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NEPHROLOGY FORUM

Microalbuminuria as a predictor of clinical diabetic nephropathy

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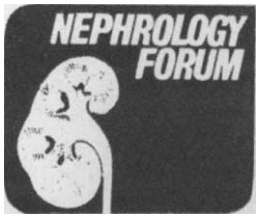

Case presentations

Patient 1. A 30-year-old man was admitted to the Aarhus Kommunehospital because of uncontrolled diabetes mellitus, which had been diagnosed 12 years earlier and had been treated with insulin and a controlled diet ever since. The blood pressure was 130/90 mm Hg. Mild retinopathy with a few microaneurysms, small hemorrhages, and one soft exudate were noted. Laboratory studies following regulation of the patient's diabetes revealed urinary albumin excretion (UAE), 15 ± 4 μg/min (mean ± SD; normal value, 5.1 ± 1.0 μg/min); glomerular filtration rate (GFR) (by labeled iothalamate clearance), 152 ml/min; and renal plasma flow (RPF) (by labeled hippuran clearance), 710 ml/min. Blood glucose values during these investigations averaged 133 mg/dl. Urine sediment was normal and urine culture was sterile.

After discharge, the patient did not attend the outpatient clinic for followup. He was hospitalized again because of poor control of his diabetes 3 years after the initial admission. He had been working hard physically on an erratic schedule and was not adhering to the recommended therapeutic regimen; he had reduced the amount of insulin he was taking (lente insulin administered twice daily) from 84 to 40 units per day and had not been following dietary advice. Blood pressure was 160/95 mm Hg. Vibration threshold measured at the right great toe had increased from 23 volts during initial evaluation to 47 volts at followup (normal value, <15 volts). Laboratory data included: UAE, 1573 ± 28 μg/min; GFR, 105 ml/min; RPF, 536 ml/min. Urine sediment was normal and urine culture was sterile.

Thereafter the patient attended clinic regularly. Over the next 2 years, blood pressure increased, eventually averaging 170/102 mm Hg; the GFR declined by 1.70 ml/min/month. Antihypertensive treatment was instituted, and over the following 7 years, the blood pressure averaged 142/90 mm Hg; GFR continued to decline in a linear fashion, the rate of reduction being 0.42 ml/min/month.

Patient 2. A young man with insulin-dependent diabetes mellitus since the age of 10 years was admitted to the clinic at the age of 23. He had been treated for 6 years with conventional insulin therapy (NPH insulin administered twice daily) and a controlled diet. Fasting plasma glucose averaged 112 mg/dl. He had early retinopathy and mild neuropathy with increased vibration threshold values. Blood pressure increased at the end of this pre-intervention phase, eventually reaching 130/103 mm Hg. The UAE increased at an average yearly rate of 28%, from a value of 22 μg/min at baseline to a value of 149 μg/min during the sixth year of followup. The GFR was well preserved throughout this 6-year period (154 to 142 ml/min). Urine sediment was normal and urine culture was sterile. Following institution of antihypertensive treatment at the age of 29, blood pressure averaged 122/88 mm Hg during the next 3 years of followup. The UAE subsequently decreased at an average yearly rate of 21%, reaching a value of 43 μg/min by the third year of treatment. The GFR remained stable at 144 ml/min.

Discussion

DR. CARL ERIK MOGENSEN (*Professor of Medicine, Second University Clinic of Internal Medicine, Aarhus Kommunehospital, Aarhus, Denmark*): Early morphologic lesions of diabetic nephropathy, such as glomerular basement membrane thickening and mesangial expansion, develop in practically all insulin-dependent diabetics within a few years after the onset of their metabolic abnormality [1]. Nonetheless, clinical diabetic nephropathy with proteinuria, hypertension, and a decline in renal function develops eventually in only about 45% of insulin-dependent diabetics, the remainder being spared clinically important renal disease [2–4]. Several benefits could be derived from knowing early in the course of diabetes whether a patient is likely to develop clinical diabetic nephropathy. First, such information would have obvious prognostic implications. Second, this knowledge, coupled with serial investigations of systemic and renal hemodynamics, might shed light on the pathogenetic mechanisms leading to the development of overt diabetic nephropathy. Third, the existence of such a marker would allow selection of patients for trials aimed at retarding progression to renal failure. Such trials might include intensified insulin treatment, low-protein diets, and early and aggressive antihypertensive treatment. In this discussion, I will make the case that "subclinical proteinuria" qualifies as such a marker or predictive instrument.

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Proteinuria is the laboratory hallmark of diabetic nephropathy and is highly predictive of uremia and early mortality [5, 6]. Until recently, most diabetes clinics have employed exclusively the Albustix test or similarly crude dipstick methods in screening patients for proteinuria. However, such methods give a positive result only when urine albumin concentration (and excretion) is increased from normal by a factor of approximately 20. Recent studies using more sensitive techniques have revealed the existence of early abnormalities in protein excretion, termed either "subclinical proteinuria" or "microalbuminuria." These studies have documented that even a slight elevation of urine albumin excretion—far below the level found in Albustix-positive "clinical proteinuria"—is a strong predictor of future overt diabetic nephropathy. Diabetic patients devoid of microalbuminuria have only a small risk of developing clinical proteinuria over the next 10 to 14 years; therefore, the excess mortality of such patients in comparison with the nondiabetic population is likely to be small [6]. Because I believe that detection of microalbuminuria is currently the best way to identify early in the course of the disease patients at risk of developing clinical diabetic nephropathy, I would like to pause for a moment to cite some of the recent work appearing on albumin measurement in diabetes and other disorders.

The past 5 years have witnessed extensive clinical investigation into the area of albumin as a marker in detecting, treating, and prognosticating disease. Individuals who wish to pursue these studies might find valuable papers relating to studies on the development of sensitive laboratory techniques for detecting albumin, such as radioimmunoassay and other immunoassay screening procedures [7–25]; methodologic investigations [26–33]; and pathophysiologic studies [34–44]. Also, studies in diabetics have appeared relating to albumin excretion during exercise [45–56] and in association with changes in blood pressure [57–60]. Metabolic control as well as intensified treatment have received attention [26, 61–69], and the 1980s have brought studies on associated microvascular diabetic lesions, especially retinopathy [70–74]. The structural correlate in the kidney to microalbuminuria is still not fully elucidated [75–78]. The use of albuminuria to predict diabetic nephropathy and to determine its progression have been studied in several centers in Europe [79–84]. Epidemiologic studies of microalbuminuria have appeared [85–88], including clinic-based surveys [89–94] and studies of specific populations such as children [95–105]; young adults [26, 106]; elderly, primarily non-insulin-dependent patients [107, 108]; and newly diagnosed patients [26, 107]. Reports also are appearing on new methods of intervention [65–69, 109–112], but this work is just beginning. Many surveys have summarized work on microalbuminuria [113–128]. Finally, microalbuminuria has been evaluated in diabetic rats [129].

Clinical research also has proceeded in non-diabetic patients, specifically those with hypertension [130–133], pre-eclampsia [134], and other generalized disorders [135–139]. My colleagues and I have investigated the urinary excretion of albumin in patients taking a variety of drugs [140–145] and hormones [146–152] and have studied the effect of glucose, amino acids, and other metabolic agents [40, 153, 154]. Protein-rich meals have no effect on albumin excretion [154]. Monitoring of early renal changes after exposure to nephrotoxic agents seems to be an important new area for investigation [155, 156].

General definition of microalbuminuria

The term *microalbuminuria* was coined in 1982 at Guy's Hospital in London [106]. The same group developed the first radioimmunoassay for detecting albumin in low concentrations in the urine in 1963 [7]. Many laboratory techniques, based on radioimmunoassay or chemicoimmunoassay, currently are available for determining urine albumin levels [8–22]. Microalbuminuria is defined as abnormally elevated UAE in the absence of clinical proteinuria (as measured by standard laboratory methods).

In one study, the UAE measured in 24-hour samples in 23 normal men and 20 normal women (age 22–40 years) averaged 4.7 ± 4.7 μg/min (SD) (range, 2.6–12.6) and 4.3 ± 4.8 (range, 1.1–21.9), respectively [128]. The day-to-day variation in UAE of 24 normal subjects, estimated as the coefficient of variance of three 24-hour samples, was 31.3% [128]. The mean UAE at rest (short-term collections over several hours, n = 18, all males) was similar (4.8 ± 1.4 μg/min), but with a somewhat narrower range (2.3–8.3 μg/min). Higher values for UAE were recorded in some elderly individuals in a population study [88].

Because the UAE varies with posture [26] and with exercise [45–56, 128], evaluation should be carried out only on urine collected under standardized conditions. Each of the following procedures is considered acceptable: (*1*) short-term collections over one or several hours in the laboratory or clinic; (*2*) overnight (approximately 8-hour) urine collection; (*3*) a 24-hour collection; (*4*) an early morning urine sample corrected for urine flow by creatinine measurement (mainly for screening purposes) [26, 33, 94]. I will discuss the utility of these various procedures in the next section. Because the coefficient of variance in UAE is approximately 45%, at least 3 urine collections are necessary [26, 29, 60].

In addition to laboratory techniques for quantitative determination of urine albumin levels, newly developed screening procedures based on immunoreaction [23] or on the protein error for pH indicators are available [24, 25]. The Microalbutest, a tablet method, is positive at a urine albumin concentration of approximately 40 μg/ml [24, 25], in contrast to the Albustix test, which is positive at a concentration of approximately 140 μg/ml. The Microalbutest can be used as a "bedside" examination for microalbuminuria [24], but quantitative methods should be employed whenever possible.

Predicting diabetic nephropathy and its progression

Studies from three centers show that the appearance of microalbuminuria predicts clinical diabetic nephropathy in insulin-dependent patients. The discrimination level of UAE, that is, the level of UAE which, if exceeded, predicts the development of clinical diabetic nephropathy, varies from center to center. This variability is likely due to differences in urine collecting procedures, differences in patient-sample composition, and differences in the duration of followup (Table 1).

We found the lowest discrimination level of UAE to be 15 μg/min when urine samples were collected over several hours in the laboratory or in the clinic and when the mean followup time was 10 years [83]. We used three excretion rates on average (Fig. 1). A somewhat higher discrimination value (30 μg/min) was found in a study employing overnight urine collections [81]. Finally, the highest discrimination value, 70 μg/min, was found

Table 1. Summary of predictive studies of diabetic nephropathy (DN) based on early microalbuminuria

	London[a]	Copenhagen[b]	Aarhus[c]
Female/male	22/41	42/29	0/43
Followup (%)	75%	100%	98%
Mean age at screening (*years*)	40 (17–60)	30 (13–50)	25 (18–31)
Mean duration of diabetes at screening (*years*)	10 (1–41)	12 (2–36)	12 (7–20)
Followup period (*years*)	14	mean, 6	mean, 10
Proposed discrimination value	30 μg/min	70 μg/min	15 μg/min
Development of DN above discrimination value	7/8	7/7	12/14
Development of DN below discrimination value	2/55	3/64	0/29
Urine sample	Overnight	24-hour	Short-term at hospital
Number of urine samples	≥1	≥3	≥3
Methods	RIA	Radial immune diffusion	RIA

[a] From Ref. 71.
[b] From Ref. 81.
[c] From Ref. 83.

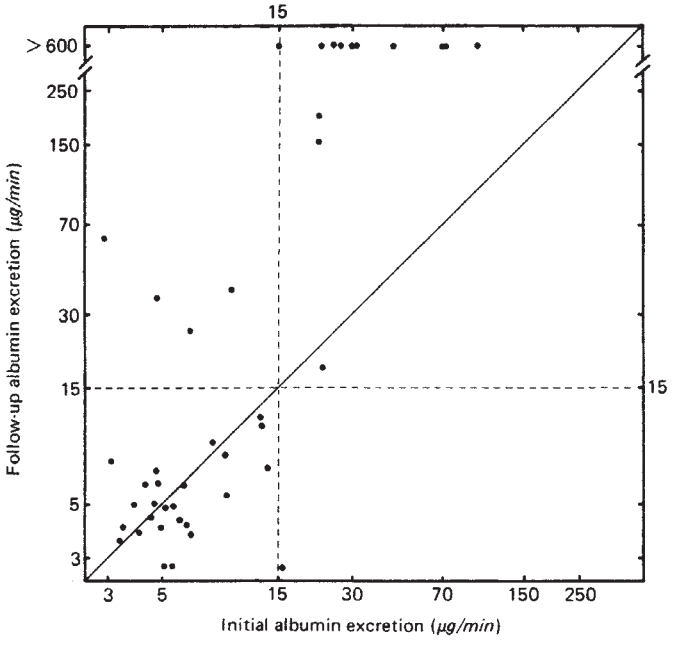

Fig. 1. Followup urinary albumin excretion rate plotted against initial albumin excretion rate in 43 male diabetics followed for 7 to 14 years [mean, 10.4 ± 3 (SD) years]. Mean age at diagnosis, 12 years; mean duration of diabetes at initial examination, 13 years.

in a study using 24-hour urine collections [71]. The differences in the discrimination values among these studies suggest that, when evaluating early nephropathy in insulin-dependent patients, one should obtain a baseline value with the patient in the supine or sitting position, preferably under supervised conditions. Nonetheless, as in Table 1, the differences in the discrimination values in the three studies do not materially affect the reliability of the test in predicting clinical diabetic nephropathy.

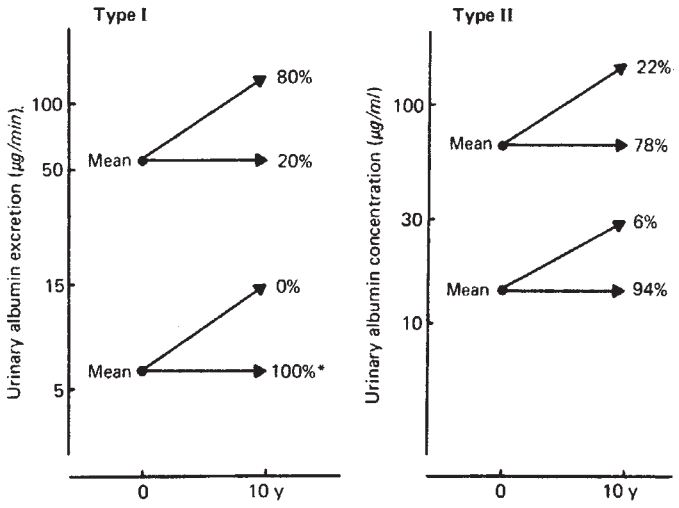

Fig. 2. Ten-year followup study showing development of clinical proteinuria (↗) and no clinical proteinuria (→) in patients with low or with elevated urinary albumin excretion rates or concentrations. A few patients developed microalbuminuria. Based on Refs. 82 and 83. Type I is insulin-dependent patients and Type II non-insulin-dependent patients.

Figure 2 summarizes our data on the predictive value of microalbuminuria for the development of clinical proteinuria in insulin- as well as non-insulin-dependent patients [82, 83]. The data indicate that the risk of clinical nephropathy at 10 years of followup is higher in young insulin-dependent patients with microalbuminuria (about 80%) than in elderly patients with microalbuminuria (about 22%). On the other hand, patients without microalbuminuria, whether young or old, have only a small risk of developing clinical proteinuria over the next decade.

The rate of progression of proteinuria in the early phases of diabetic renal disease has been incompletely evaluated [60, 69]. Evidence suggests that the rate of progression is slow, namely, a mean rise in UAE of approximately 20% per year [60]. Therefore, the microalbuminuria phase, that is, the stage of incipient diabetic nephropathy, is likely to last an average of approximately 8 to 10 years. In some diabetic patients, however, UAE progresses more rapidly, as fast as a 60% increase in albumin excretion per year, usually in association with poor blood pressure control. Also, I suspect that proteinuria progresses more rapidly in poorly controlled diabetic patients, for example, in noncompliant patients [3, 5], as in the first patient presented here. For obvious reasons, however, controlled studies are difficult to carry out. In the case of extraordinarily rapid progression of proteinuria, nondiabetic renal or systemic disease should be suspected, but poor control of diabetes as well as high blood pressure are also possibilities that should be borne in mind.

We used multiple regression analysis in young male patients with microalbuminuria to study the factors that influence (*1*) an increase in UAE, (*2*) the rate of fall in GFR, and (*3*) development of hypertension. The patients' age at diagnosis was less than 20 years. The initial duration of illness was 3 to 20 years, and the followup period was more than 7 years. We required the UAE to be less than 70 μg/min at entry. The UAE, GFR, and RPF were measured initially and at followup. All of the 31

Table 2. Clinical and renal function data in patients with incipient diabetic nephropathy[a]

	Initial[b]	At followup[b]
Age at diagnosis of diabetes (*years*)	14 ± 4.0 (5–20)	14 ± 4.0 (5–20)
Systolic blood pressure (*mm Hg*)	124 ± 8.9 (110–150)	127 ± 12.2 (110–160)
Diastolic blood pressure (*mm Hg*)	81 ± 7.7 (65–95)	86 ± 8.9 (70–105)
Mean blood pressure (*mm Hg*)	95 ± 7.2 (82–113)	100 ± 9.5 (87–123)
Plasma glucose (*mmol/liter*)	10 ± 3.9 (4–18)	11 ± 5.5 (4–21)
GFR (*ml/min*)	140 ± 12.4 (117–168)	126 ± 25.0 (13–157)
RPF (*ml/min*)	580 ± 73 (446–746)	512 ± 118.5 (75–772)
UAE (*μg/min*)[c]	11 ± 8.6 (2.3–28.7)	253 ± 673.2 (1.2–2730)

[a] Multiple regression analysis was used to identify the correlates of follow-up UAE, rate of fall in GFR, and elevated blood pressure.
[b] Mean ± SD and ranges shown (n = 31).
[c] Log-transformed in calculations.

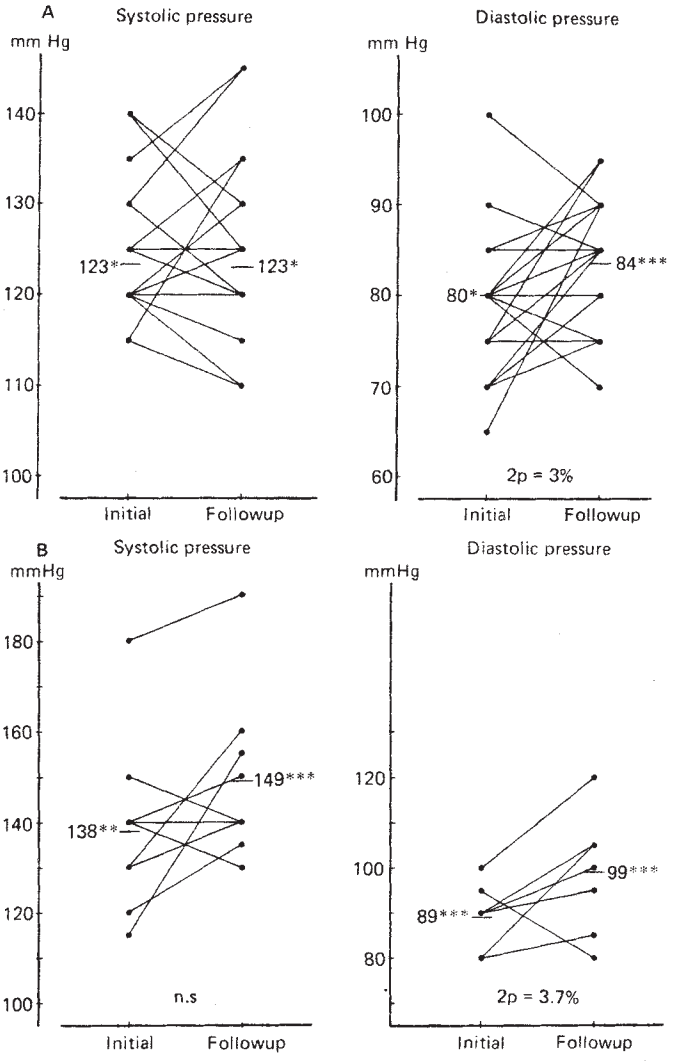

Fig. 3. **A** Systolic and diastolic blood pressures in young, male, insulin-dependent diabetics not showing progression in UAE. Difference from controls (115 ± 9.8/73 ± 8.0, n = 18), *2 $p < 2.5\%$, ***2$p < 0.01\%$. **B** Systolic and diastolic blood pressures in young, male, insulin-dependent diabetics showing progression in UAE. For both Figs. 3A and 3B, mean age at diagnosis, 12 years; diabetes duration at initial evaluation, 13 years; mean followup, 10.4 years. Difference from controls (115 ± 9.8/73 ± 8.0, n = 18), **2$p < 0.1\%$, ***2$p < 0.01\%$.

patients fulfilling these criteria accepted reevaluation, which took place at a mean of 11.5 years after the initial examination. Two patients with diabetes for 3 years were excluded from the study because in both instances an initially high UAE rapidly returned to normal [59].

Clinical data and results of renal function tests in these 31 patients both at entry and at followup are shown in Table 2. We examined the relative roles of all parameters from the initial evaluation (listed in Table 2) in determining the change in UAE (log-transformed), GFR, and mean blood pressure. Initial high UAE and initial high GFR appeared to be the major correlates of followup UAE. With respect to the rate of fall in GFR, if initial GFR was included in the analysis, the initial GFR was shown to be the dominant factor; interestingly, the higher the initial GFR, the poorer the late prognosis. If initial GFR was excluded, however, the initial UAE was the only determinant, without any significant contribution from other variables. Finally, initial high UAE was the major determinant of subsequent elevated mean blood pressure.

Although microalbuminuric patients who progress to overt diabetic nephropathy as a group tend to have higher initial blood pressure levels than do those who do not progress (Figs. 3A, 3B), the predictive power of elevated blood pressure is much less pronounced in comparison to early increases in UAE and GFR. Indeed, our analysis revealed that the latter two parameters are the most powerful factors with respect to predicting progression to overt diabetic nephropathy, whether focusing on final UAE or on the rate of fall in GFR.

The observation that an elevation of UAE, an increase in glomerular filtration, and an early rise in blood pressure coexist in incipient diabetic nephropathy might prove to be extremely important from the therapeutic standpoint.

Redefinition of diabetic nephropathy

The observation that microalbuminuria is a predictor of subsequent clinical diabetic nephropathy and the recent description of an early hyperfunction-hypertrophy stage of this disease [119] underline the need for redefinition of diabetic nephropathy. We have proposed a new scheme that encompasses various developmental stages of diabetic nephropathy [119]. These stages as well as their main characteristics are outlined in Table 3. *Stage I*, present at the time of diagnosis of insulin-dependent diabetes, is characterized by glomerular hyperfunction and hypertrophy. Certain features of this stage also can accompany diabetes of longer duration, when metabolic control is imperfect. *Stage II*, the "silent" stage, is characterized by the development of renal lesions (predominantly in the glomerulus), but albumin excretion is normal. *Stage III*, incipient diabetic nephropathy, is characterized by microalbuminuria, and causes a high risk of development of overt diabetic nephropathy. I will elaborate on this stage in a moment. *Stage IV*, overt (clinical) diabetic nephropathy, is characterized by proteinuria, hypertension, and a subsequent fall in GFR. *Stage V* corresponds to end-stage renal failure with uremia.

Table 3. Stages in diabetic nephropathy (DN)

Stage	Designation	Main characteristics	Main structural changes	GFR (*ml/min*)	Albumin excretion (*UAE*)	Blood pressure	Suggested main pathophysiologic change
Stage I	Hyperfunction and hypertrophy stage[a]	Large kidneys and glomerular hyperfiltration	Glomerular hypertrophy; normal basement membrane and mesangium	≈150	May be increased	N (May fall initially during insulin treatment)	Glomerular volume expansion and increased intraglomerular pressure
Stage II							
In short-term diabetes (2–15 years)	"Silent" stage with normal UAE but structural lesion present	Normal UAE	Increasing basal membrane (bm) thickness and mesangial expansion	With or without hyperfiltration[b]	N (Often increased in stress situations)	N	Changes as indicated above but quite variable (dependent on metabolic control?)
In long-term diabetes			No or few studies	With or without hyperfiltration[b]	N (Often increased in stress situations)	N or slightly elevated	In addition increased synthesis of bm and bm-like-material
Stage III							
Early	Incipient DN	Persistently elevated UAE	Severity probably in between II and IV	≈160	20–70 μg/min	Often elevated compared to healthy subjects; also blood pressure elevated during exercise	Glomerular closure probably starts in this stage
Late				≈130	70–200 μg/min		In some patients high intraglomerular pressure
Stage IV							
Early		Clinical proteinuria or UAE >200 μg/min <200 μg/min	Increasing rate of glomerular closure	≈130–70	>200 μg/min	Often frank hypertension	High rate of glomerular closure and advancing mesangial expansion
Intermediate	Overt DN	<200 μg/min	Hypertrophy of remaining glomeruli (as in III)	≈70–30		Hypertension almost ubiquitous	
Advanced				≈30–10		Hypertension almost ubiquitous	Hyperfiltration in remaining glomeruli (deleterious)
Stage V	Uremia	End-stage renal failure	Generalized glomerular closure	0–10	Decreasing	High but often controlled by dialysis treatment	Advanced lesions and glomerular closure

[a] Changes present probably in all stages when control imperfect.
[b] Marker of future nephropathy (if GFR > 150 ml/min).

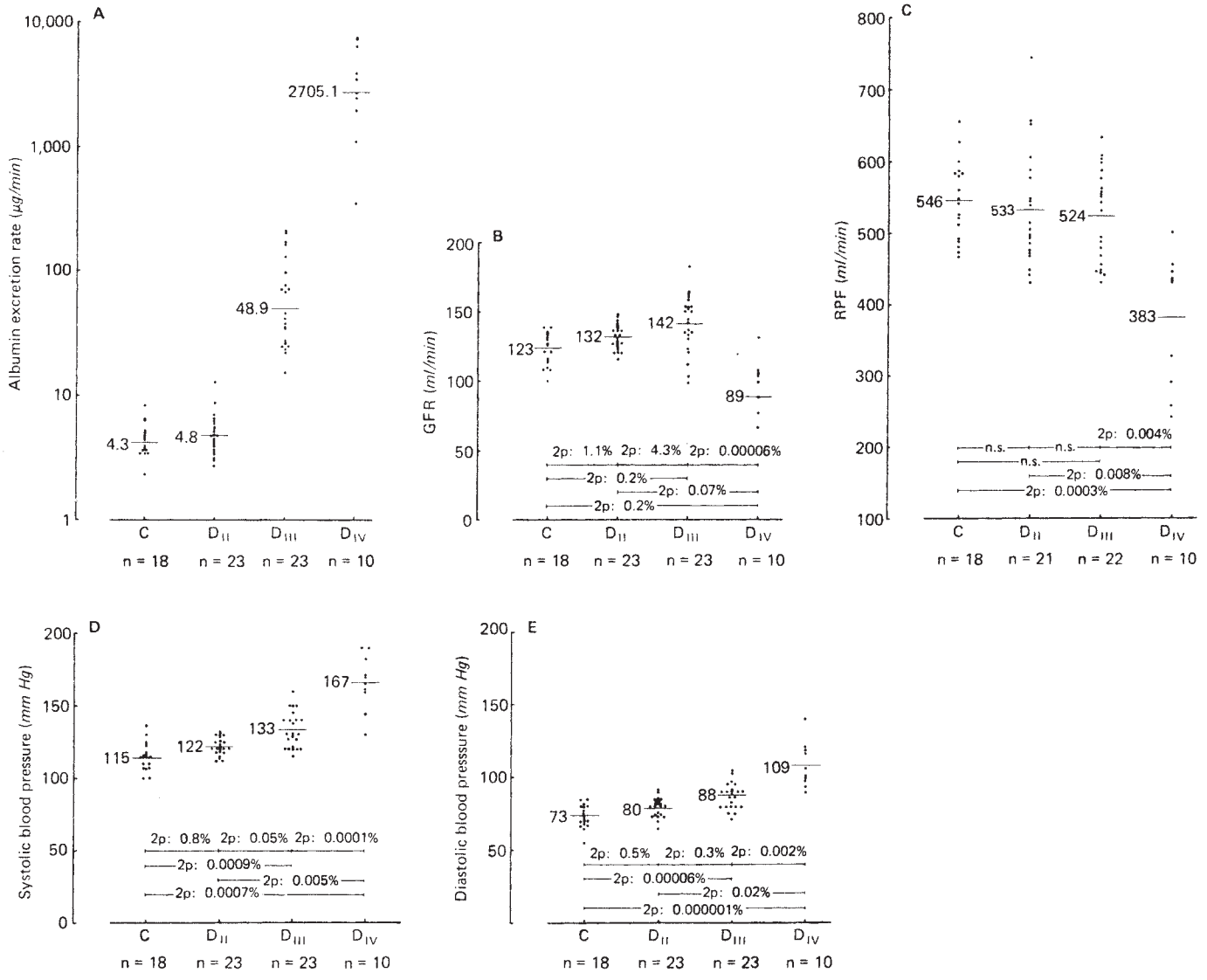

Fig. 4. **A** UAE in the various stages of diabetic nephropathy. C, controls; D_{II}, stage of normal urinary albumin excretion rate; D_{III}, incipient diabetic nephropathy; D_{IV}, overt diabetic nephropathy. **B** GFR in the various stages of diabetic nephropathy. Abbreviations are as in Fig. 4A. **C** RPF in the various stages of diabetic nephropathy. Abbreviations are as in Fig. 4A. **D** Systolic blood pressures in the various stages of diabetic nephropathy. Abbreviations are as in Fig. 4A. **E** Diastolic blood pressures in the various stages of diabetic nephropathy. Abbreviations are as in Fig. 4A.

Microalbuminuria and incipient diabetic nephropathy

I am using recently accepted definitions in assessing patients with early diabetic nephropathy [157]. *Microalbuminuria* is considered present when the UAE is greater than 20 μg/min and less than or equal to 200 μg/min. This level of UAE corresponds to approximately 30 to 300 mg per 24 hours. *Incipient diabetic nephropathy* (Stage III) is considered present when microalbuminuria is found in 2 of 3 urine samples collected consecutively, preferably within a period of 6 months. If more than 3 samples are available, the mean UAE should lie within the microalbuminuric range of 20 to 200 μg/min. Urine should be sterile and obtained in the non-ketotic state. The best possible control of diabetes should be achieved prior to determining the UAE. Other causes of increased UAE should be excluded, especially if diabetes has been present for less than 6 years. *Overt diabetic nephropathy* (Stage IV) is considered present when the UAE is greater than 200 μg/min in at least 2 of 3 urine samples collected within 1 to 6 months, or when the mean value of the UAE of multiple collections exceeds 200 μg/min. As is the case for incipient diabetic nephropathy, urine samples should be sterile and obtained in the non-ketotic state; other causes of increased UAE should be excluded. According to these definitions, the dipstick test for urine protein should not be applied when classifying diabetic renal disease.

Several abnormalities have been documented in patients with persistent microalbuminuria, that is, incipient diabetic nephropathy (Stage III):

(*1*) During the early stages of incipient diabetic nephropathy (UAE of 20 to 70 μg/min), the GFR can be elevated above

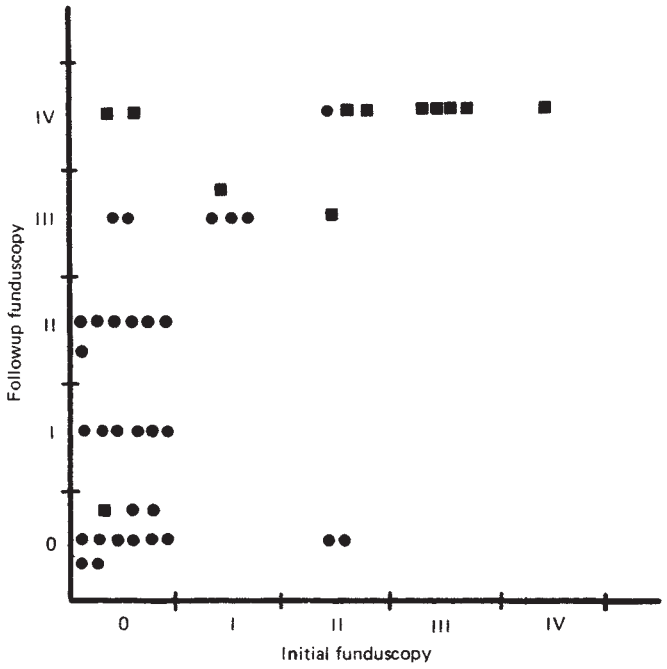

Fig. 5. Followup funduscopy plotted against initial funduscopy in patients with insulin-dependent diabetes (10.4 year followup), with and without initial microalbuminuria. ●, Initial UAE <15 μg/min or no progression in elevated albumin excretion (2 patients with albumin excretion rate at 15.9 and 23.3 μg/min did not have increased albumin excretion at followup). ■, Initial UAE ≥15 μg/min and increasing albumin excretion.

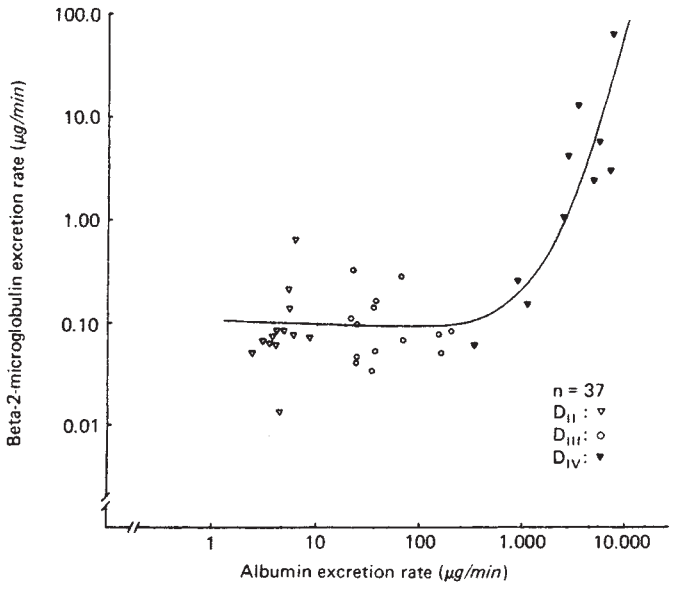

Fig. 6. Beta-2-microglobulin excretion plotted against urinary albumin excretion rate in the various stages of diabetic nephropathy. D_{II}, patients with normal urinary albumin excretion rate; D_{III}, incipient diabetic nephropathy; D_{IV}, overt diabetic nephropathy.

normal. This hyperfiltration is not accompanied by corresponding changes in RPF. As microalbuminuria progresses, GFR returns to the normal range [83]. Finally, patients who enter the stage of clinical proteinuria exhibit gradual decreases in GFR and RPF. Figures 4A, 4B, and 4C depict changes in UAE, GFR, and RPF in the various stages of diabetic nephropathy.

(2) Several studies have recognized that elevated blood pressure is an early accompaniment of incipient diabetic nephropathy; the magnitude of the elevation is in the range of 10% to 15% above values in control subjects [57–60, 71, 83]. In a recent study of microalbuminuric patients, mean arterial blood pressure increased by a mean of 4.5 mm Hg during 2 years of followup [69]. Figures 4D and 4E depict changes in systolic and diastolic blood pressure in the various stages of diabetic nephropathy.

(3) Diabetic retinopathy is more advanced in patients with microalbuminuria than in patients with silent, Stage II disease [72]. Importantly, patients at risk of proliferative diabetic retinopathy can be identified on the basis of microalbuminuria [73, 74] (Fig. 5).

(4) Transcapillary escape rate of albumin is increased in incipient diabetic nephropathy [69].

Pathogenesis and morphologic correlates of incipient diabetic nephropathy

On the basis of these and other observations, it is likely that a combination of hemodynamic [120, 125, 158–160] and biochemical changes [161, 162] characteristically found in diabetic patients given standard insulin therapy are responsible for the pathogenesis of microalbuminuria and diabetic nephropathy. It is possible that the mechanisms responsible for the transient microalbuminuria associated with the poor metabolic control characteristically seen at the time of first presentation (rapidly reversible microalbuminuria) [26, 61] are different from those leading to persistent microalbuminuria and incipient diabetic nephropathy, typically seen after 7 to 15 years of diabetes. I believe, however, that both transient and persistent microalbuminuria have some pathogenetic mechanisms in common. According to my hypothesis, glomerular hypertension is involved both in transient microalbuminuria and hyperfiltration and in the long-term disruption of the structural integrity of glomeruli. In addition, the altered metabolism of the diabetic state probably produces increased basement membrane thickening and mesangial expansion, as well as changes in the structural and functional characteristics of the basement membrane. I further believe that the structural changes are at least partially independent of the changes in intraglomerular blood pressure [1, 75, 127]. That the persistent microalbuminuria of incipient diabetic nephropathy is of glomerular origin has been well documented (Fig. 6); the excretion of beta-2–microglobulin, a marker of tubular damage, does not increase until UAE rises to approximately 1000 μg/min.

In all probability, systemic blood pressure rises only when structural glomerular changes become prominent. Even a slight elevation in blood pressure appears to be an accelerating factor in the course of diabetic nephropathy [59, 69]. In fact, blood pressure generally is normal in diabetics with minor degrees of microalbuminuria but tends to be elevated in diabetics with more pronounced microalbuminuria [58, 83]. The coexistence of increased systemic blood pressure, diabetic retinopathy [72], and an enhanced transcapillary escape rate of albumin [69, 70]

Table 4. Causes of microalbuminuria in insulin-dependent diabetes

Causes	Approximate level of albumin excretion rate[a] (μg/min)
Newly diagnosed diabetes	≈5–60
Poor metabolic regulation	≈5–60
Physical exercise	≈5–60
Essential hypertension in diabetes (seldom)	≈5–20
Urinary tract infection	Moderate increase
Non-diabetic renal or systemic disease	Variable
Early phases of diabetic nephropathy (incipient nephropathy	20–200

[a] Baseline values, except for physical exercise

in patients with incipient diabetic nephropathy argues for the existence of generalized vascular disease early in the course of diabetes. This view is supported by the finding of excess mortality even in microalbuminuric patients with non-insulin-dependent diabetes [82, 84].

Only a few studies have examined the structural correlates of incipient diabetic nephropathy. Evidence suggests that the morphologic changes are similar to those occurring in overt diabetic nephropathy but are less pronounced [75]. However, the histologic findings of patients with incipient diabetic nephropathy have not been compared systematically with those of a comparable group of diabetic patients who do not have persistent microalbuminuria.

In a cross-sectional study of patients with variable degrees of diabetic renal involvement, Mauer et al found an association between the percentage of fibrotic glomeruli and the level of microalbuminuria [76]. Fibrotic or occluded glomeruli are not likely to leak proteins into the urine, but the number of fibrotic glomeruli probably correlate with the number of damaged glomeruli. The percentage of glomeruli that are in the process of disruption and closure need not be high, and I hypothesize that these glomeruli are responsible for generating the microalbuminuria. In addition, segmental changes in individual glomeruli, that is, localized dilation of glomerular loops, might contribute to the proteinuria. Thus, the morphologic correlate of microalbuminuria might be both focal and segmental in nature. Whether disturbances in charge in the basement membrane play a role remains to be proven [162, 163].

Differential diagnosis of microalbuminuria

Before concluding that a diabetic patient has the microalbuminuria associated with incipient diabetic nephropathy, other causes of microalbuminuria must be excluded. Certain transitory and permanent forms are listed in Table 4.

Poor metabolic control of either a profound or long-term nature in diabetic patients can result in transitory microalbuminuria [26, 61, 62, 106–108]. Examples include ketoacidosis [61] and newly diagnosed diabetes [26]. In both instances, institution of metabolic control readily reverses the microalbuminuria. A correlation between UAE and plasma glucose concentration is not present in patients under conventional insulin treatment of diabetes with blood glucose levels ranging from about 50 to 360 mg/dl [70]. Some, but not all, studies have described a weak correlation between UAE and metabolic control, for example, as measured by glycosylated hemoglobin [58, 71, 72, 101–106]. Recent observations from our laboratory have confirmed that acute administration of glucose in diabetic patients does not increase UAE significantly [40]. As I mentioned before, protein-rich meals also do not change albumin excretion [154].

Moderate physical exercise typically produces a higher level of UAE in diabetics than in nondiabetics [45–56]. Some evidence suggests that the level of albumin excretion during exercise is related to the quality of metabolic control; for example, exercise-induced microalbuminuria is more pronounced in newly diagnosed patients, and this abnormality is reversed by insulin treatment [54]. Exercise-induced microalbuminuria generally is not well correlated with the duration of disease and does not predict clinical nephropathy.

Superimposition of essential hypertension on diabetes can result in microalbuminuria. However, in non-diabetic patients with essential hypertension, much higher blood pressure levels are required to produce levels of microalbuminuria characteristic of those in patients with incipient diabetic nephropathy [55, 133]. Borderline increases in UAE were found in elderly, non-insulin-dependent diabetics who had laboratory evidence of urinary tract infection [88]. Finally, non-diabetic renal disease or systemic diseases, such as congestive heart failure, should be excluded in evaluating a diabetic patient with microalbuminuria. These conditions are rare in young insulin-dependent patients, however.

In the absence of the conditions I have described, only a few patients with diabetes and long-term increased urinary albumin excretion show spontaneous reversal; when it occurs, it is most often seen in patients whose microalbuminuria falls into the lower range (UAE less than 30 μg/min) and is associated with a low blood pressure.

Proposed clinical management and possible influence of intensified treatment

In my opinion, insulin-dependent diabetic patients require repeated careful physical and laboratory examination for early signs of vascular and neurologic complications. At a minimum, I propose that the physician should measure the UAE with the patient at rest, perform ophthalmoscopy, determine the blood pressure, measure the vibration threshold, take a cardiovascular history, and examine and evaluate the patient's legs. A thorough evaluation, including measurement of UAE, should be performed early in the course of the patient's diabetes and should minimally be repeated every 3 years for the first 9 years and at yearly intervals thereafter (Table 5). Some diabetologists may advocate more frequent examination, at least of some of the parameters. Patients should be informed about the nature of complications occurring with diabetes during the early examination, before such complications become apparent. In fact, patient education should be one of the major reasons for early examination.

I believe that management for patients with incipient diabetic nephropathy should encompass the following:

Table 5. Followup in diabetic patients

Examinations
Measurements for micro- or macroalbuminuria
Eye examination including ophthalmoscopy
Screening for peripheral neuropathy
Vibration threshold examination (on Biothesiometer)
Clinical examination
Resting blood pressure
Clinical history and examinations regarding cardiovascular disease
Foot examination
Multiple measurements of blood glucose and HbA_{1c}
Time course[a]
Without symptoms, signs, or laboratory changes
At admission
Every third year during the first 9 years of diabetes
Blood pressure measurements more often
Annually thereafter
With symptoms, and/or signs, and/or laboratory changes (e.g., high UAE)
Immediate examination
Time course to be decided in the individual patient (examination every 3–6 months)
Metabolic control and visit at the clinic every 1–3 months

[a] Some clinicians prefer yearly examination from onset of diabetes

(*1*) Urinary albumin excretion should be monitored at frequent intervals, about every 3 to 6 months in patients with elevated UAE, otherwise as I have already indicated. Careful ophthalmoscopic evaluation is important. Patients should be informed that an elevated UAE indicates a major risk for the development of overt diabetic nephropathy. They should be advised to cooperate in achieving the best possible control of their diabetes and to adhere to close followup. In my experience, diabetic patients usually are highly concerned about long-term complications and take an active part in the treatment of their disease, including home monitoring of blood glucose, self monitoring of blood pressure, regular followup, and frequent ophthalmoscopic evaluations. Some authors recommend a renal biopsy in the evaluation of renal complications [77].

(*2*) Optimal conventional insulin treatment and self monitoring of blood glucose should be employed to achieve the best possible control of diabetes. Multiple injection therapy by new devices such as the "Insulin-Pen" should be considered [164]. Optimal general medical care, including treatment of urinary tract infection, clearly is important. Evaluation for peripheral and autonomic neuropathy should be carried out, specifically with regard to diabetic cystopathy.

A recent randomized study examined the influence of pump insulin therapy versus conventional insulin treatment on the microalbuminuria of incipient diabetic nephropathy. No significant differences between the two regimens could be found after 12 months of followup [66], a finding comparable to that in overt diabetic nephropathy [165]. Long-term studies over several years will be required and indeed the 2-year followup of this study [69] is much more optimistic, since microalbuminuria was arrested or reversed in the pump group. Progression was seen in the conventionally treated control patients. Therefore it is likely that years of poor metabolic control lead to significantly accelerated progression in incipient diabetic nephropathy and that progression can be reversed by good control. Notably, poor metabolic control, with elevated HbA_{1c} values, has been identified as a risk factor in overt diabetic nephropathy [166].

In the Kroc study [65], which had an 8-month followup period, patients with microalbuminuria who were treated with pump insulin therapy showed a greater tendency toward a reduction in UAE than did patients treated conventionally [65]. An important criticism of this study, however, is that the patients were not randomized initially according to careful estimates of UAE levels; further, a number of patients appeared to be classified as having microalbuminuria on the basis of a single initial measurement of UAE [65].

(*3*) Most authors currently would agree that blood pressure should be monitored closely in young diabetics at the incipient stage, and if the level exceeds 140/90–95 mm Hg, antihypertensive treatment should be instituted [59, 111]. Cardioselective beta blockers and, if needed, diuretics are likely to be effective [167, 168]. Resting blood pressure should be reduced to less than 140/90 mm Hg.

Recent longitudinal studies in a small group of patients with incipient diabetic nephropathy have shown that the progression of disease, as measured by the yearly change in UAE, can be reversed by antihypertensive treatment [111]. Six young, male microalbuminuric patients were followed for a mean of 5 years prior to treatment and for a mean of 3 years following institution of antihypertensive therapy with cardioselective beta blockers and, subsequently, diuretic therapy. Blood pressure was reduced by approximately 10% from a baseline of 135/93 mm Hg to 125/84 mm Hg. The yearly increase in UAE averaged 18% before treatment and converted to a mean yearly decrease of 21% following institution of therapy. The GFR was supernormal at baseline (mean, 146 ml/min) and did not change significantly during the treatment period [111].

These encouraging results require further randomized studies that include a parallel placebo group. Nonetheless, the results of this trial are clearly in line with earlier studies on the effect of antihypertensive treatment in overt diabetic nephropathy [166, 167]. Because the rate of decline in GFR was reduced by 60%, these studies suggest a delay in the development of uremia in these patients. It is quite possible that an even greater benefit might be realized if treatment were initiated earlier, that is, in patients with incipient diabetic nephropathy or with early overt nephropathy.

Finally, additional treatment modalities that deserve consideration for vigorous testing in incipient diabetic nephropathy include low-protein diet regimens, agents that specifically may reduce intraglomerular pressure (also in stress situations) [169–172] and, possibly, therapy with thromboxane synthetase inhibitors [109].

Both patients presented today had microalbuminuria during their initial presentation. Both patients experienced progression of their nephropathy. Progression was rapid in the first patient and occurred during a period of time when metabolic control was poor. Disease in the second patient progressed at a slower rate. Both patients improved following institution of antihypertensive treatment.

Conclusion

Studies over the last few years have identified incipient diabetic nephropathy as a precursor of overt diabetic nephropathy. The incipient stage of the disease is characterized by

microalbuminuria and, early in the course, a supernormal GFR; subsequently, GFR tends to decline before clinical proteinuria supervenes. Blood pressure starts to rise in the incipient stage. Early renal changes also predict a high risk for subsequent proliferative retinopathy. Data on insulin pump treatment have most recently been encouraging; microalbuminuria can be arrested or reversed with this new form of therapy. New longitudinal studies show that antihypertensive treatment can reverse the increase in urinary albumin excretion. Randomized controlled trials of this and other potential therapeutic modalities deserve consideration.

Questions and answers

DR. MICHAEL W. STEFFES (*Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota*): Currently there is no clear consensus on the definition of incipient diabetic nephropathy. This probably reflects the fact that presently we do not understand the disease as well as we would like. I would like to ask Dr. Myers to address the definition of incipient diabetic nephropathy.

DR. BRYAN D. MYERS (*Division of Nephrology, Stanford University School of Medicine, Stanford, California*): I think there is a need to distinguish a transient phenomenon characterized by a functional increase in the albumin excretion rate, and a much more sinister entity, which is probably the first stage of overt diabetic glomerulopathy. The notion of functional microalbuminuria versus incipient diabetic glomerulopathy has been a real source of confusion to many of us. It seems to me that there is a consensus that an albumin excretion rate of 200 or 300 μg/min is clearly pathologic and should not be included in the definition of functional microalbuminuria. Several pieces of evidence suggest that when albuminuria reaches about 70 μg/min, there is a difference in the physiologic behavior of the kidney. An albumin infusion will predictably increase albuminuria when the infusion rate is 70 μg/min or more. Dr. Viberti has shown that the selectivity index changes at exactly this level of microproteinuria, meaning that IgG, a large protein, is now starting to leak into the urine. I propose that there is now a basis for considering microalbuminuria as potentially a transient phenomenon that we can dispel with treatment, and which does not yet signify an established intrinsic disease of the glomerulus. Perhaps we could agree to set some level of albumin excretion, probably less than 30 μg/min, below which this is likely to be true. Conversely, we could set a new, lower boundary for the early stage of diabetic glomerulopathy, say 60 or 70 μg/min. Values above this level are likely to signify that the process is no longer a reversible one.

DR. MOGENSEN: Patients with albumin excretion rates of more than 70 μg/min are clearly at high risk. Also, patients with albumin excretion at or above that level already show a decline in GFR. It seems that the decline in GFR starts at an albumin excretion of about 50 to 70 μg/min; therefore, patients excreting more than 70 μg/min are clearly high-risk patients. On the other hand, patients with UAEs ranging from 20 to 70 μg/min also are clearly at risk, but their risk is not as high as that of patients with UAEs exceeding 70 μg/min; approximately 80% of the former group (21–70 μg/min) will develop nephropathy later, and it is not surprising that there is a grey area in the lower range of UAE. We also have to consider that the albumin excretion rate can, in some instances, be increased by different mechanisms, for example, in the presence of poor metabolic control or during physical exercise. Such elevations of albumin excretion are transient and are much less likely to predict overt nephropathy. In conclusion, it seems appropriate to deal with high-risk and low-risk patients, but still I would think that the range of UAE I have mentioned for incipient diabetic nephropathy is most relevant, namely 20 to 200 μg/min in patients studied in the resting position and not exposed to stress.

DR. GIANCARLO VIBERTI: (*Unit for Metabolic Medicine, Guy's Hospital Medical School, London, England*): We have argued against any definition of incipient diabetic nephropathy at all, and we have given some reasons for this view [32]. The situation is somewhat reminiscent to me of what formerly was called "borderline diabetes," and what is now called "impaired glucose tolerance." In those days we thought that if one had an impaired glucose tolerance, one was an "incipient diabetic," but this proved an incorrect assumption. Approximately 30% of patients with impaired glucose tolerance become diabetic, but an equal proportion regresses to the mean, and their glucose tolerance returns towards normal. We have to learn much more than what we already know about the phenomenon of supernormal albumin excretion rate and its natural evolution. Our knowledge concerning the progression or regression of this condition, its quantitative aspects, its relation to blood glucose control, and its responsiveness to correction of hyperglycemia is rather limited. I don't think the time is ripe to set new levels of albumin excretion rate to distinguish between the presence or absence of disease. We run the risk of repeating the same mistake we made years ago by setting a level of protein excretion of 0.5 g/24 hours as a definition of clinical nephropathy. We have discovered now that the disease is in fact part of a continuum, not a stepwise phenomenon. I support the recommendation of not using any new classification such as persistent microalbuminuria or incipient nephropathy for the time being, but simply of limiting ourselves to calling it supernormal levels of albumin excretion. The significance of this phenomenon will be much clearer in a few years when natural history studies have been carried out.

DR. MOGENSEN: There still is a marked difference with regard to the expected development of subsequent disease in microalbuminuric patients as compared with patients with glucose intolerance. In the latter, the risk is rather low, but in patients with persistently increased albumin excretion rates, the risk is much higher. I also have said that it might not be necessary to use any kind of label; if you can use the raw figure, 20, 70, or 100 μg/min for an individual patient, you will be able to identify the approximate level of risk for subsequent overt nephropathy [128]. Still, it might be very useful to use a label if you are going to communicate this phenomenon to the general medical community. Personally, I think it is necessary to have a label, and that label could be patients "at risk," or those with "persistent microalbuminuria," "early diabetic nephropathy," or "incipient diabetic nephropathy." All these labels are appropriate, at least to my mind.

DR. ELI A. FRIEDMAN (*Division of Nephrology, Downstate Medical Center, Brooklyn, New York*): Dr. Mogensen, your presentation strongly suggests two subpopulations of diabetic patients who can be distinguished on the basis of albumin excretion. Furthermore, your data indicate that the subset of diabetic patients with microalbuminuria is at greater risk of

developing renal disease and renal insufficiency than is the group without microalbuminuria. It follows, therefore, that intensive medical control of diabetes should be directed to those with microalbuminuria. By contrast, if I understood Dr. Viberti correctly, he professes that in diabetes there is a continuum of protein excretion, and that your postulate of two subpopulations (microalbuminuric and non-microalbuminuric) might or might not be easily separable. How shall we reconcile these divergent views? Should we identify the microalbuminuric patients because they are to be intensively treated, whereas patients lacking microalbuminuria can be routinely treated?

DR. MOGENSEN: First, I believe that the albumin excretion rate in diabetic patients is not a clear-cut continuum in diabetic populations. Some patients are normal, some clearly abnormal. In addition, microalbuminuria or increased albumin excretion is only one abnormality in these patients. As I indicated, these patients have a number of associated abnormalities. Patients with persistent microalbuminuria have increases in blood pressure, and in some studies they show glomerular hyperfiltration; these patients also have increased transcapillary escape of albumin. All these findings suggest that these patients have more pronounced vascular abnormalities in general. In addition, they have more advanced retinopathy. Indeed, patients with proliferative retinopathy can be identified early using these methods. You are perfectly right that these patients need intensive followup and treatment.

DR. STEFFES: Dr. Mogensen, am I correct that you have data demonstrating a continuum of albuminuria in patients you followed for several years?

DR. MOGENSEN: Yes, when followed longitudinally, but I must stress that patients can have completely normal urinary albumin excretion rates despite a very long duration of diabetes.

DR. VIBERTI: It is important to realize that when we talk about a continuum in the progression from moderate to severe elevation of the urinary excretion of albumin, we are referring to the patients who develop the disease, and not to the 60% who do not develop the disease. In those who develop the disease, the available evidence strongly suggests a continuum in the rise of urinary albumin excretion. Microalbuminuria, or rather, certain supernormal levels of albumin excretion rate, identify patients at risk, and these should be the object of more intensive treatment.

DR. TORSTEN DECKERT (*Niels Steensens Hospital, Gentofte, Denmark*): Dr. Mogensen, I think it's important that we recall your distinction between microalbuminuria on the one hand, and incipient nephropathy on the other. Whereas microalbuminuria is only an expression of the supernormal albumin excretion, which can be influenced by several factors such as exercise, blood pressure, and degree of metabolic regulation, incipient nephropathy means persistent microalbuminuria. I think we are justified in using the expression "incipient nephropathy" because several other abnormalities are linked to this abnormality. Dr. Mogensen has shown that it is linked to a sinister renal prognosis as well as to progression of retinopathy. Research has shown that patients with incipient nephropathy as a group have significantly increased mean blood pressures [71, 83]. We also have shown that these patients have an increased transcapillary albumin escape rate and decreased plasma albumin concentration [173]. Thus, not only are renal abnormalities connected with this state, but also extrarenal abnormalities. I therefore think we are justified in having a special expression for patients with persistent microalbuminuria.

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center Hospitals, Boston, Massachusetts*): Dr. Mogensen, what therapeutic recommendations do you suggest for patients with microalbuminuria, and what is the evidence that these maneuvers will alter the course of the disease?

DR. MOGENSEN: Patients with persistent microalbuminuria should be offered the best possible conventional treatment or even pump insulin treatment [69]. As I have indicated, there is now evidence that treatment with insulin pumps during a 2-year period can alter the course [69]. We should recognize, however, that these patients were not too badly controlled before entering the trial. We also should remember that these patients should not be subjected to any antihypertensive therapy unless they have a certain degree of elevated blood pressure. There is no firm consensus regarding the level, but most authors agree that a young diabetic patient with persistent microalbuminuria and a blood pressure of greater than 145/95 mm Hg, or even greater than 140/90 mm Hg should be given antihypertensive treatment.

DR. MYERS: Is there a consensus among the people here about a lower level of albumin excretion rate that is likely to be associated with structural glomerular disease? If, for example, that level is around 70 μg/min, could one not make a case for doing a biopsy and making careful morphometric measurements? If we could confirm a functional-structural association at the earliest stage of the disease, we could explore ways of treating the entity at this early stage in the hope of preventing damage.

DR. FRIEDMAN: Clinicians frequently are compelled to treat patients on the basis of fragmentary and undigested evidence. In this regard, when you were characterizing therapeutic maneuvers appropriate to the management of diabetic nephropathy, you omitted three that I would like to hear your specific comments about. The first is a low-protein diet as advocated by Giordano for anyone in jeopardy of developing progressive renal insufficiency [174]. The second is a reduction in blood pressure below current conventional "normal" levels, perhaps to 110/70 mm Hg, not just the upper limit of normal. The third is the lesson taught 40 years ago by Kempner, who advocated an extremely sodium-restricted rice diet. He was the first clinician of whom I am aware to show that the clinical expression of advanced diabetic nephropathy could be arrested, and in some patients even reversed, by a very low-sodium diet. What is rational in 1986 as a treatment strategy that must be utilized before prospective controlled studies are completed, and before we find out whether microalbuminuria is really predictive? How do we handle today's patient?

DR. MOGENSEN: I must repeat that whereas microalbuminuria is not a perfect predictor, it is an excellent one. What should we do with the patients? Should we put them on a low-protein diet? I doubt that we should. There is some evidence that by doing that you can reduce the GFR from high values to somewhat lower values, but still we do not know the long-term effects of such maneuvers, nor do we know whether patients can adhere to such diets. Future trials are clearly important. Regarding antihypertensive treatment, we suggest

that only if the blood pressure exceeds 145/95 or 140/90 mm Hg should the patient be treated. Regarding a low-sodium rice diet, it remains an unexplored issue in diabetes. To my knowledge, there are no firm indications that it alters the course.

DR. OLE ORTVED ANDERSEN (*Hillerod Central Hospital, Denmark*): There is another problem in the definition of "incipient nephropathy." If we arrive at a definition of incipient nephropathy that means that microalbuminuria is a risk factor, we must be aware that this may be of significance for the patients, their employment, insurability, and other factors in their social life. If you establish such a definition, you must be sure that the methods for detection are routine.

DR. MOGENSEN: Measurement of the urinary albumin excretion rate in low concentration should be performed in clinical laboratories. It is a rather easy method.

DR. S. MICHAEL MAUER (*Division of Pediatric Nephrology, University of Minnesota Medical School, Minneapolis, Minnesota*): I wish to clarify what I hope will not be a confusing point. When we examined patients with microalbuminuria at a certain time in their course, we were unable to find any specific relationship between renal function and structure. However, progressive structural renal injury is an absolute prerequisite for the ultimate deterioration of renal function. The question therefore is clear: Are patients undergoing change in structure over time that indicates the ultimate loss of renal function? Dr. Østerby's findings and our findings are converging on this. Ultimately, in the glomerulus, the filtration surface becomes altered in a way that leads to deterioration in GFR and ultimately to uremia. If these lesions don't develop, uremia doesn't occur. The problem we are trying to focus on is how to prevent those lesions from developing. But only investigations into renal structure will yield an answer to our question.

DR. RUTH ØSTERBY (*Stereologic and Electron Microscopic Laboratory for Diabetes Research, University Institute of Pathology, Aarhus, Denmark*): I couldn't agree more with what Dr. Mauer has said. We looked at structural parameters in a group of diabetic patients with incipient or early nephropathy characterized by slightly raised urinary albumin excretion and normal GFR. The severity of glomerular pathology was between that in patients with short duration of diabetes who have not yet developed any sign of renal impairment, and that of patients with overt nephropathy. I think it is clear, as Dr. Mauer just said, that if these patients do not develop diabetic glomerulopathy, they will not manifest microalbuminuria. There are two important points to remember in our discussion. First, all of these diabetic patients with microalbuminuria were earlier normoalbuminuric; second, we do not yet know whether, by the time these patients become microalbuminuric, it is too late to try to prevent the progression to overt nephropathy. We need more information about what happens structurally before the functional signs appear.

DR. MADIAS: Is there a particular mode of chronic antihypertensive therapy versus another that makes a difference in terms of the decrement in the albuminuria? Does an acute decrease in blood pressure affect albumin excretion?

DR. MOGENSEN: In our long-term study in patients with incipient diabetic nephropathy, and also in patients with overt diabetic nephropathy, we used a conventional scheme of treatment. That is, we started with cardioselective beta blockers and later added, if appropriate, diuretics and, in some cases, vasodilators. Most patients experienced a satisfactory reduction in blood pressure with this conventional treatment. Masking of hypoglycemia was not a problem in our patients when we used cardioselective beta blockers in moderate doses. Of course there are other types of antihypertensive treatment, but all data so far indicate that the method of reducing blood pressure is not important; rather, it is the degree of reduction in blood pressure that counts. It might be somewhat different with ACE inhibitors. In patients with early or with overt diabetic nephropathy, and also in patients with essential hypertension, the albumin excretion rate declines markedly after an acute reduction in blood pressure. After a few hours of reduction in blood pressure (which may still be moderately elevated), we see a clear reduction in urinary albumin excretion rate. We therefore can conclude that both in early and in overt diabetic nephropathy the urinary albumin excretion rate is at least partly pressure dependent. The same is true in patients with essential hypertension, but in those patients, the blood pressure increase has to be very pronounced to produce microalbuminuria.

DR. HANS-HENRIK PARVING (*Hvidöre Hospital, Klampenborg, Denmark*): Regarding renal morphology and microalbuminuria, we need a morphometric method that predicts the later development of overt clinical diabetic nephropathy. To my knowledge we do not have such a method. If we compare renal biopsies from patients with microalbuminuria with biopsies from normoalbuminuric patients with the same duration of diabetes, we cannot tell which of the patients will develop overt diabetic nephropathy. That issue is the main concern in performing renal biopsies in the "at-risk" patients. Although a good correlation exists between the GFR and the glomerular capillary surface area in diabetic nephropathy, the same kind of morphologic lesions can exist in patients without proteinuria. Therefore I think we are looking into the wrong window. Biochemical studies on the composition of the glomerular basement membrane and charge/size selective properties might give us a better clue than would structural studies alone.

DR. STEFFES: Are you saying that the functional data are sufficiently predictive that you don't have to do morphologic analysis?

DR. PARVING: I think that the best current predictor of clinical diabetic nephropathy is elevated urinary albumin excretion. The main reason we are not doing a lot of renal biopsies on our patients in Copenhagen is that do not know what to look for. I do hope, however, that some investigators will try to elucidate which morphologic lesions will turn out to be of predictive or prognostic value.

DR. MAUER: Dr. Parving, I do not agree. All the evidence we have so far suggests that lesions progress over time. Only renal transplant recipients have been biopsied serially at 2, 5, 10, and 15 years after the "onset of diabetes." It is clear from these studies that diabetic nephropathy progresses at a faster rate in some patients than in others, and that it does not progress at all in some patients. Returning to the microalbuminuric patients, when we measure urinary albumin excretion and look at the structure of the kidney, there is no necessary relationship. I would argue, however, that if you biopsied the patients who have microalbuminuria when they had clinical proteinuria, you would find that they all would have developed significant lesions. We can agree, based on our current studies, that in microalbuminuria, a clear structural correlate has not been

identified, but that somehow it predicts later pathology. It has to; it can't work any other way. The question is, when you begin to manipulate that functional finding, are you in fact influencing the rate of development of pathology? One approach is to wait until end-stage renal failure develops to answer this critical question. But this would take a very long time and it would not allow us to understand mechanisms that will help us develop better treatment approaches. Further, studies over an extended period tend to break down because of noncompliance, patients' geographic dispersal, and other factors. Twenty-year studies are hard to sustain. Structural measures could allow us to make our studies manageable.

DR. MOGENSEN: I think it is important to stress the one situation in which we know that the course can be altered. Antihypertensive treatment in overt diabetic nephropathy is associated with a clear reduction in the urinary albumin excretion rate. This observation suggests that in other stages of the disease, a reduction in the urinary albumin excretion rate is likely to be beneficial because the rate of decline of the GFR is also considerably reduced, thus postponing the development of severe renal failure [167, 168].

DR. PARVING: Dr. Mauer, your points are well taken. However, this does not solve the problem I put forward. If I gave you 100 biopsy specimens, you could not tell me which of the insulin-dependent diabetic patients would or would not develop clinical diabetic nephropathy. A single biopsy is of little value in predicting the clinical outcome of renal disease in an individual patient. It really doesn't matter if the kidneys look bad, as long as they are functioning. I suggest that longitudinal studies of urinary albumin excretion rate and GFR are the best methods for evaluating treatment in microalbuminuric patients, even though it can take 5 years or more for us to reach a valid conclusion.

DR. STEFFES: But Dr. Parving, it could take much longer than 5 years for us to reach a conclusion. I think Dr. Mauer's point is that you might see a morphologic end-point more quickly than the final functional end-point—renal failure.

DR. PARVING: Longitudinal morphologic studies could turn out to be a faster method for monitoring the effect of treatment in incipient diabetic nephropathy. But this method is not validated. In my opinion, albuminuria and GFR still are the most crucial variables to be monitored in clinical trials.

DR. MADIAS: Dr. Mogensen, is there any physiologic insight as to why poor metabolic control or ketosis increases urinary albumin excretion in the diabetic patient?

DR. MOGENSEN: The pathophysiologic background of the increase in urinary albumin excretion during poor metabolic control is not clearly defined, at least not in humans. But much experimental evidence indicates that the pathophysiologic basis is an increase in the transcapillary pressure in the glomerulus. Also, to some extent, decreased tubular reabsorption of proteins plays a role, but probably only a minor one. I must stress that there are no measurements in humans, but it is well documented that poor metabolic control in the rat is associated with an increased transglomerular pressure [158–160].

DR. PARVING: We have some circumstantial evidence in humans. The filtration fraction is high when a diabetic patient is in poor metabolic control; reduction of the blood glucose causes the filtration fraction to fall. These observations suggest that we are dealing with an elevated glomerular pressure during poor metabolic control. Furthermore, poor metabolic control is characterized by increased cardiac output and increased flow to nearly all organs and tissues: the brain, the eye, muscle, subcutaneous tissue, and the kidney. Finally, the transcapillary escape rate of albumin, which is a measurement of the overall microvascular leakage of albumin, is increased in poorly controlled diabetes and is completely normalized during strict metabolic control. The findings of normal arterial and venous pressures and of a reduced vascular resistance, mainly precapillary, suggest that the mean capillary hydrostatic pressure must be increased in insulin-dependent diabetic patients in poor metabolic control.

DR. MADIAS: Dr. Mogensen, you have made reference to exercise-induced microalbuminuria. What sort of exercise are you talking about? What are the renal hemodynamic effects of this exercise? What is the meaning of these results?

DR. MOGENSEN: In many patients with standard control of diabetes, we observed an abnormally high increase in urinary albumin excretion rate during physical exercise. We also observed a clear reduction in GFR and a more pronounced reduction in RPF during exercise, that is, an increase in the filtration fraction. Therefore it is likely that the exercise-induced microalbuminuria is associated with an increased intraglomerular pressure as well. We have studied patients longitudinally, but so far we have no evidence that exercise-induced microalbuminuria can predict overt diabetic nephropathy or even baseline microalbuminuria. Yet, as I have indicated, it is important to eliminate exercise as the cause of microalbuminuria because it is a confounding factor; in contrast to exercise-induced albuminuria, the resting albumin excretion rate is strongly predictive of overt diabetic nephropathy. Therefore you should be quite sure that the patients are collecting urine samples while at rest.

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