

# Diabetic Nephropathy

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Any discussion of morbid events in diabetes is going to emphasize cardiovascular and peripheral vascular problems. Renal disease accounts for a relatively small percentage of the mortality in diabetes; yet the overall incidence of diabetes mellitus in the population so greatly exceeds that of the various types of glomerulonephritis that it has become one of the most common causes of end-stage renal failure in this country. It is difficult to assign exact numbers because the figures in the medical literature vary considerably; however, it is estimated that in the United States today there are some 10 million people who are known to be diabetic, who would be found to be diabetic if tested, or who during the course of their lives will develop overt diabetes. In autopsy series of diabetics the prevalence of glomerulosclerosis has varied from 15% to 82%, with a mean of approximately 30%. This figure will vary depending on how carefully the kidneys are studied, particularly with respect to the use of special stains for identifying glomerulosclerosis; the incidence will also increase with the proportion of juvenile to adult onset diabetics included in the sample. Renal failure is listed as the cause of death of 6% to 12% of diabetics, and its incidence is increased seventeenfold in the diabetic population as compared to the nondiabetic. These figures are probably applicable to those diabetics who have many complications and who require referral to major medical centers for treatment. In terms of the general diabetic population renal failure is probably in the range of 1% to 2%. This means that the prevalence of glomerulosclerosis is severalfold higher than

the prevalence of renal failure, and that simply finding the lesion on biopsy does not indicate that kidney function itself has been impaired or that there will be any abnormalities present on urinalysis. As a cause of end-stage renal failure, diabetes now accounts for some 15% to 25% of all new cases.

Five years' survival after onset of proteinuria in diabetics compared to age-matched controls is 65% opposed to 73% for diabetics who do not develop proteinuria and 83% for non-diabetics. This does not mean that these people are dying of renal disease but that proteinuria heralds increased mortality from all causes. For juvenile diabetics it is extremely unusual for proteinuria to develop before 10 years' duration of the disease or to appear after a protein-free interval greater than 30 years. This means that there are essentially two populations of juvenile diabetics with regard to the kidney; those who will have their disease for an unlimited amount of time and never develop renal complications, and those who during the period between 10 and 30 years will note the onset of renal problems. Finally, in juvenile diabetes mellitus, azotemia defined as BUN in excess of 30 mg percent implies end-stage renal failure within three years. An important point to note is the rarity of a decline in the glomerular filtration rate before the onset of proteinuria when the cause is diabetic nephropathy. Once renal failure does ensue it has been calculated that the glomerular filtration rate falls at an average rate of 1 ml/min each month. With other forms of renal disease, hypertension greatly accelerates the rate of decline in the glomerular filtration rate, an important point in treatment.

Diabetic nephropathy and microangiopathy are the main topics under discussion here, but there are several other factors which contribute in varying de-

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gree to the progression of renal failure in diabetics. As there is no therapy for diabetic nephropathy itself, these other factors assume an importance in line with their response to treatment. Infection, in particular pyelonephritis and papillary necrosis, becomes an extremely important factor in the management of the diabetic. This is true because the autonomic neuropathy that may complicate diabetes favors development of a neurogenic bladder with high residual urine which may lead to reflux up the ureter, if the urine is infected, this reflux will result in secondary pyelonephritis and subsequent papillary necrosis with rapid loss of renal function. In patients who already have some type of renal failure, infection, even without involvement of the renal parenchyma, can result in a further decline in renal function. One of the theories that has been advocated to explain this is that certain types of bacteria can attach themselves to the cells of the ureter and thereby compromise the peristaltic action of the ureter which is important in propelling urine from the renal pelvis into the bladder. This results in a type of functional obstruction which acts in the same way as a true obstruction. Treatment of these patients with antibiotics to eradicate the bacteriuria improves ureteral peristalsis and renal function as well.

Diabetes is also frequently complicated by hyperlipidemia and hyperuricemia. Uric acid crystals are a cause of interstitial nephritis, and high uric acid levels which lead to increased uric acid excretion can set the stage for uric acid calculi, obstruction, and subsequent infection. In the evaluation of a diabetic patient, the potential adverse effect of uric acid should be considered as this cause of renal failure is subject to therapy either by alkalization of the urine or the use of allopurinol.

A number of cardiovascular problems will also contribute to the declining glomerular filtration rate. Hypertension has already been mentioned; this can accelerate the vascular degenerative changes in the kidney, leading to nephrosclerosis which in turn can accelerate the hypertension, creating a cycle which may be interrupted if the hypertension is successfully controlled through the careful use of antihypertensive medication. Another complication of hypertension is its deleterious effect on the myocardium, leading to hypertensive cardiomyopathy and congestive heart failure. This will have an adverse effect on renal function, for as the kidney is damaged secondary to diabetes or other processes and as the vascular disease in the kidney progresses, autoregulation of blood flow

in the face of a reduced cardiac output is compromised; thus low-output congestive heart failure will result in prerenal azotemia superimposed on the preexisting renal failure. In general, this situation is handled by the combination of digitalization and diuretics; however, it is worth pointing out the problems associated with excessive use of diuretics in these patients. They may get too dehydrated, a factor that will superimpose a prerenal type of azotemia upon their already preexisting level of renal failure. A compromise has to be worked out in terms of controlling the symptoms of congestive heart failure without, at the same time, contributing further to the impairment of renal function. Diabetics are prone to develop atherosclerosis, and particularly those patients who have extremely severe atheromatous disease of the aorta are subject to embolization to the renal vessels. This can present as episodic elevations of blood pressure associated with fluctuations in the level of renal function reflected by BUN and creatinine and accompanied by microscopic or even gross hematuria, depending on how much of the kidney is damaged or destroyed by infarction.

The actual role of platelets in renal disease is still largely uncertain, although there is strong circumstantial evidence that platelets may be an important factor in the decline in renal function not only in diabetes but in glomerulonephritis as well. However, the abnormal properties of platelets in diabetes increase the level of suspicion that they have a major role in the pathogenesis of the renal disease.<sup>1</sup> In the laboratory, platelets are studied by incubating them with various agents such as adenosine diphosphate, epinephrine, and collagen, which induce aggregation. The Table shows that the percent aggregation of platelets in diabetics to all three aggregating agents exceeds the control sample; moreover, platelets from diabetics aggregate at a lower concentration of these agents than the control sample. The reason for this is not exactly clear, but there is current evidence for a disturbance of prostaglandin synthesis by the platelets of diabetics. The Figure shows the synthesis of immunoreactive prostaglandin E following the addition of a precursor of prostaglandin synthesis, arachidonic acid. Diabetic platelets show enhancement of prostaglandin formation following addition of the precursor. Thus with the evidence that platelets are more sticky in the diabetic and aggregate more easily, the possibility has been raised that within the microcirculation of the kidney, platelet aggregation occurs and leads to occlusion of the small blood vessels,

TABLE  
Percent Aggregation Four Minutes After the Addition of Each of the Aggregating Agents

AGGREGATING AGENT	AGGREGATION (%)		P VALUE*
	CONTROLS	DIABETIC SUBJECTS	
ADP:			
1 $\mu$ M	22 $\pm$ 7†	80 $\pm$ 4 (9)‡	<0.001
2 $\mu$ M	69 $\pm$ 4	88 $\pm$ 4 (9)	<0.005
5 $\mu$ M	76 $\pm$ 4	86 $\pm$ 3 (9)	NS§
Epinephrine:			
1 $\mu$ M	39 $\pm$ 8	82 $\pm$ 5 (10)	<0.001
2 $\mu$ M	60 $\pm$ 6	85 $\pm$ 3 (9)	<0.01
5 $\mu$ M	66 $\pm$ 6	84 $\pm$ 2 (10)	<0.005
Collagen:			
1 $\mu$ g/ml	53 $\pm$ 10	80 $\pm$ 3 (8)	<0.05
2 $\mu$ g/ml	69 $\pm$ 8	84 $\pm$ 4 (8)	NS
10 $\mu$ g/ml	77 $\pm$ 8	86 $\pm$ 3 (8)	<0.05

\* Difference between % aggregation seen in the platelet-rich plasma obtained from control and that in diabetic subjects.

† Mean  $\pm$  SEM.

‡ Figures in parentheses denote no. of subjects

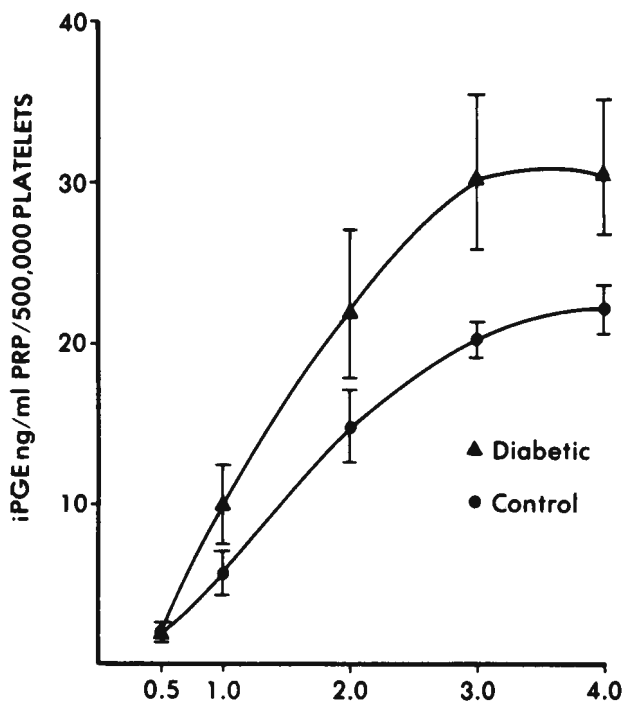
§ Not significant.

resulting in glomerular ischemia and glomerulosclerosis. There is some further evidence that involves platelets: thromboglobulin, a protein which is derived from the platelet, has been found to be increased in the circulation of those diabetics who have microangiopathy. There are also tests for the presence of circulating platelet aggregates, and those diabetics who have the most severe small vessel disease are also the ones who show the highest levels of these circulating platelet aggregates. A recent study<sup>2</sup> reported on the efficacy of sulfinpyrazone in the prevention of morbid events in patients who have severe coronary artery disease. There are active studies in progress to evaluate antiplatelet drugs in a variety of diseases that affect blood vessels, particularly coronary artery disease, atherosclerosis, and different types of renal disease.

Amyloidosis is always listed as associated with diabetes mellitus. Certainly the onset of nephrotic syndrome or heavy proteinuria in a patient with long-standing diabetes does raise the possibility that secondary amyloidosis may be present. With respect to immunologic factors which crop up in consideration of almost every type of renal disease, immunoglobulins and complements are found within the glomerulus of the diabetic kidney. Their presence in a rather nonspecific pattern together with several other serum proteins has been interpreted not to represent a specific immunologic event such as immune complex disease or anti-glomerular basement membrane

(anti-GBM) disease. Still, there are some lines of evidence which do not exclude completely the idea that immunologic problems are present in the diabetic and may be contributing to the renal disease. It was recently reported that juvenile diabetes mellitus can be viewed as a genetic disease transmitted as an autosomal recessive gene.<sup>3</sup> More interesting, perhaps, is the close association of the diabetic gene with the HL-A locus. This area of the chromosome is concerned with a variety of immunologic responses, and many other diseases which have a close association with the HL-A locus have been more firmly established as being the result of an immunologic abnormality. Based on this there is still speculation that the diabetic may have altered immunologic responses and that this in turn may lead to primary or secondary renal damage.

Drug-induced disease of the kidney, while not confined to the diabetic, may assume increased significance for these patients. There have been several reports of acute renal failure following the use of iodine contrast agents; for the most part, this can be prevented in the nondiabetic population by avoiding dehy-



MINUTES AFTER ADDITION OF ARACHIDONIC ACID

Figure—Time course for the production of iPGE in platelet-rich plasma (PRP) from exogenous arachidonic acid (0.5mM). The values are the mean  $\pm$  SEM for nine subject pairs.

dration which is part of the preparation of patients for radiologic examinations. Diabetics, however, tend to develop acute renal failure with a greater frequency than nondiabetics; moreover, avoiding dehydration does not seem to be protective. This suggests that something about the diabetic kidney predisposes it to damage in the face of a quantity of hyperosmotic material. The question arises whether the diabetic kidney is more susceptible to other nephrotoxic agents such as the aminoglycoside antibiotics and a host of other medications which have potential nephrotoxicity. The lack of a definite answer suggests that in the management of diabetics both diagnostic and therapeutic agents should be selected for their reduced incidence of nephrotoxicity.

Several studies have attempted to identify factors of importance in determining the development and progression of diabetic nephropathy. The data to be presented were derived from a small number of patients with biopsy-proven glomerulosclerosis who were followed for several years at which time a repeat biopsy was performed.<sup>4</sup> As far as the type of diabetes is concerned, of the 11 adult onset diabetics, 9 showed no progression of their glomerulosclerosis, and 2 became worse. In contrast, of the 6 juvenile diabetics, 1 showed no change and 5 showed progression of the disease. With regard to blood glucose control, 6 of the patients maintained good sugar control for the whole length of the study and none of the 6 showed progression of their glomerulosclerosis. By contrast, 13 patients were rated to be poorly controlled and 10 of them showed a progression of their renal lesions. In respect to the age of onset of these diabetics, patients in the group that showed no change were considerably older at the time of the onset of their diabetes than were those in the group that became worse. Obviously these three variables are not independent since, by and large, in older patients the adult onset type of diabetes can easily be managed by diet and weight reduction. But the results do suggest that blood glucose control may be important in terms of slowing down or averting the development of glomerulosclerosis.

There appear then to be at least three phases in the renal disease that accompanies diabetes. The first is a pre-proteinuria phase. Phase 2 is marked by the onset of proteinuria, and phase 3 would be development of azotemia. Several groups have tried to study the question, Is there anything abnormal about the kidney in the pre-proteinuric phase?, that is, before proteinuria becomes manifest and at a time when the

other renal function tests are also normal.<sup>5</sup> If glomerulosclerosis progresses slowly with time, there might be a gradual increase in the excretion of albumin in the urine as the function of the duration of the diabetic process until such time as the amount of albumin in the urine definitely reaches an abnormal quantity. In a study of 97 young male diabetics who were followed from 1-19 or more years after the diagnosis of diabetes, there was no increase in albumin excretion throughout this period of time. Those who develop proteinuria are clearly distinguished from those who do not. Because strenuous exercise increases albumin excretion, a group of 13 juvenile diabetics were exercised at a rate which had not affected urinary albumin levels in 9 normal controls. The diabetics showed a statistically significant increase in protein excretion that returned to baseline after stopping the exercise. Another element that has been examined is the excretion of low molecular weight proteins by diabetics; these represent proteins that are considerably smaller than albumin and are freely filtered at the glomerulus. Almost none, however, appear in the urine because most of these filtered proteins are reabsorbed by the cells of the proximal tubule. In the pre-proteinuric phase, diabetics show an increase in excretion of low molecular weight proteins. These results, together with additional information on albumin excretion, suggest that the metabolic state of diabetes can adversely affect renal cell function so that when the diabetic is poorly controlled, the cells are less able to reabsorb filtered proteins, including albumin.

In addition to studies on patients, there have been attempts to gain information about diabetes through the use of animal models. Diabetes may be induced in animals either by removing the pancreas or by destroying the insulin-producing cells with a chemical such as streptozotocin. These animals then develop hyperglycemia and over the next several months their kidneys will show the kind of lesions that are present in humans: namely, there is an increase in the mesangial matrix and an increase in the degree of glomerulosclerosis together with deposition of immunoglobulins and complement. If the kidneys from a diabetic animal are transplanted into a normal animal, the diabetic changes rapidly disappear. On the other hand, if kidneys from a normal animal are transplanted into a diabetic animal, diabetic changes will develop. When pancreatic tissue is successfully transplanted into the diabetic animal, then coincident with the rise in insulin level, there is striking improve-

ment in the appearance of the diabetic kidney. This indicates that the changes seen in the glomerulus are at least initially reversible and that metabolic control of blood glucose, or at least the presence of insulin in appropriate quantities to keep the blood glucose normal, is a contributing factor to the development of diabetic changes.

The outline for therapy of diabetic kidney disease calls for the best blood glucose control circumstances will permit. Antihypertensive therapy has to be emphasized together with optimal management of congestive cardiac failure in order to maintain a high cardiac output and avoid prerenal azotemia. The patient should be evaluated for obstruction and for urinary tract infection. Nephrotoxic agents should be avoided as much as possible. As for vascular complications, anticoagulation offers little value as, by and large, patients who have renal disease also have retinal disease which is aggravated by these drugs. The antiplatelet drugs, based on available evidence, are quite promising, although unproven at the present time. As far as the treatment of end-stage renal disease in the diabetic is concerned, the same four modalities are open to these patients as anyone else: living related transplants, cadaver transplants, hemodialysis and peritoneal dialysis. Because of technical advances, greater experience in dealing with diabetics, and earlier acceptance of diabetics into end-stage renal failure programs, the prognosis has improved considerably during the past couple of years.<sup>8</sup> Transplantation from a living related donor seems to be as good in diabetics as in the general population, so that this would seem to be the treatment of choice for a diabetic with end-stage renal disease. The results with cadaver kidney transplantation tend to be poorer than those of the general population and until we have some better methods of managing cadaver kidney transplants in general, this is probably the least

promising mode of therapy for the diabetic. Hemodialysis is the treatment that will be applied to the majority of these people. The problems are in establishing a suitable blood access site because of severe vascular disease and the requirement for anticoagulation during dialysis which frequently leads to a deterioration of vision. Many nephrologists now feel that the treatment of choice if a living related donor is not available is peritoneal dialysis; the major problem here is peritonitis as well as the necessity for using high-glucose containing solutions in the peritoneal cavity which can lead to severe degrees of hyperglycemia, but the complications associated with bleeding in the eye are avoided and vascular access is not necessary.

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