: Renal transplantation in patients with diabetes mellitus – revisited. *Transplant Proc.* **11**, 55–59 (1979)
 71. Joint Scandinavian Report: Renal transplantation in insulin-dependent diabetics. *Lancet* **1978 II**, 915–917
 72. Bennett, W., Kloster, F., Rosch, J., Barry, J., Porter, G.: Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. *Am. J. Med.* **65**, 779–784 (1978)
 73. Seyer-Hansen, K.: Renal hypertrophy in experimental diabetes: A comparison to compensatory hypertrophy. *Diabetologia* **14**, 325–328 (1978)
 74. Mauer, S., Miller, K., Goetz, F., Barbosa, J., Simmons, R., Najarian, J., Michael, A.: Immunopathology of renal extracellular membranes in kidneys transplanted into patients with diabetes mellitus. *Diabetes* **25**, 709–712 (1976)
 75. Barbosa, J., Burke, B., Buselmeier, T., Carpenter, A. M., Goetz, F., Harris, J., Kennedy, W., Kjellstrand, C., Michael, A., Najarian, J., Recker, L.: Neuropathy, retinopathy and biopsy findings in the transplanted kidney in diabetic patients. *Kidney Int.* [Suppl. 1] **6**, 32–36 (1974)
 76. Kjellstrand, C., Simmons, R., Goetz, F., Clein, M., Buselmeier, T., Najarian, J.: Mortality and morbidity in diabetic patients accepted for renal transplantation. *Proc. Eur. Dial. Transplant. Assoc.* **9**, 345–358 (1972)
 77. Ramsay, R., Knobloch, W., Barbosa, J., Sutherland, D., Kjellstrand, C., Najarian, J., Goetz, F.: The visual status of diabetic patients after renal transplantation. *Am. J. Ophthalmol.* **87**, 305–310 (1979)
 78. Ramsay, W., Ramsay, R., Purple, R., Knobloch, W.: Involuntional diabetic retinopathy. *Am. J. Ophthalmol.* **84**, 851–858 (1977)
 79. Buselmeier, T., Najarian, J., Simmons, R., Rattazzi, L., von Hartitzsch, B., Callender, C., Goetz, F., Kjellstrand, C.: A-V fistulas and the diabetic: ischemia and gangrene may result in amputation. *Trans. Am. Soc. Artif. Intern. Organs* **19**, 49–51 (1973)
 80. Simmons, R., Schilling, K.: Social and psychological rehabilitation of the diabetic transplant patient. *Kidney Int.* [Suppl. 1] **6**, 152–158 (1974)
 81. Haymond, M., Recker, L., Willmert, J.: Vocational rehabilitation status of 125 diabetic transplant recipients. *Dial. Transplant.* **8**, 52–56 (1977)
 82. Recker, L., Haymond, M., Goetz, F., Willmert, J.: Rehabilitation status: 175 diabetic kidney transplant recipients. *Diabetes* **26**, 371 (1977)
 83. Spanos, P., Simmons, R., Lampe, E., Rattazzi, L., Kjellstrand, C., Goetz, F., Najarian, J.: Complications of related kidney donation. *Surgery* **76**, 741–747 (1974)
 84. Roberts, S., Maxwell, D., Gross, T.: Cost-effectiveness of end stage renal disease treatment. *Clin. Res.* **26**, 337 A (1978)
 85. Watkins, P., Blainey, J., Brewer, D., Fitzgerald, M., Malins, J., O'Sullivan D., Pinto, J.: The natural history of diabetic renal disease: a follow up study of a series of renal biopsies. *Q. J. Med.* **41**, 437–456 (1972)
 86. The Diabetic Retinopathy Study Research Group: Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic Retinopathy Study findings. *Ophthalmol.* **85**, 82–106 (1978)
 87. Letters to the editor: *Lancet* **1979 I**, 41 (Depperman, D., Ritz, E.); 153 (Jones, R., and others); 497 (Glass, N.); 778 (Zincke, H.)
 88. Passer, J., Ware, F., Steenburg, R., Stone, D.: A comparison of hemodialysis and transplantation in the treatment of end-stage renal failure secondary to diabetic nephropathy. *Nebr. Med. J.* **61**, 459–463 (1976)
 89. Thomsen, A.: The kidney in diabetes mellitus. A clinical and histological investigation based on renal biopsy material. Copenhagen: Munksgaard 1965
 90. Watkins, P., Parsons, V., Bewick, M.: The prognosis and management of diabetic nephropathy. *Clin. Nephrol.* **7**, 243–249 (1977)

Received: July 16, 1979

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