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Author(s): Frank Brosius, M.D, 2011

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Kidney Systemic Disease Diabetes

Frank Brosius, M.D.

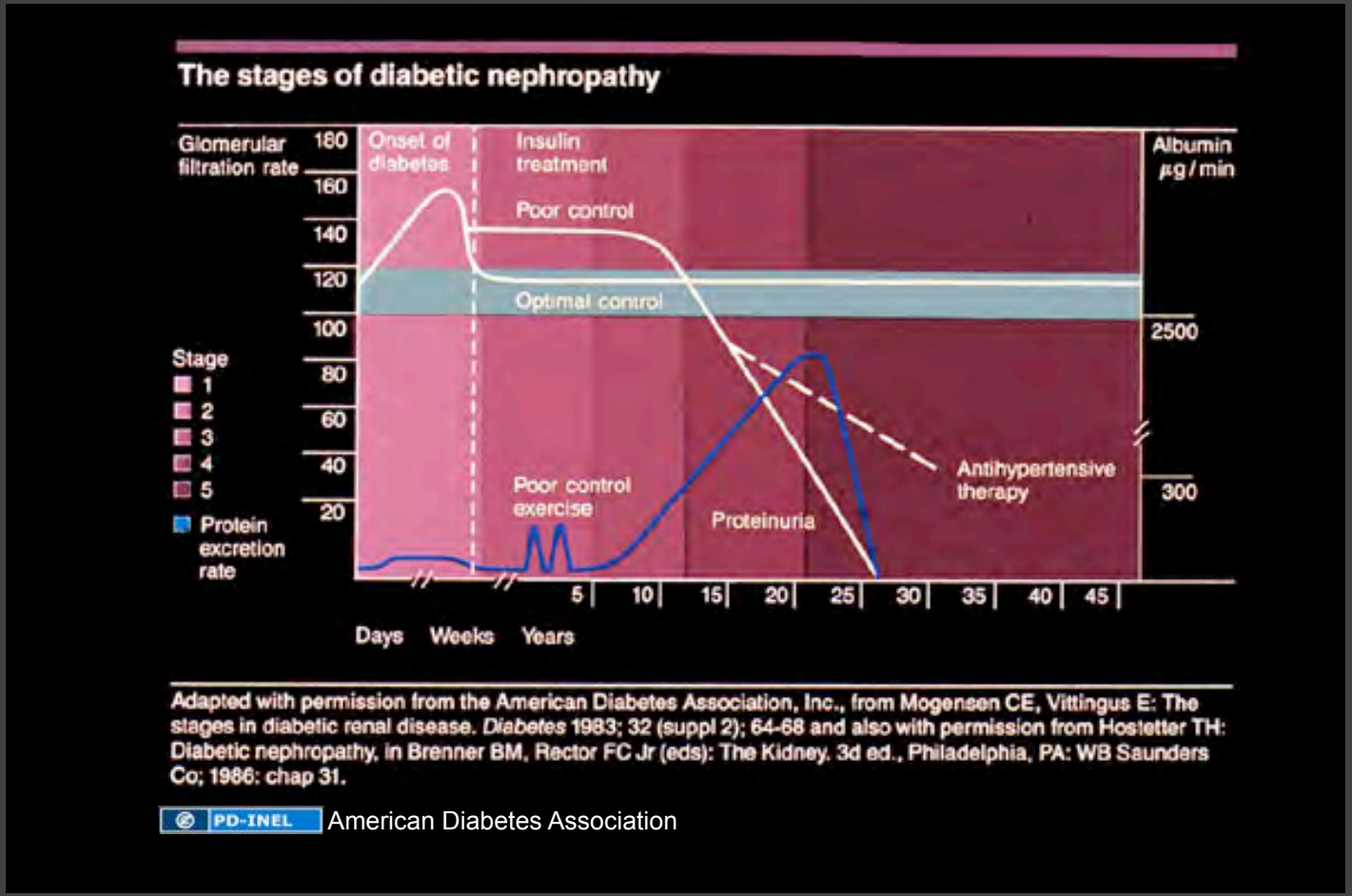
Fall 2010

Diabetic Nephropathy--Objectives

- Understand pathology and pathogenesis
- Identify early clinical predictors or indicators
- Describe most important therapeutic interventions to prevent progression

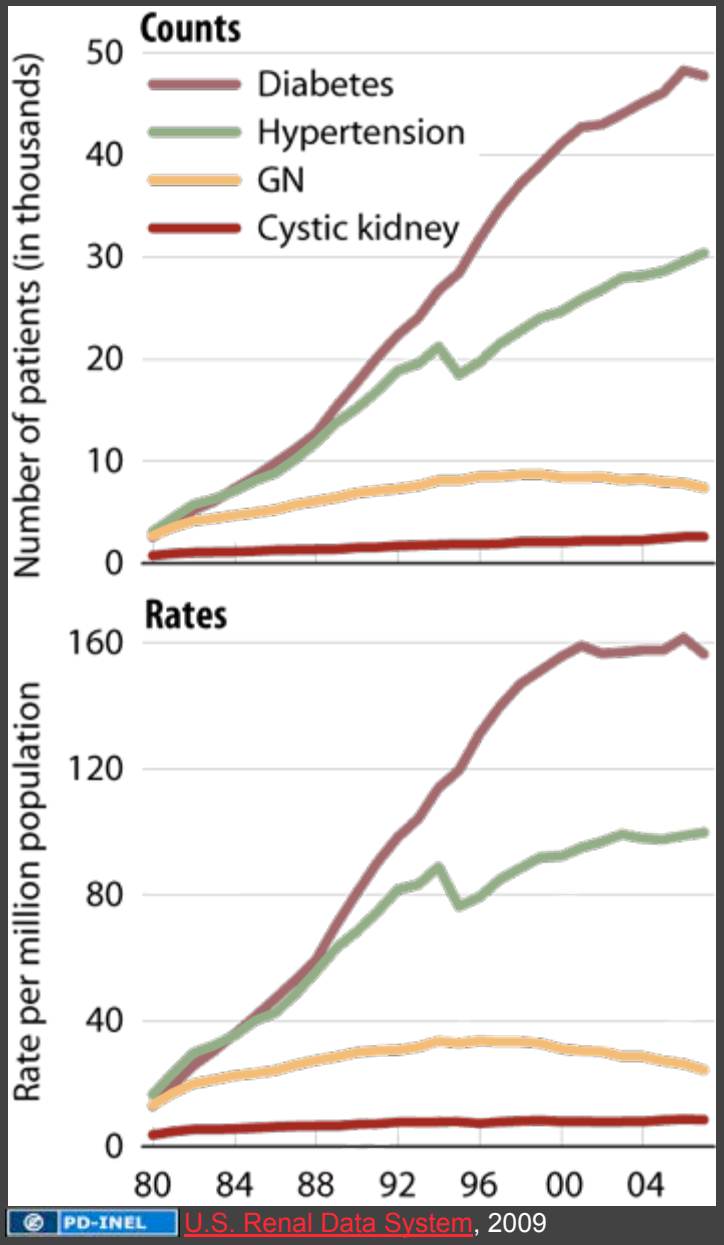
Diabetic Nephropathy:
“You can't cure it so you have to endure it”

King, et al. Qual Health Res. 2002;12:329-46



Adapted with permission from the American Diabetes Association, Inc., from Mogensen CE, Vittingus E: The stages in diabetic renal disease. *Diabetes* 1983; 32 (suppl 2); 64-68 and also with permission from Hostetter TH: Diabetic nephropathy, in Brenner BM, Rector FC Jr (eds): The Kidney. 3d ed., Philadelphia, PA: WB Saunders Co; 1986: chap 31.

PD-INEL American Diabetes Association



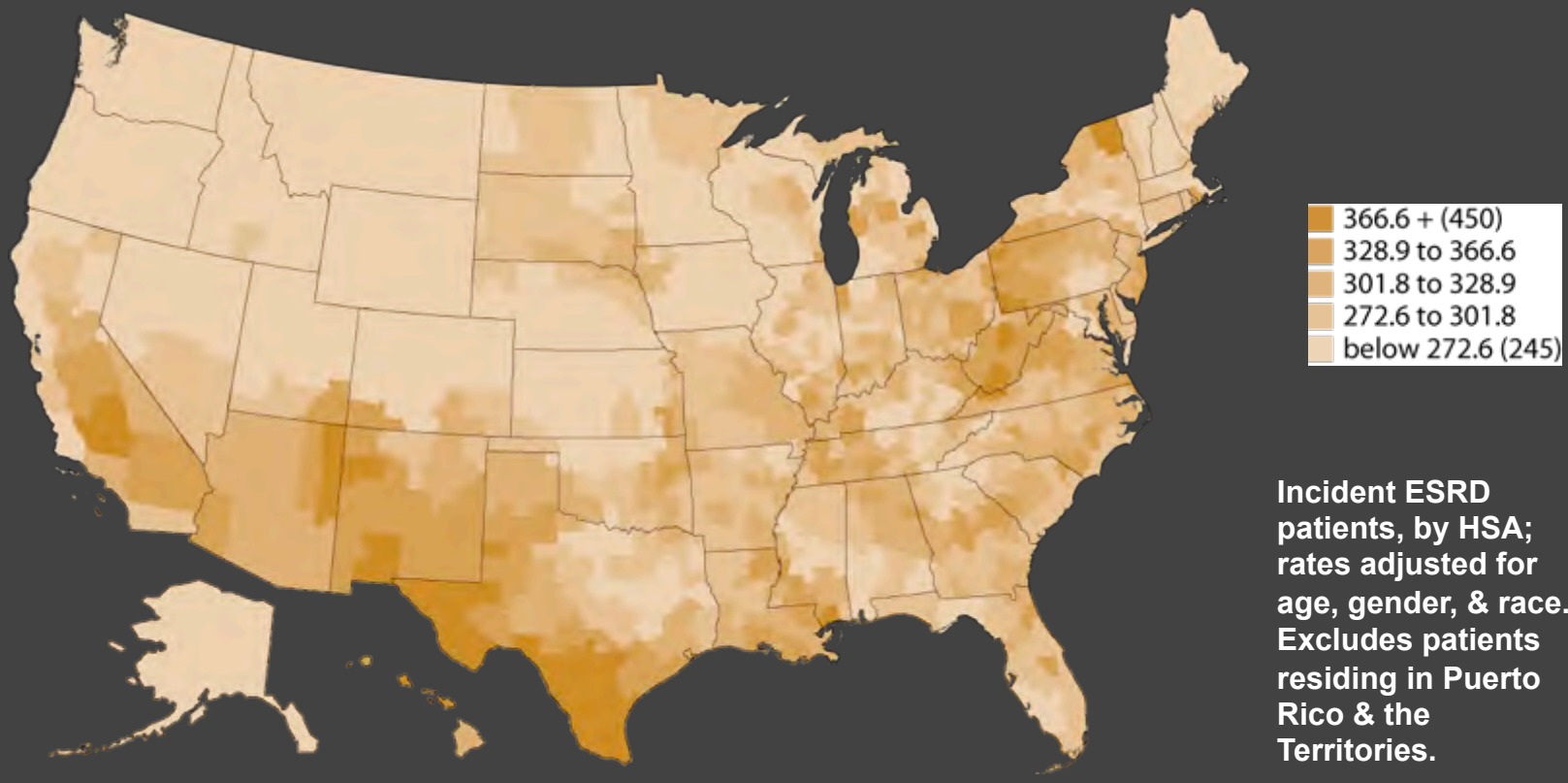
PD-INEL U.S. Renal Data System, 2009

Diabetes is the dominant cause of ESRD in USA

Incident ESRD patients; Medical Evidence form data; rates adjusted for age, gender, & race.

USRDS 2009

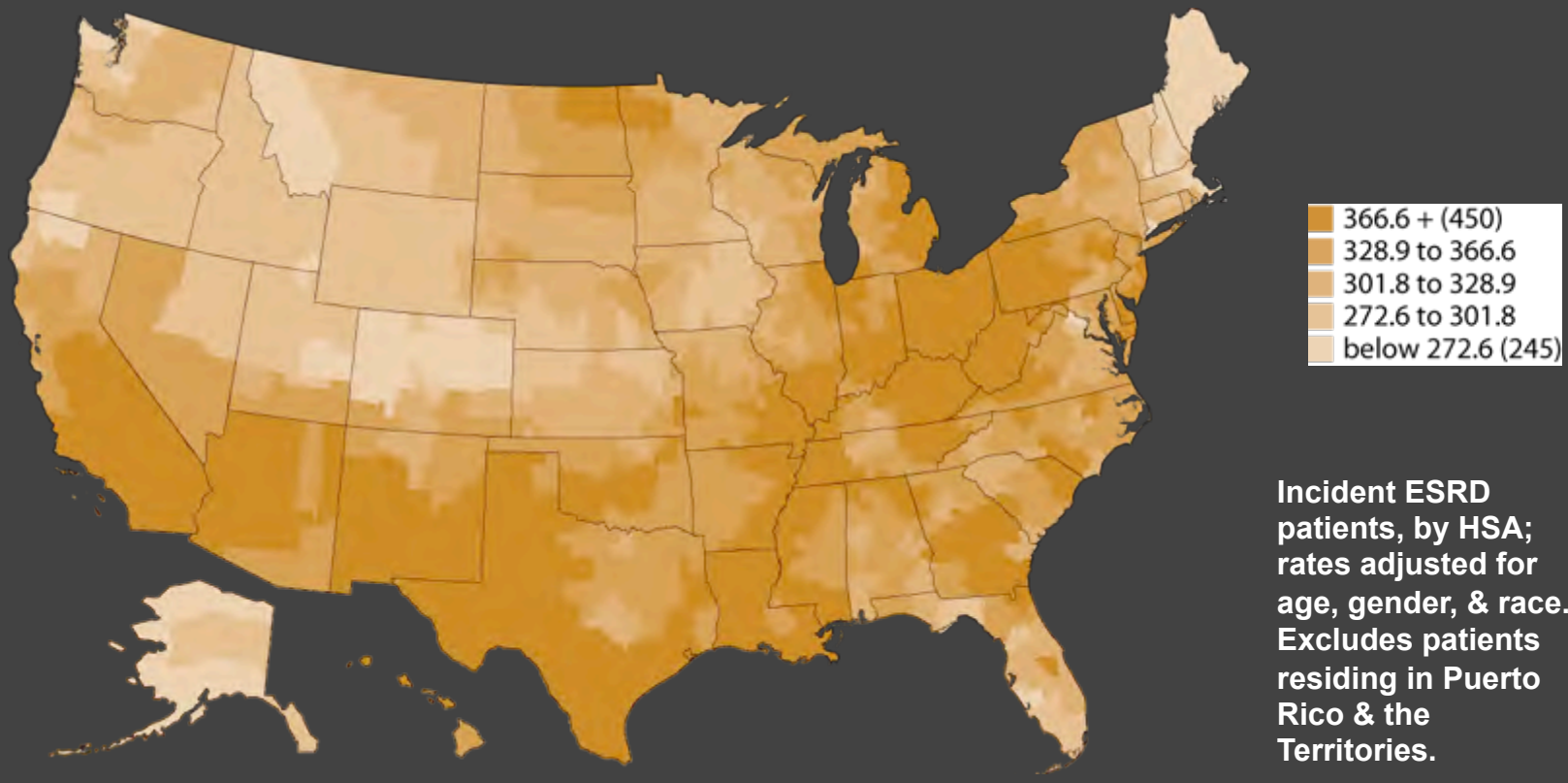
Incidence rates of ESRD (per million population): 1997



Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

PD-INEL U.S. Renal Data System, 2009

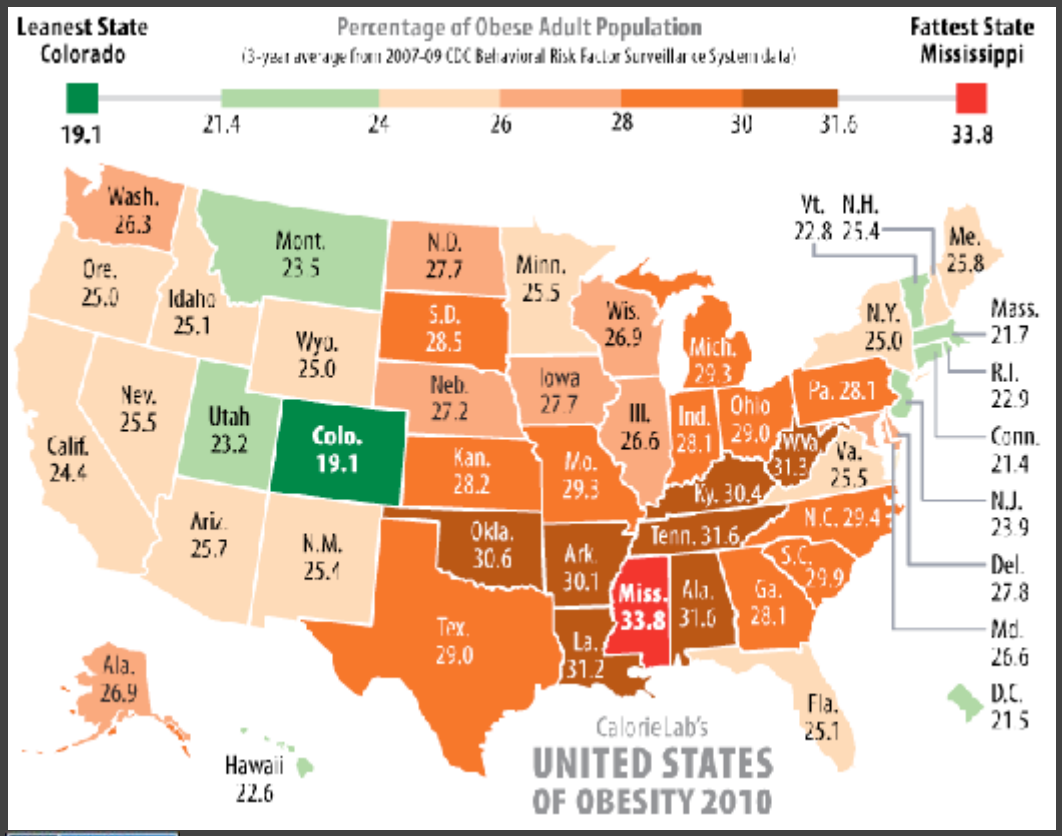
Incidence rates of ESRD (per million population): 2007



Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

PD-INEL U.S. Renal Data System, 2009

Obesity, metabolic syndrome and type 2 diabetes mellitus

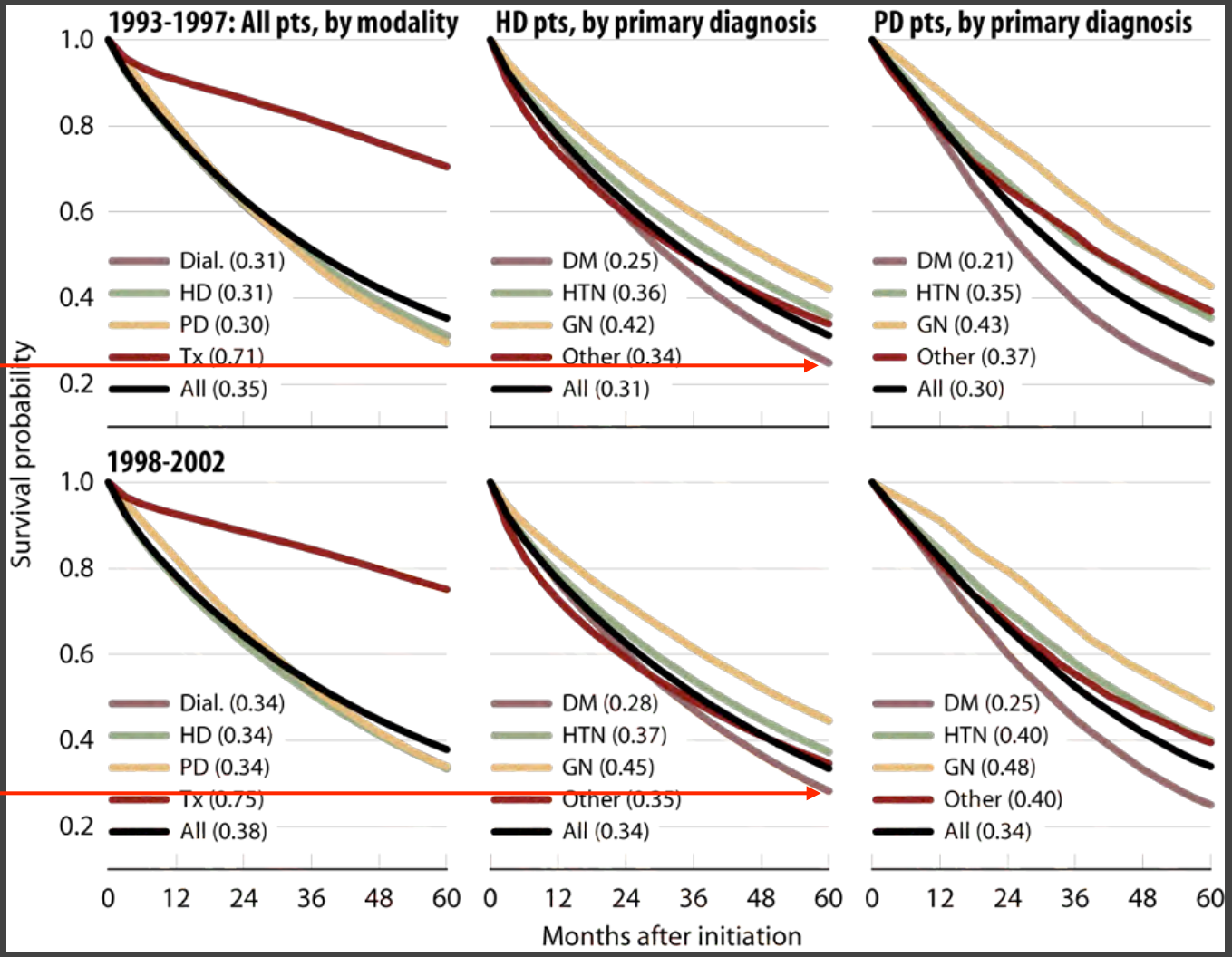


PD-INEL CalorieLab

CalorieLab® based on the Behavioral Risk Factor Surveillance System database maintained by the CDC. Rankings use a three-year average for smoothing.

Adjusted five-year survival, by modality & primary diagnosis: 1993-2002: still lousy

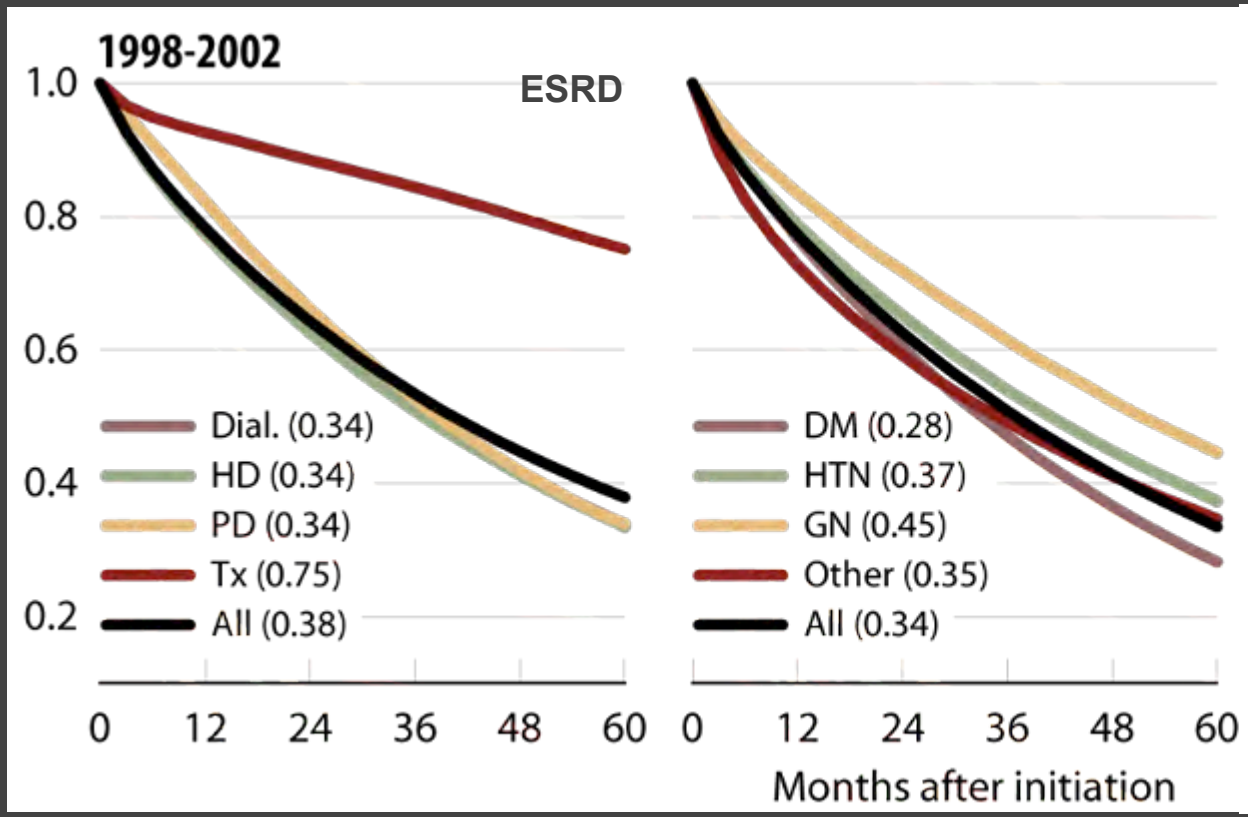
Incident dialysis patients & patients receiving a first transplant in the calendar year. All probabilities are adjusted for age, gender, & race; overall probabilities are also adjusted for primary diagnosis. All ESRD patients, 1996, used as reference cohort. Modality determined on first ESRD service date; excludes patients transplanted or dying during the first 90 days (five-year survival probabilities noted in parentheses).

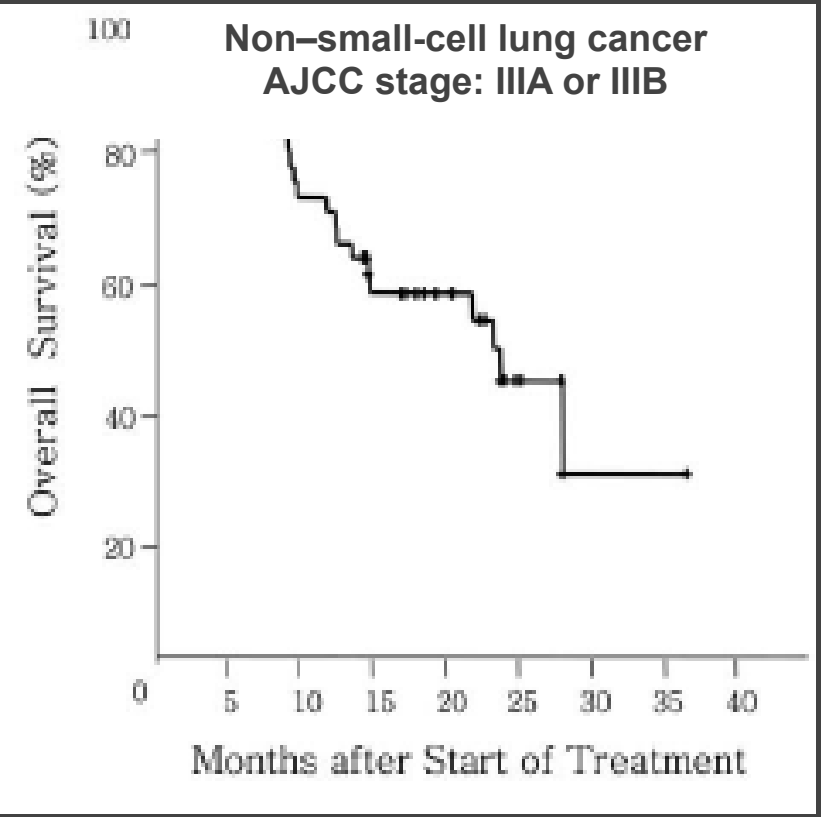


PD-INEL U.S. Renal Data System, 2009

USRDS 2009

Adjusted five-year survival, by modality & primary diagnosis: 1998-2002: still lousy





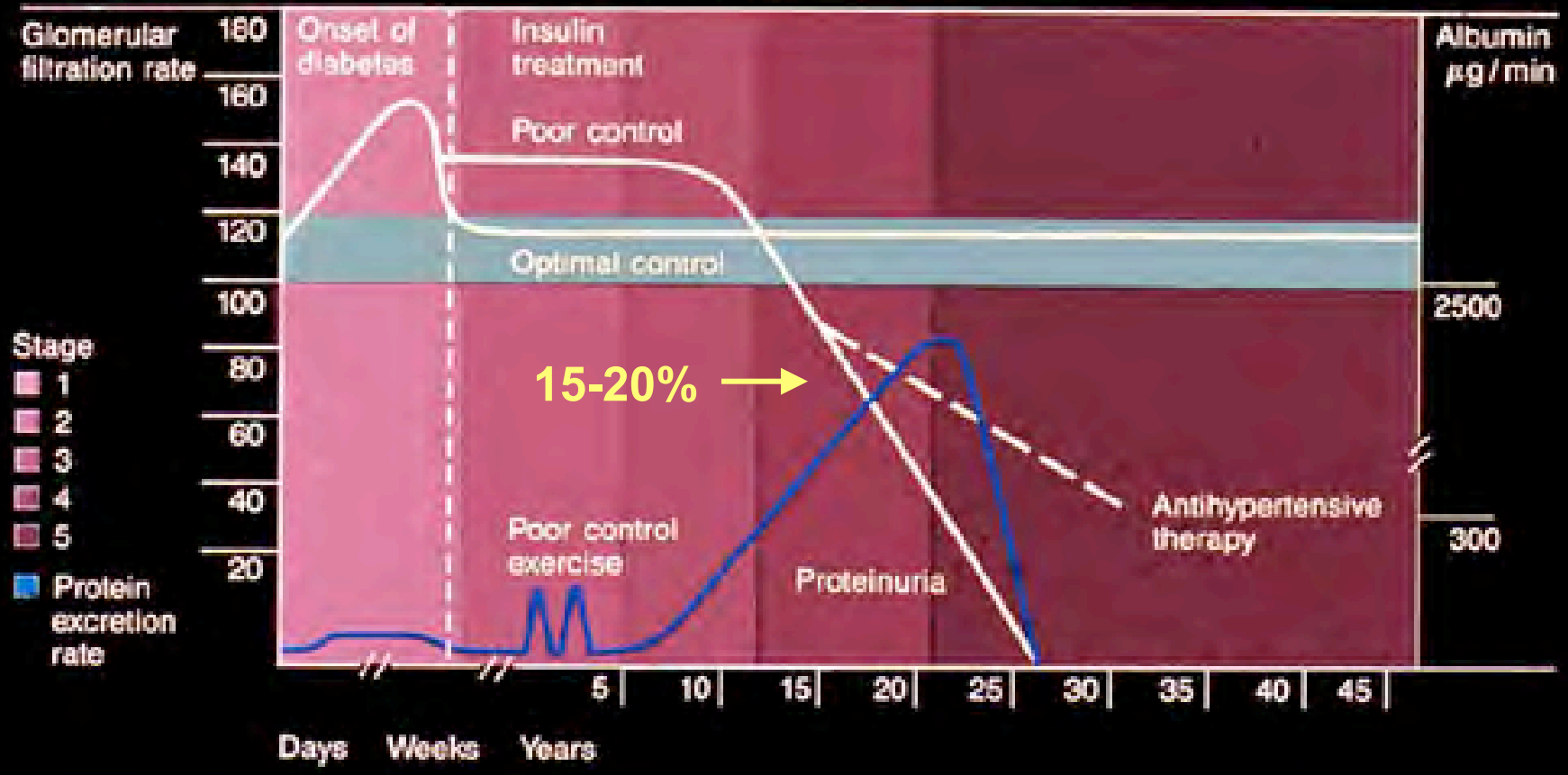
Diabetic nephropathy = Cancer

USRDS 2009

Int J Radiat Oncol Biol Phys. 2005 Jul 15

PD-INEL U.S. Renal Data System, 2009

The stages of diabetic nephropathy



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PD-INEL American Diabetes Association

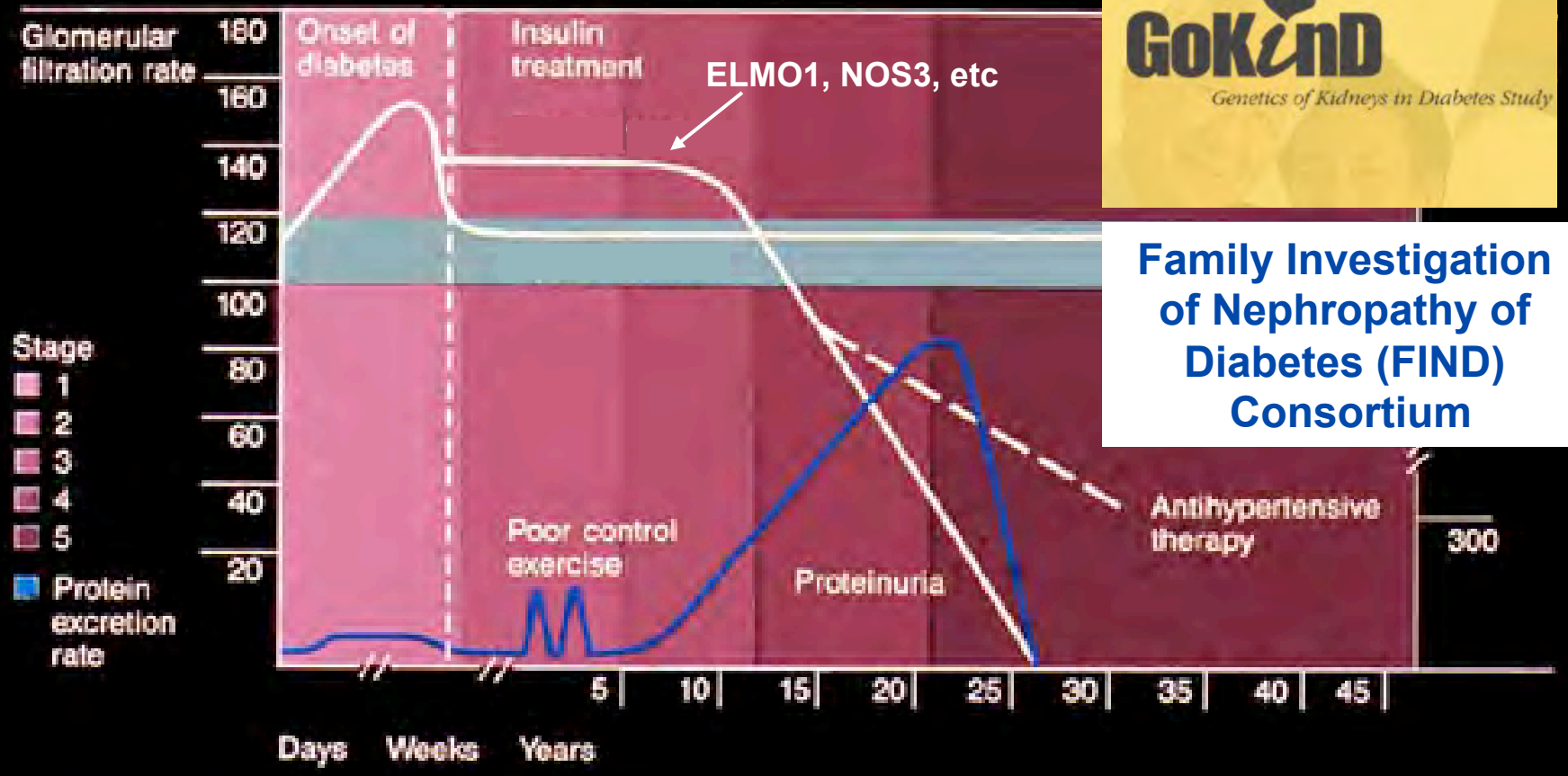
Risk factors for renal disease in Type II DM

- Genetic factors (familial clustering)
- Hyperglycemia
- Hypertension
- Glomerular hyperfiltration/hypertension
- Smoking
- Male gender
- Advanced age
- Race

UpToDate, 2010

Genetic factors

The stages of diabetic nephropathy



GoKinD
Genetics of Kidneys in Diabetes Study

Family Investigation of Nephropathy of Diabetes (FIND) Consortium

Adapted with permission from the American Diabetes Association, Inc., from Mogensen CE, Vittingus E: The stages in diabetic renal disease. *Diabetes* 1983; 32 (suppl 2): 64-68 and also with permission from Hostetter TH: Diabetic nephropathy. In Brenner BM, Rector FC Jr (eds): The Kidney. 3d ed., Philadelphia, PA: WB Saunders Co; 1986: chap 31.

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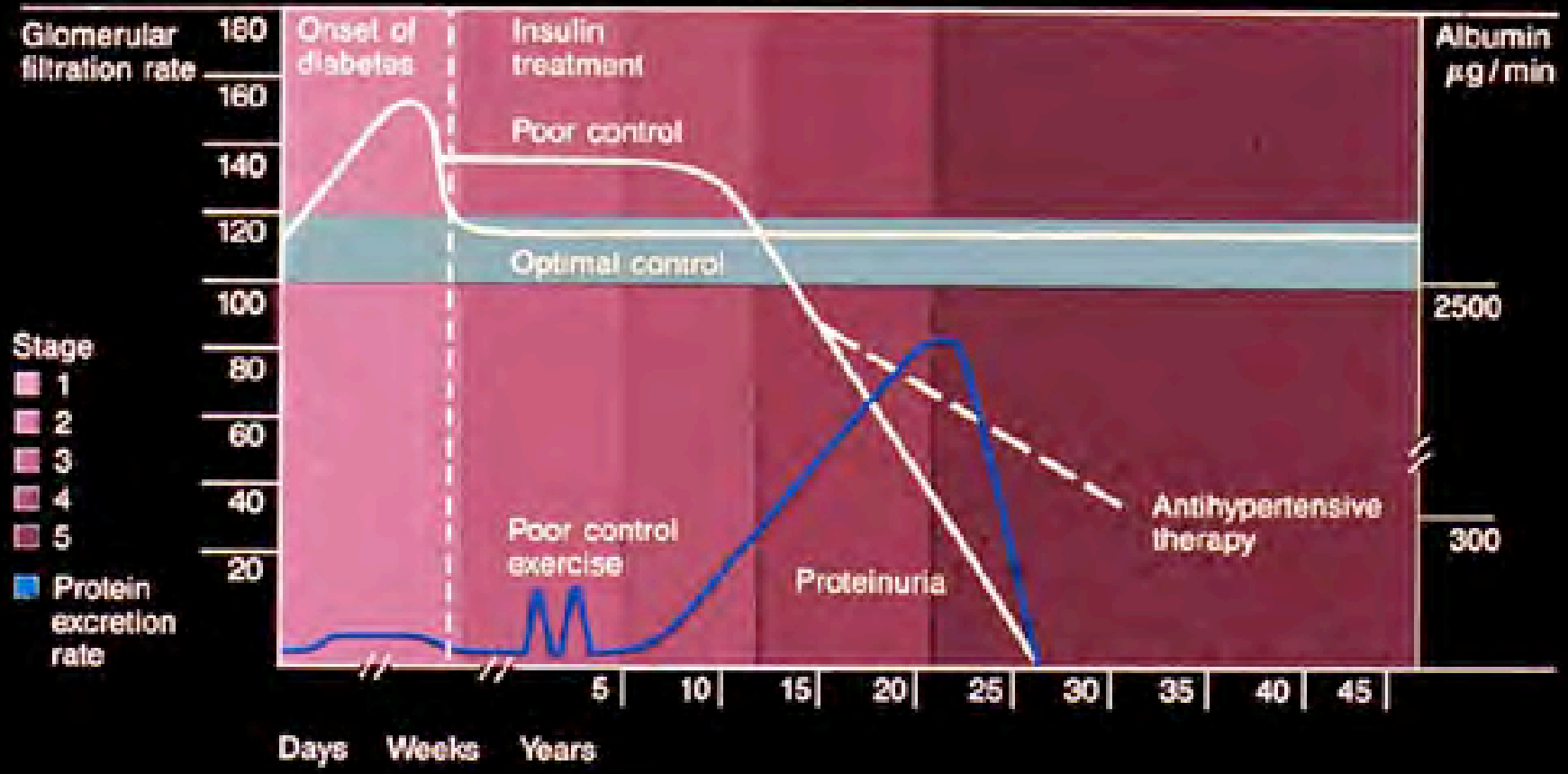
Hyper-
glycemia

The stages of diabetic nephropathy



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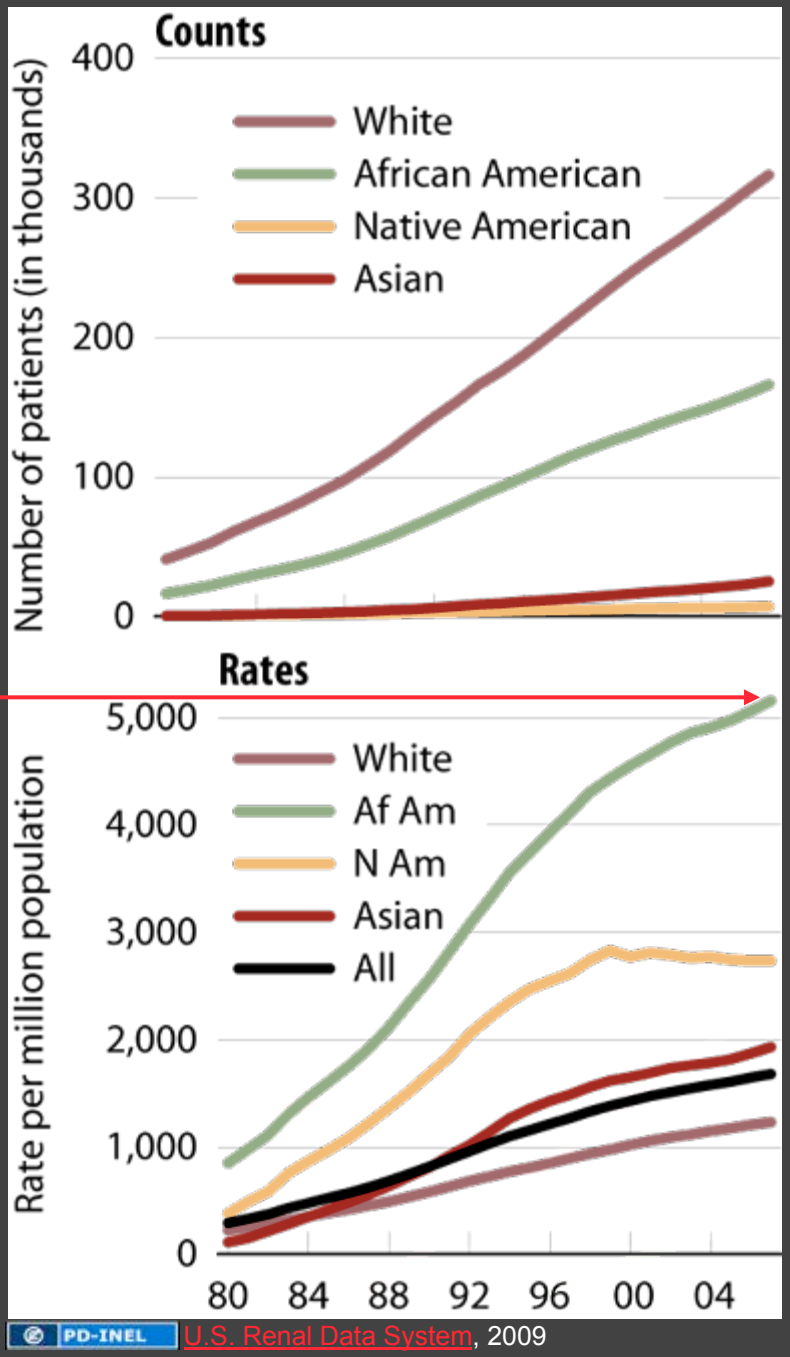
PD-INEL American Diabetes Association

Race: Diabetes is the dominant cause of ESRD in USA …more so in AAs



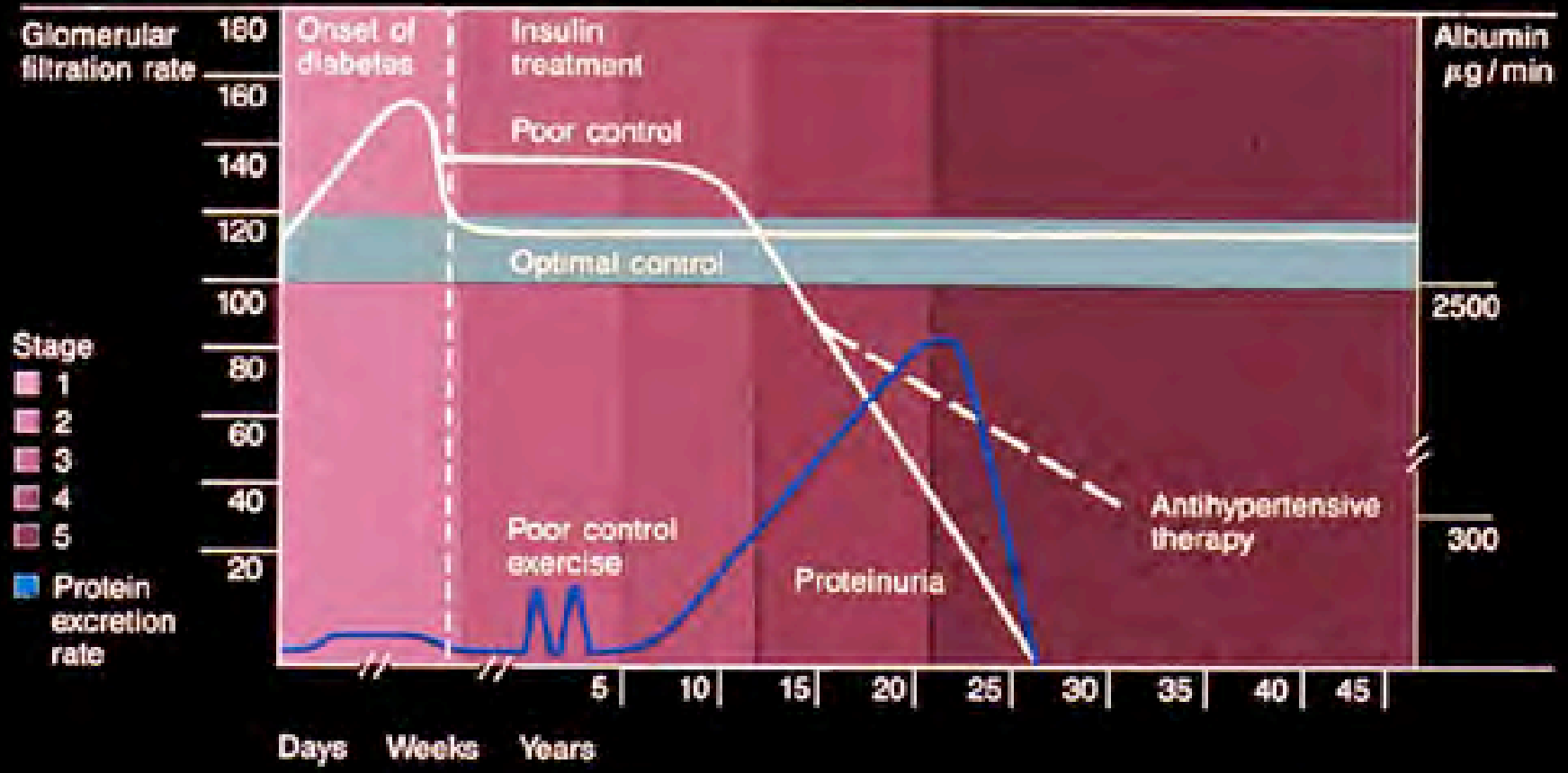
PD-INEL U.S. Renal Data System, 2009

December 31 point prevalent ESRD patients; rates adjusted for age & gender.

USRDS 2009

Screening

The stages of diabetic nephropathy



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Screening for diabetic nephropathy: 1) Microalbuminuria

Category	Spot collection (µg/mg creatinine)
Normal	<30
Microalbuminuria	30–299
Macro (clinical)-albuminuria	≥300

PD-INEL
from Standards of Medical Care in Diabetes—2010
DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010

Evaluation of microalbuminuria

- Test type 1 patients after 5 years and every year thereafter
- Test type 2 patients every year
- If positive, rule out transient causes of microalbuminuria (e.g., CHF, exercise (within 24 hr), infection, fever, severe HTN)
- Repeat 2 times in 3-6 months

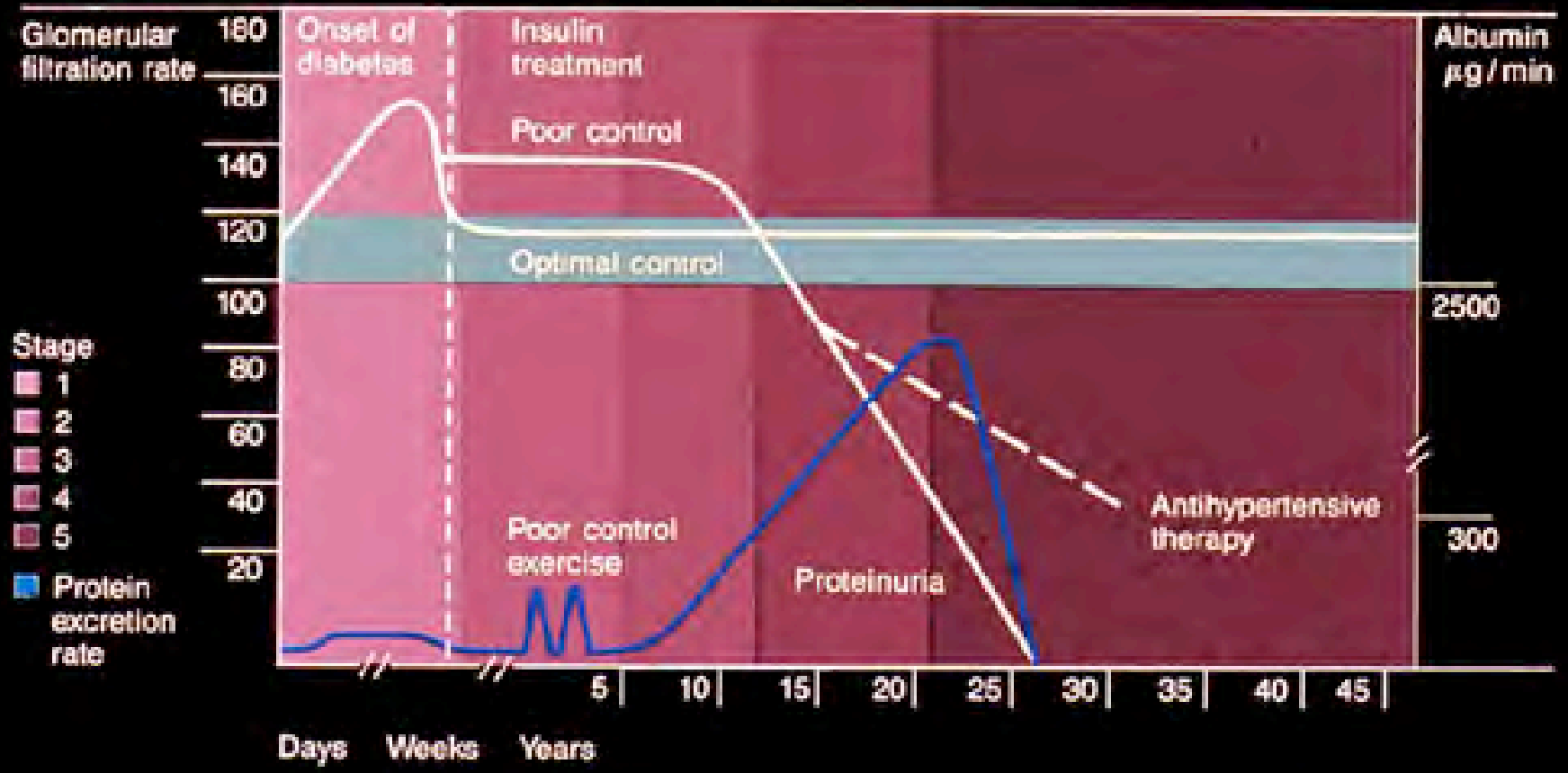
  – Microalbuminuria = 2/3 tests positive.

Screening for diabetic nephropathy: 2) Estimate GFR

"Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present."

from Standards of Medical Care in Diabetes-2010
DIABETES CARE, VOLUME 32, SUPPLEMENT 1, JANUARY 2010

The stages of diabetic nephropathy



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The normal glomerulus

Proximal convoluted tubule

Endothelial cell

Visceral epithelial cell (Podocyte)

Bowman's space

Mesangium

Efferent arteriole

Distal convoluted tubule

Parietal epithelial cell

Capillary lumen

Basement membrane

Mesangial cell

Extraglomerular mesangium

Macula densa

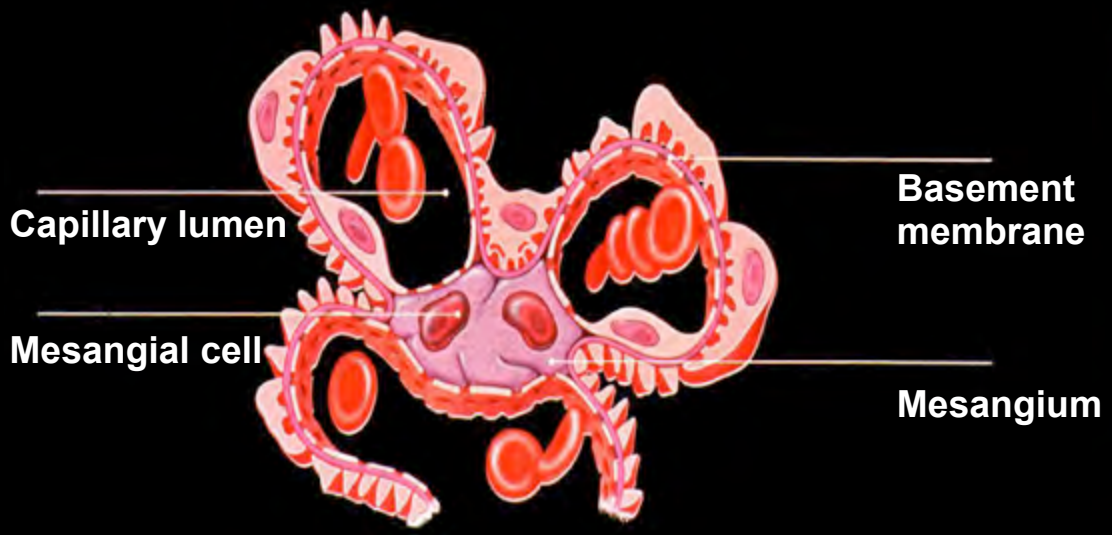
Afferent arteriole

Juxtaglomerular apparatus

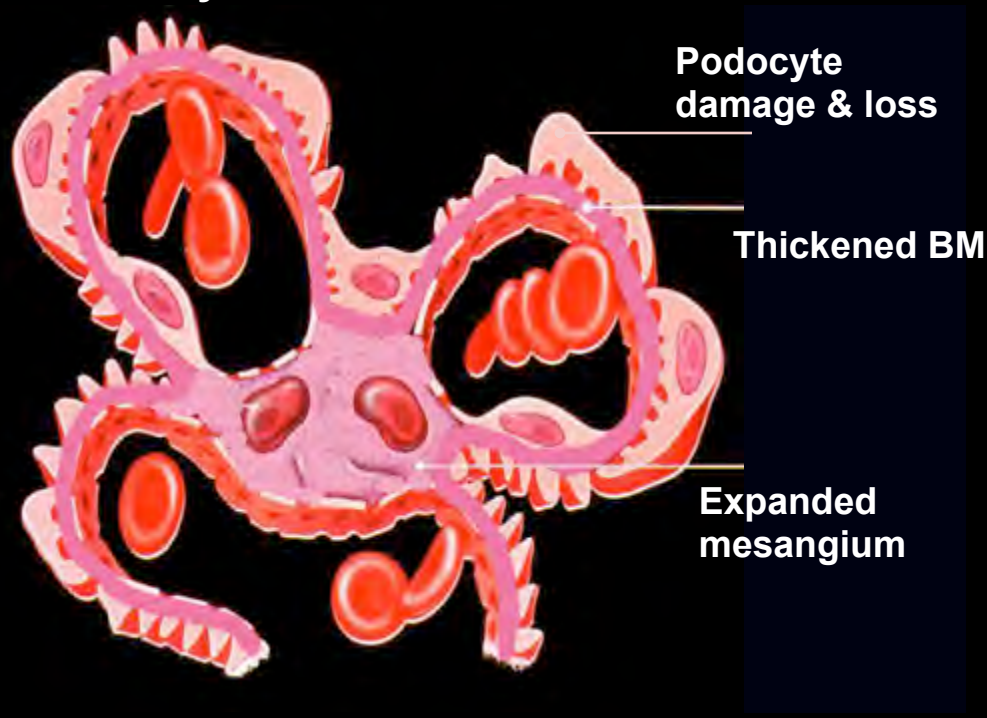
PD-INEL Source Undetermined

Pathology of DM nephropathy

Normal Glomerulus



Early Diabetic Glomerulus



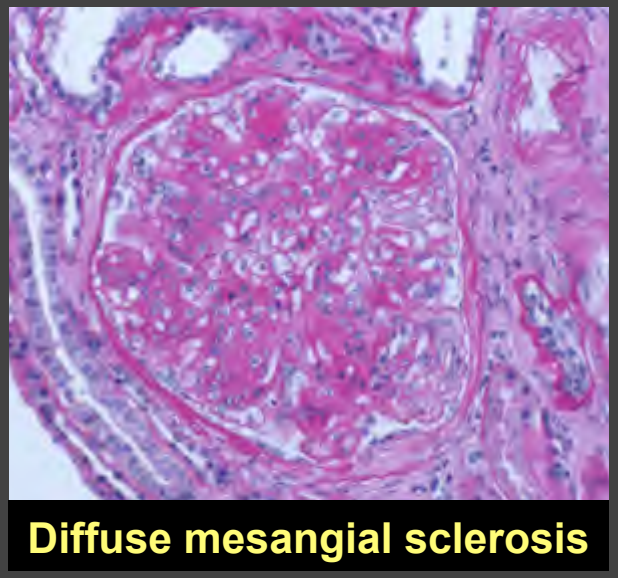
– Afferent and efferent hyaline arteriolosclerosis
– Interstitial fibrosis and tubular atrophy

PD-INEL Source Undetermined

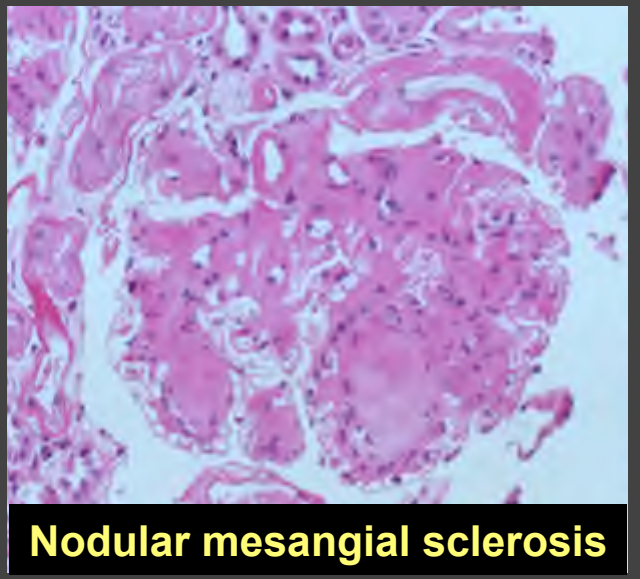
Pathology of DM nephropathy

Normal glomerulus

PD-INEL Source Undetermined

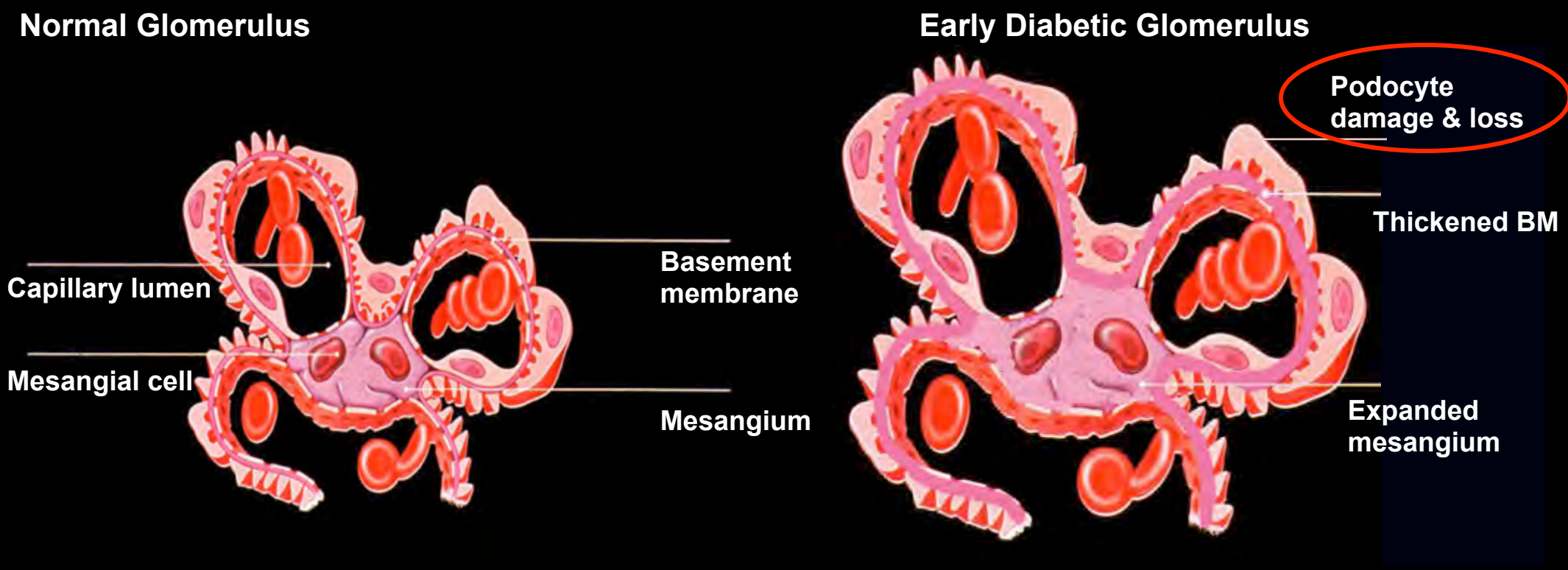


Diffuse mesangial sclerosis



Nodular mesangial sclerosis

Pathology of DM nephropathy



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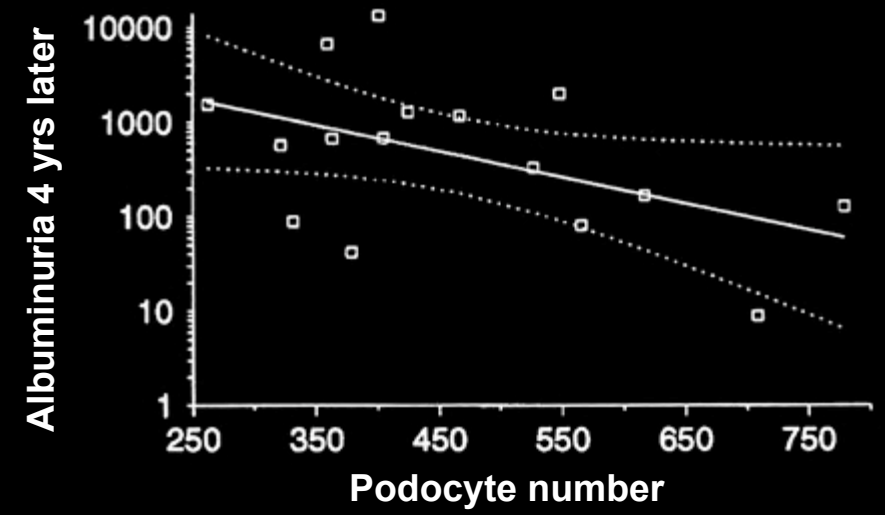
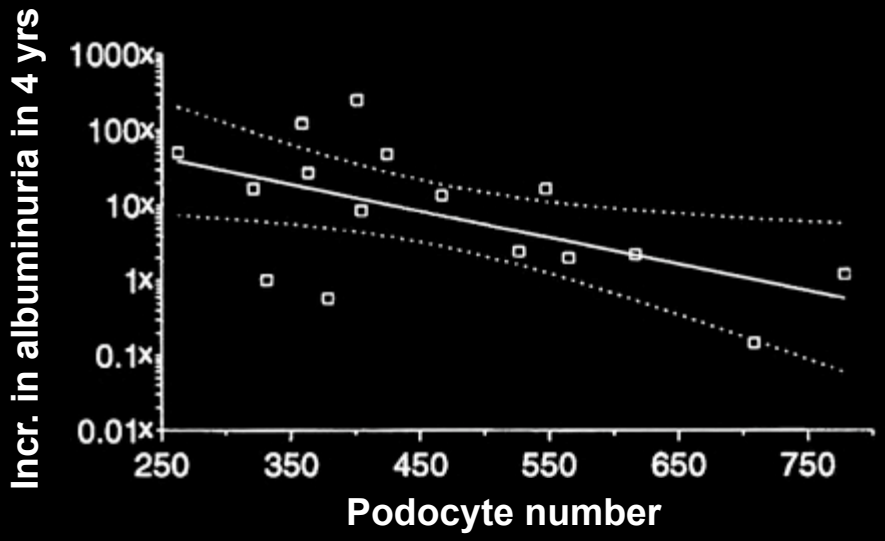
– Interstitial fibrosis and tubular atrophy

PD-INEL Source Undetermined

Podocyte loss predicts progression of nephropathy

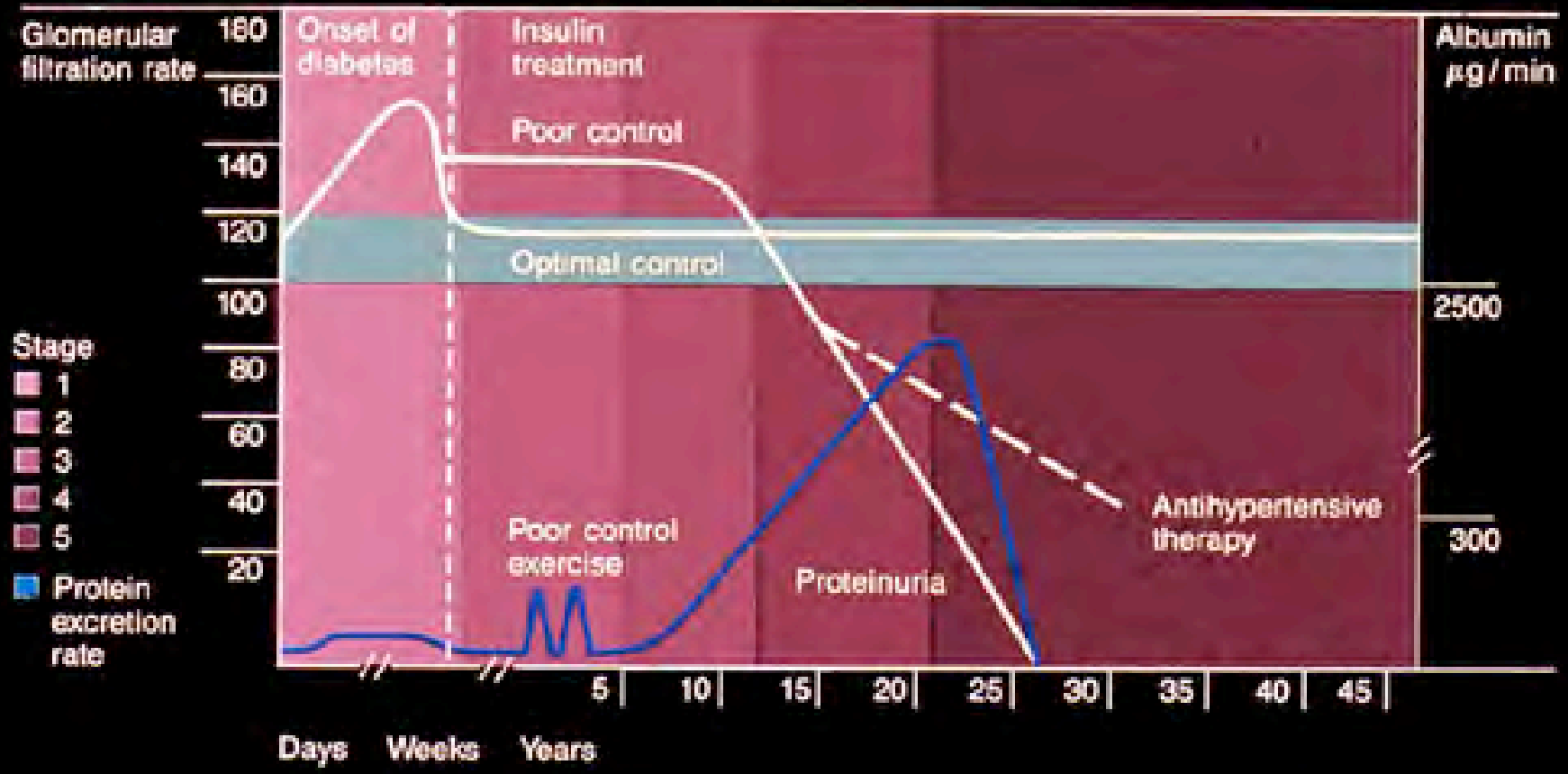




PD-INEL Meyer, et al. Diabetologia. 1999;42:1341

Pathogenesis

The stages of diabetic nephropathy



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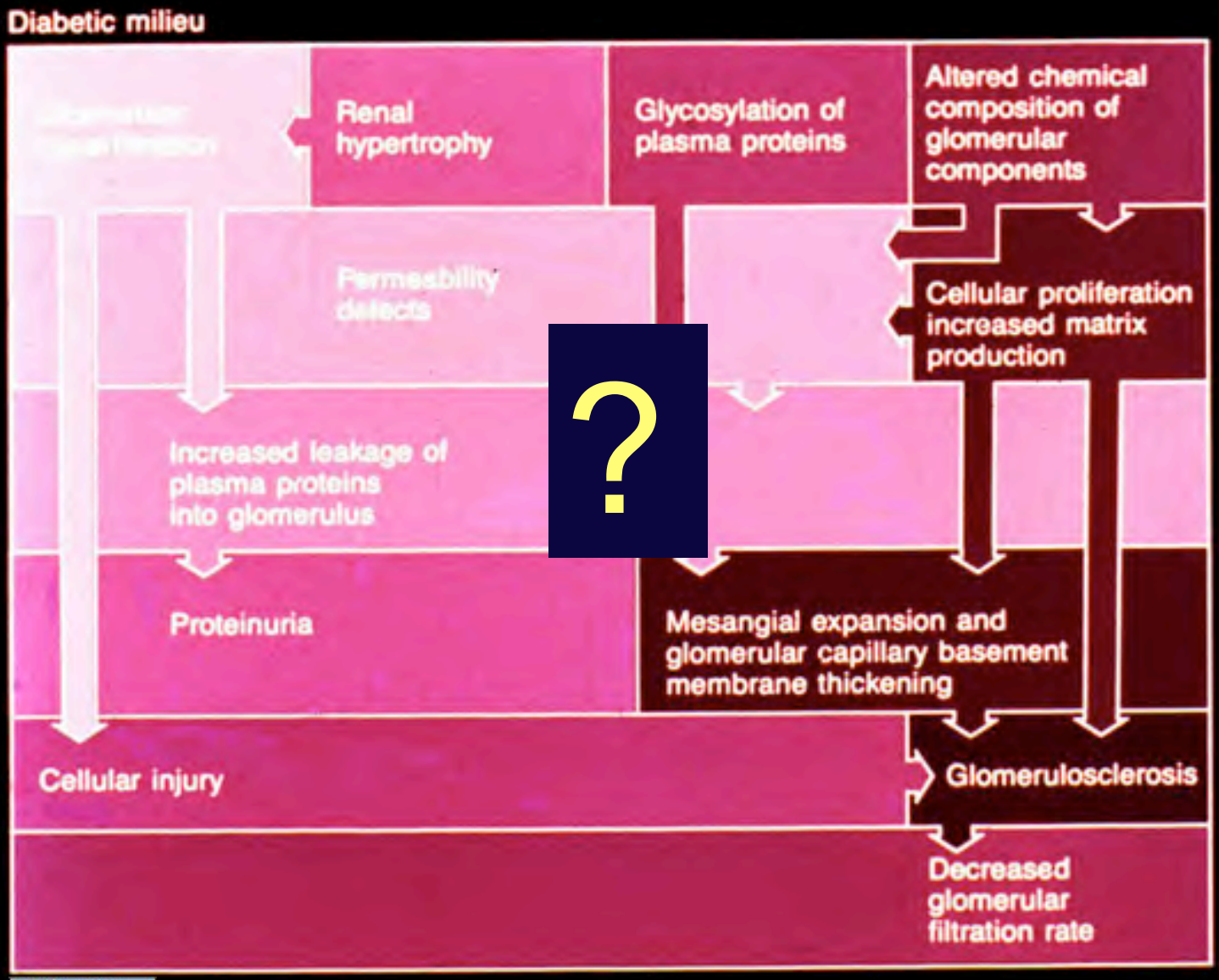
The pathogenesis of diabetic nephropathy: A proposed schema



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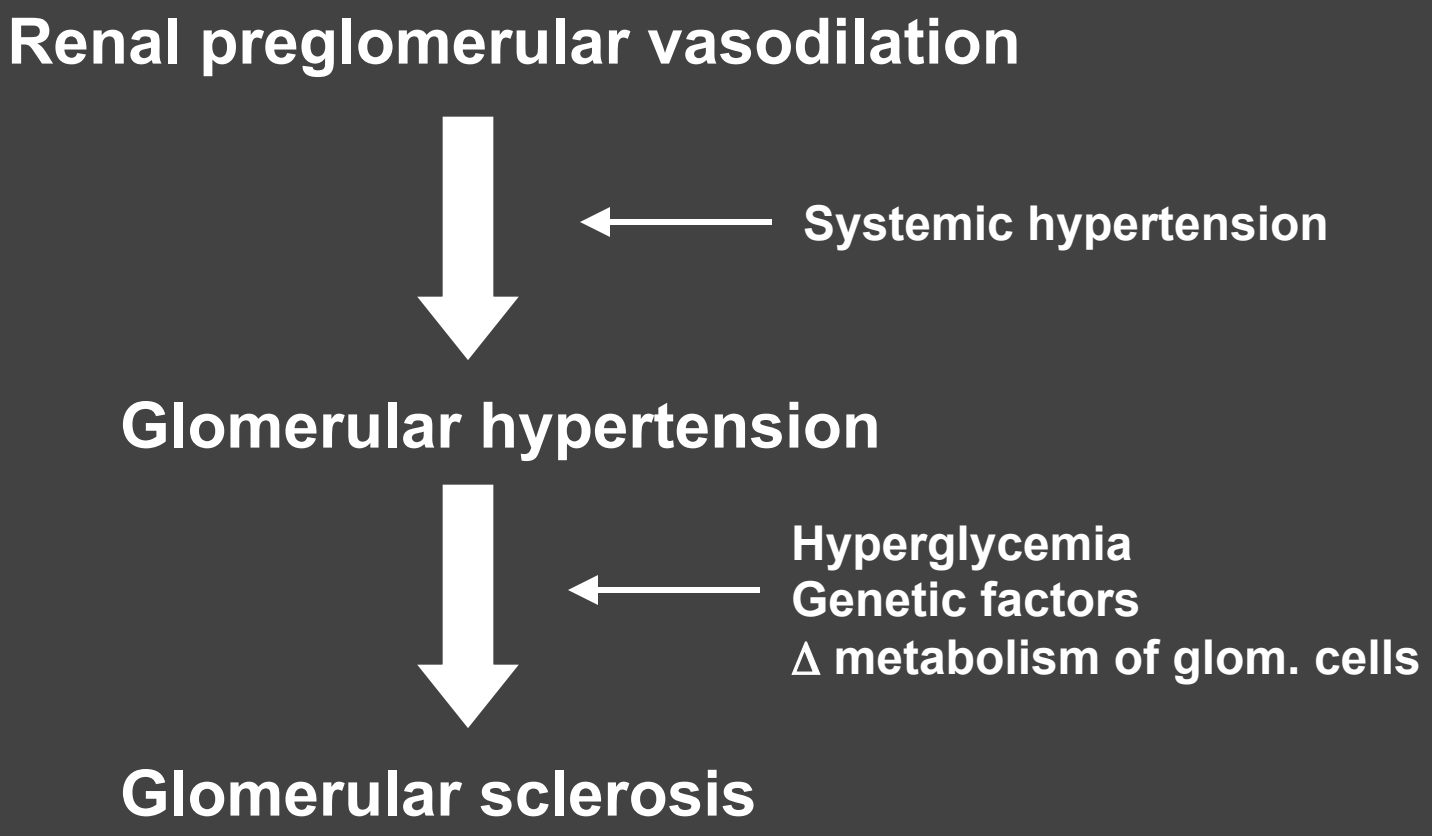
Simpleminded model of pathogenesis of DM nephropathy



from T. Hostetter

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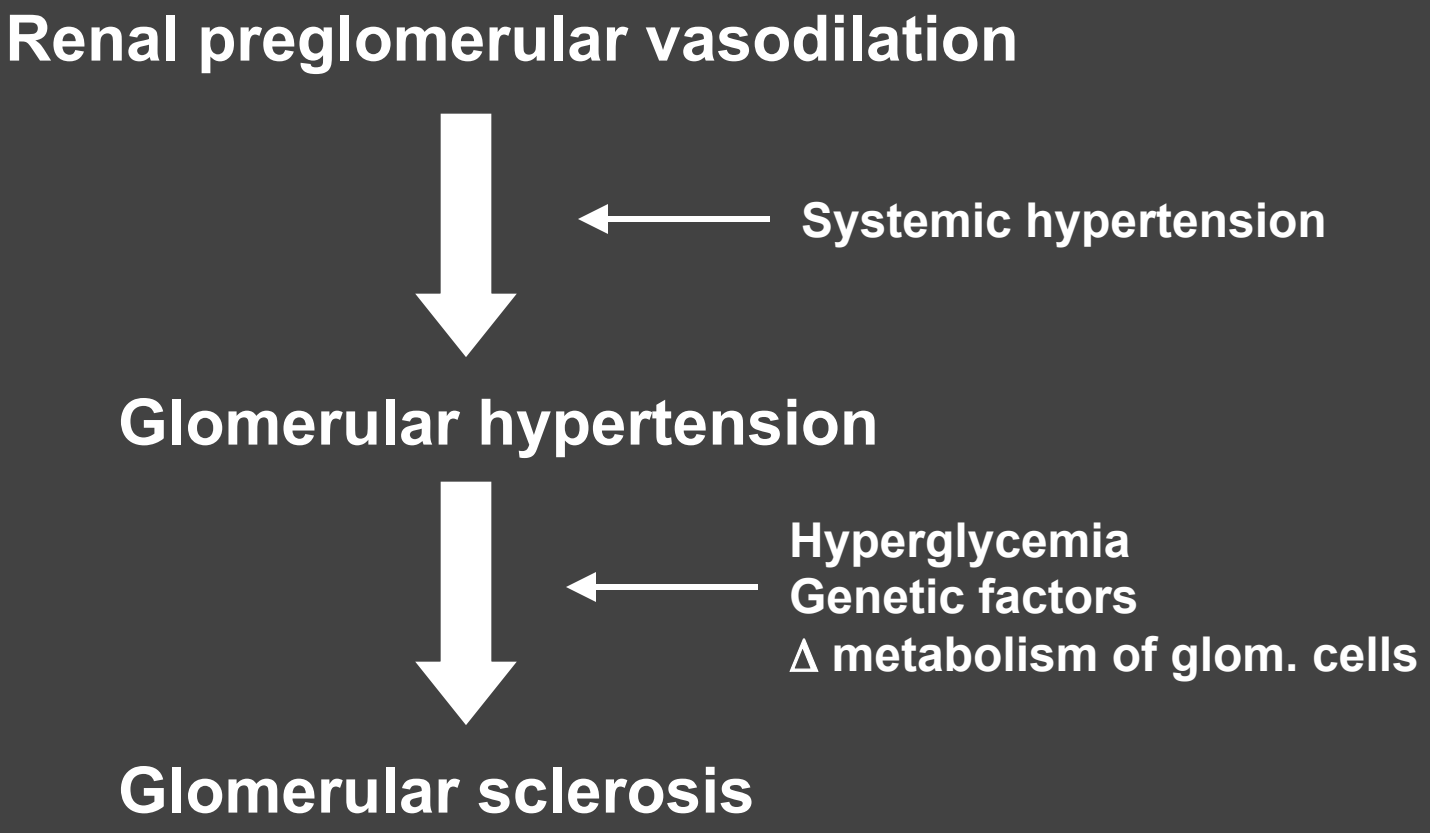
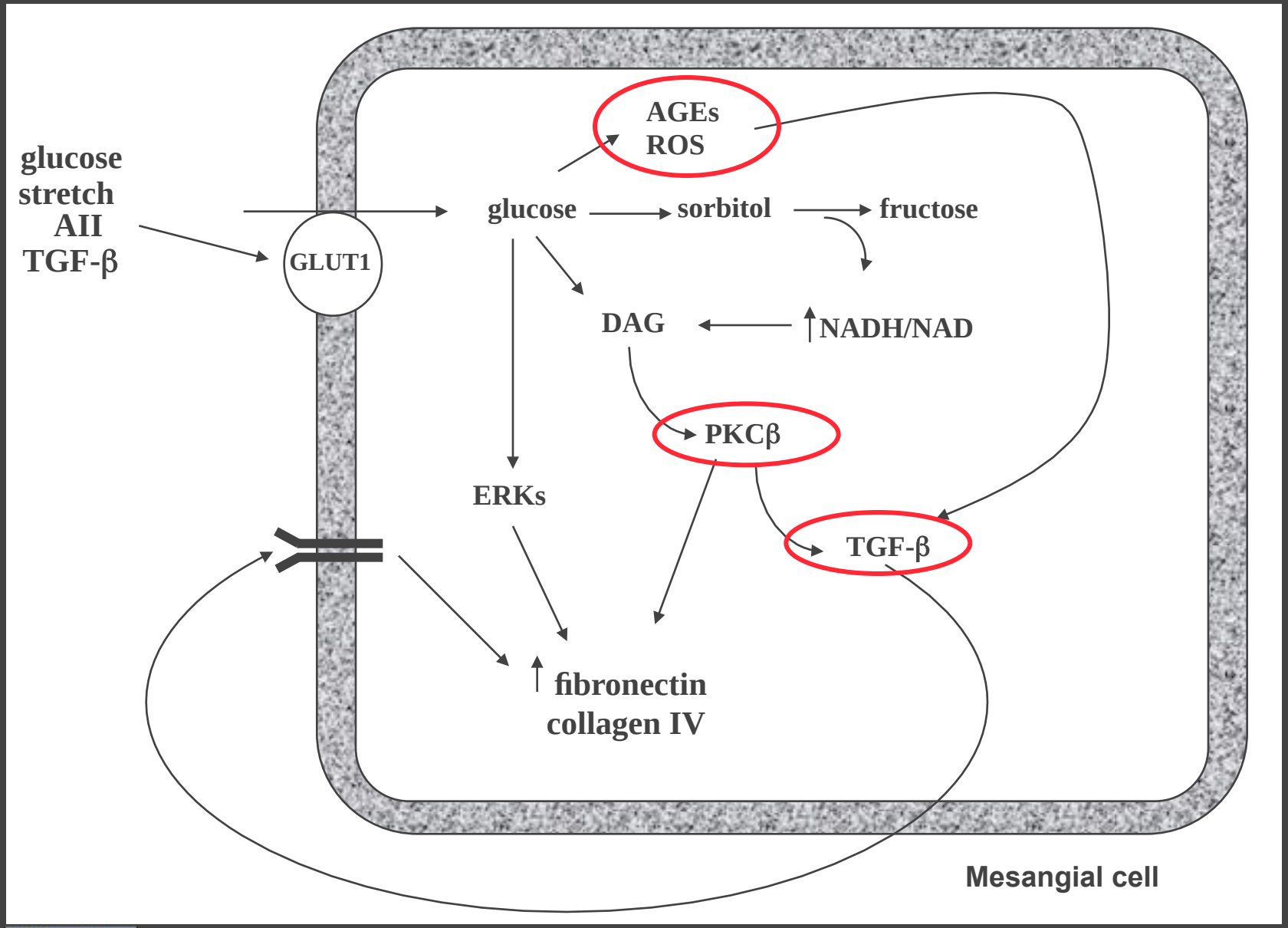


from T. Hostetter

Potential mechanisms for increased matrix production in hyperglycemia



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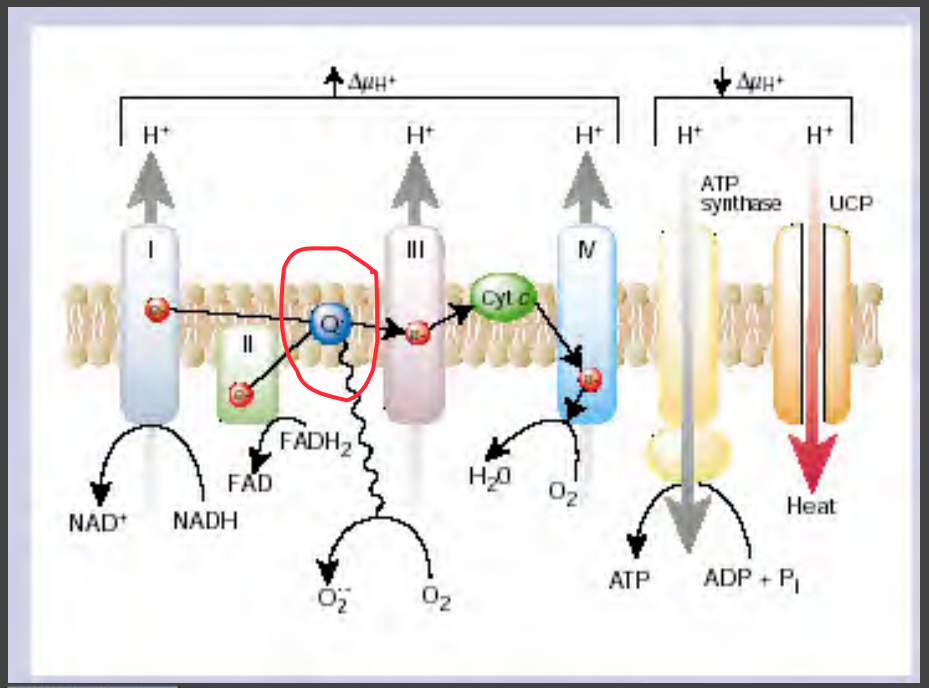
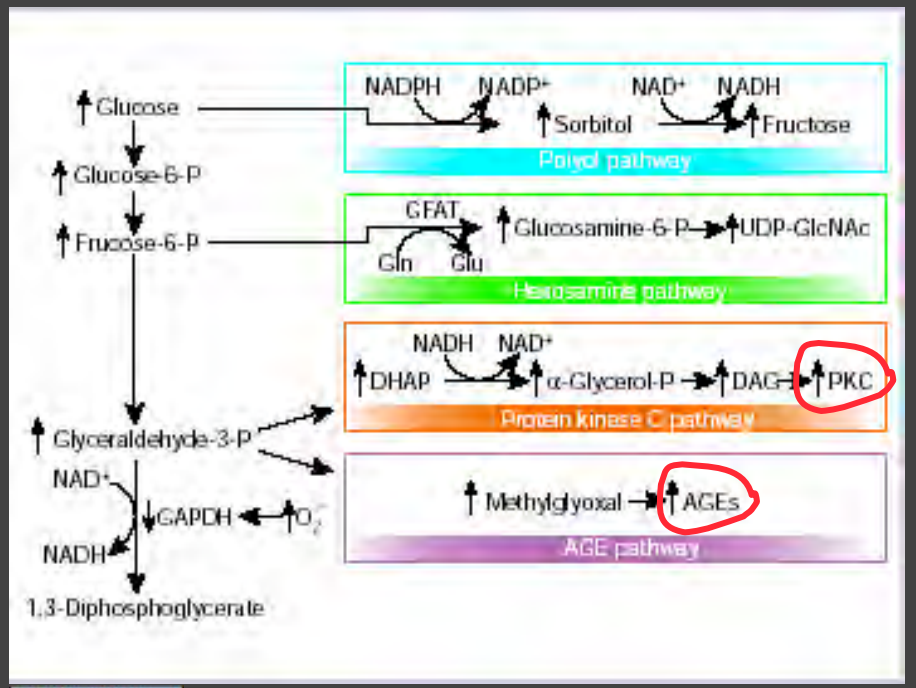
Unified field theorem for diabetic complications: oxidative stress rules

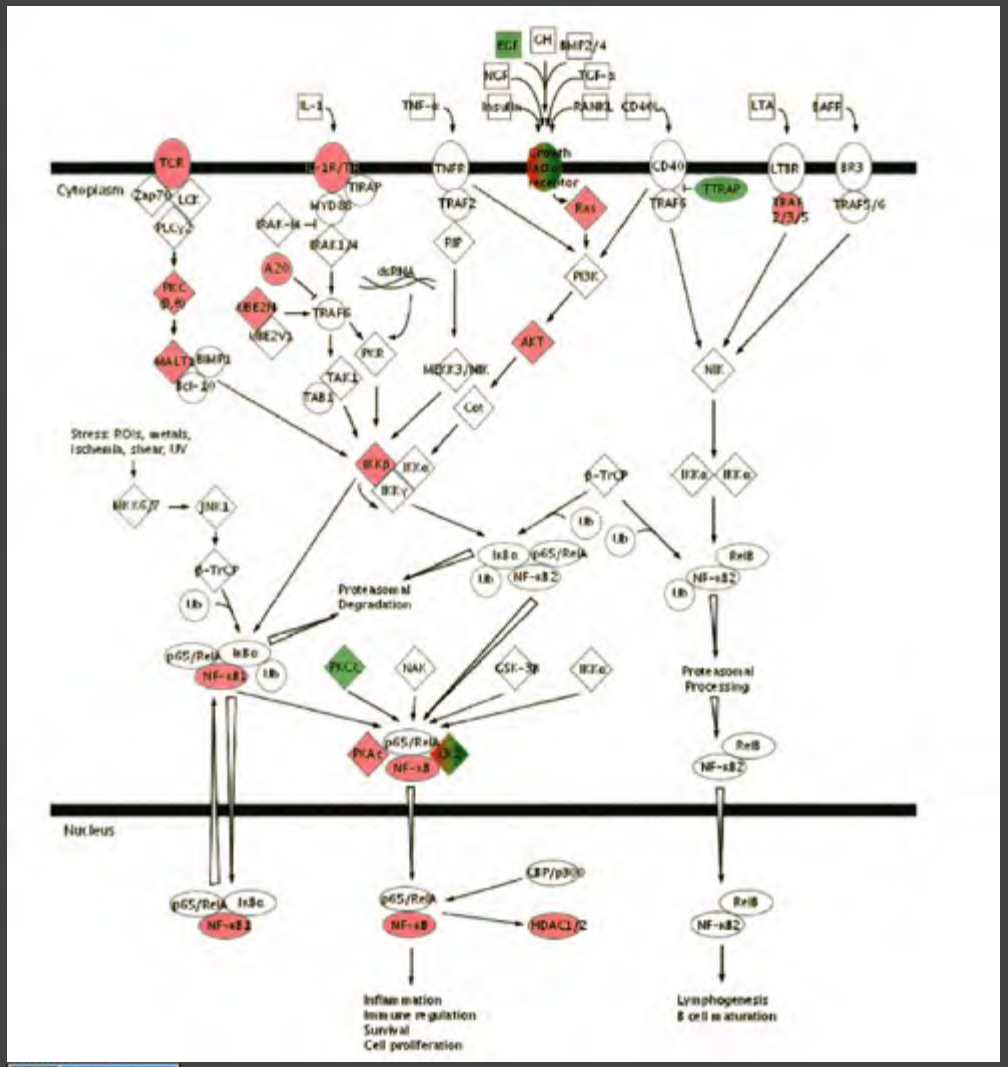


PD-INEL Brownlee, Nature, 414:813, 2001



PD-INEL Brownlee, Nature, 414:813, 2001

…or maybe it's all inflammation?



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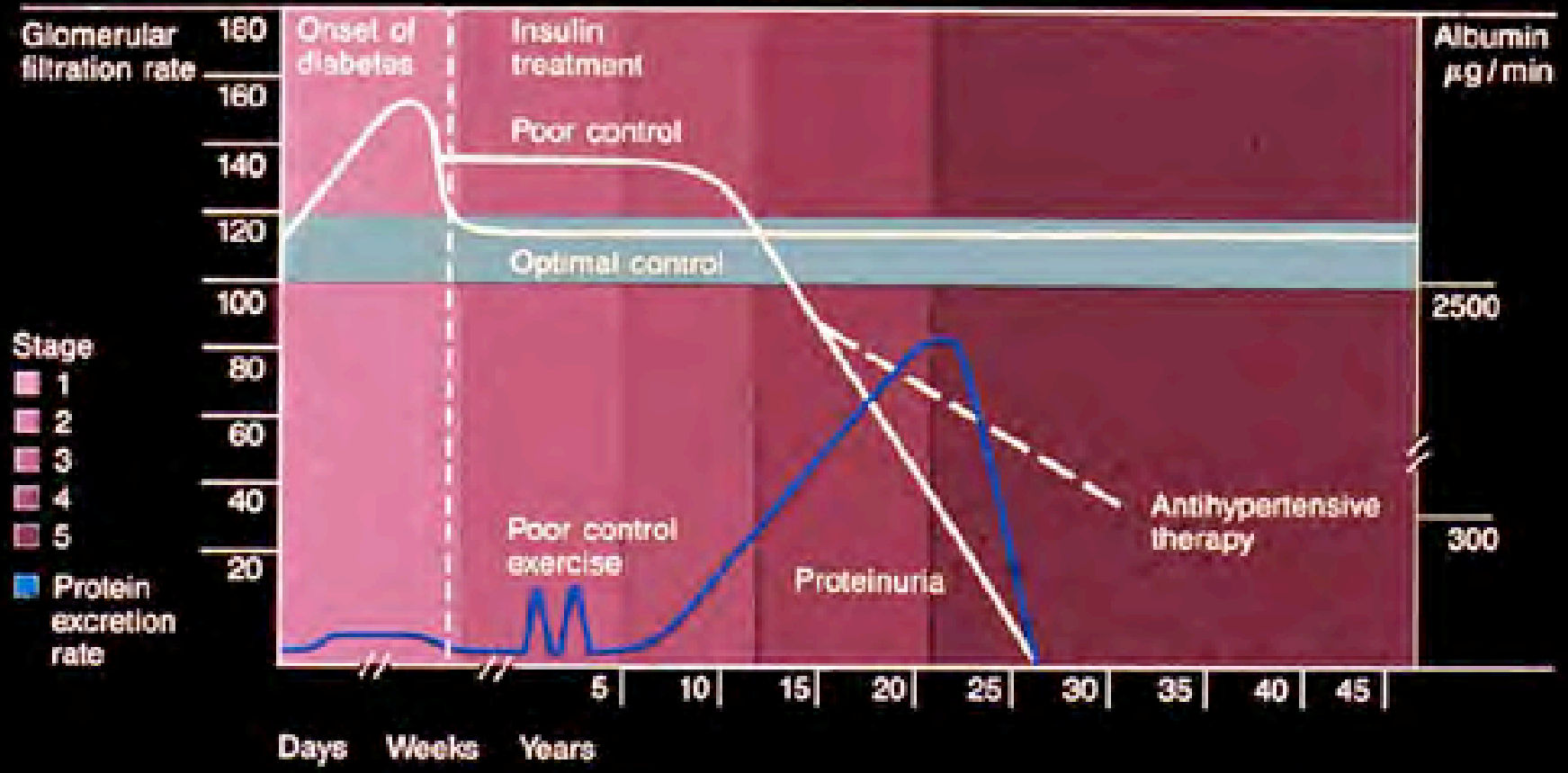
Scmid et al., Modular activation of nuclear factor-kappaB transcriptional programs in human diabetic nephropathy. Diabetes, 2006; 200;55:2993

Treatment

The stages of diabetic nephropathy



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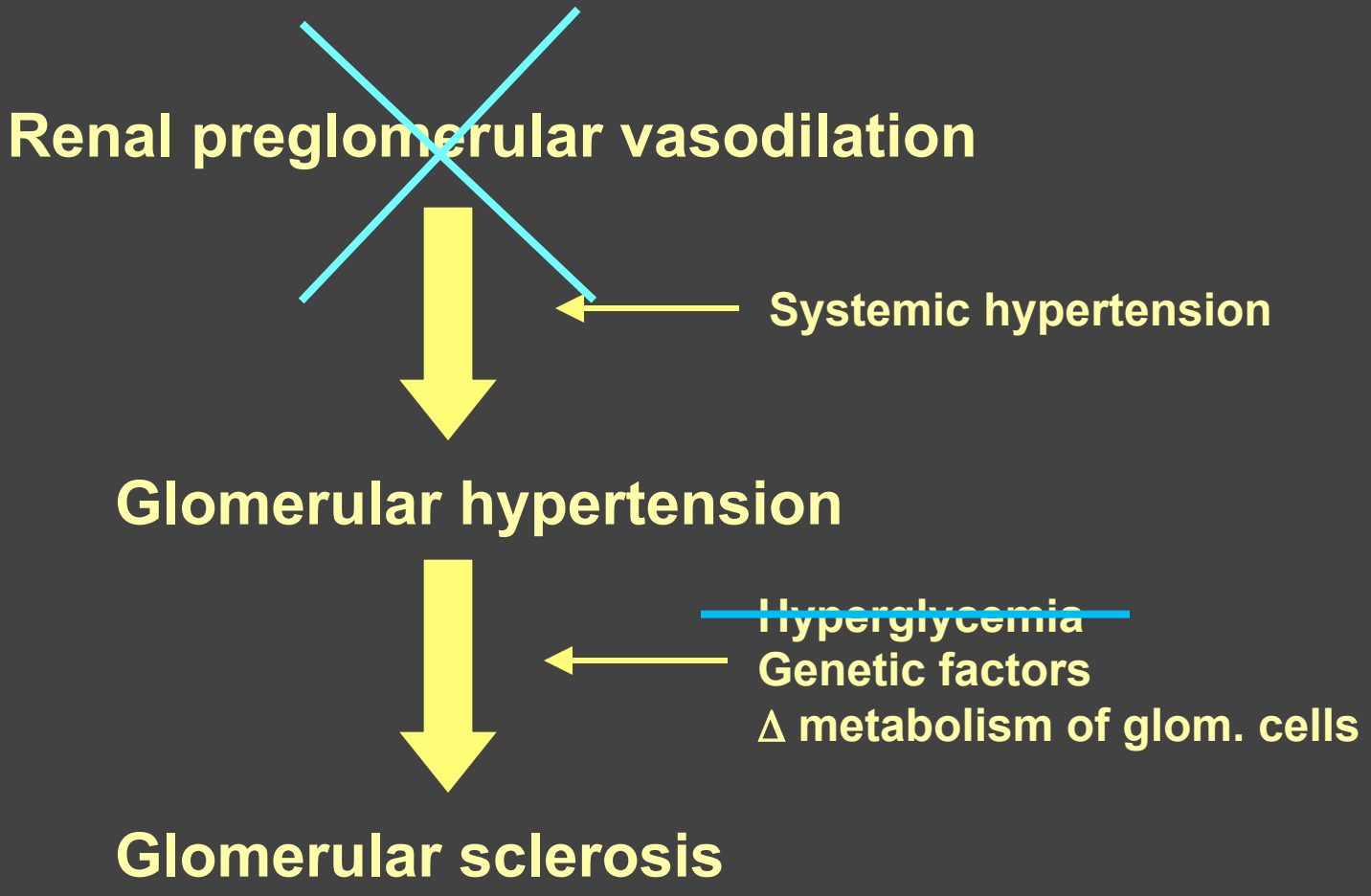
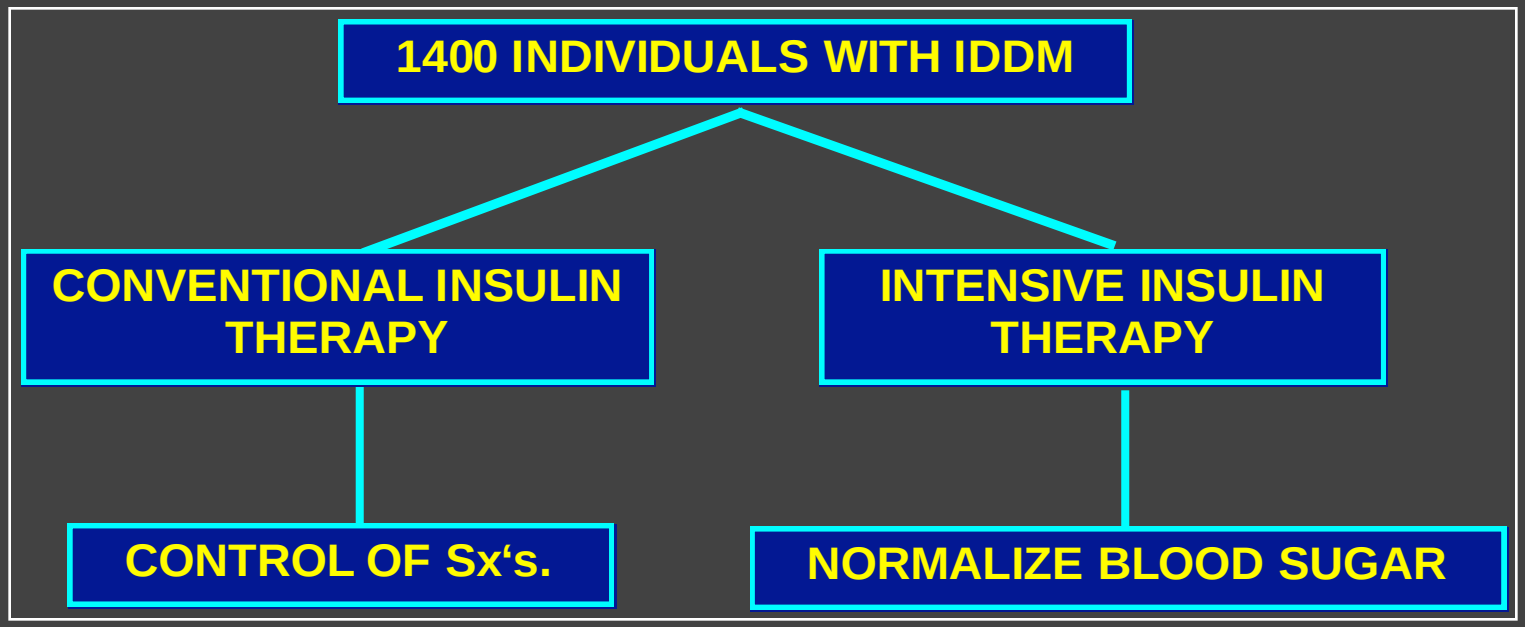
Treatment of DM nephropathy: Glucose control



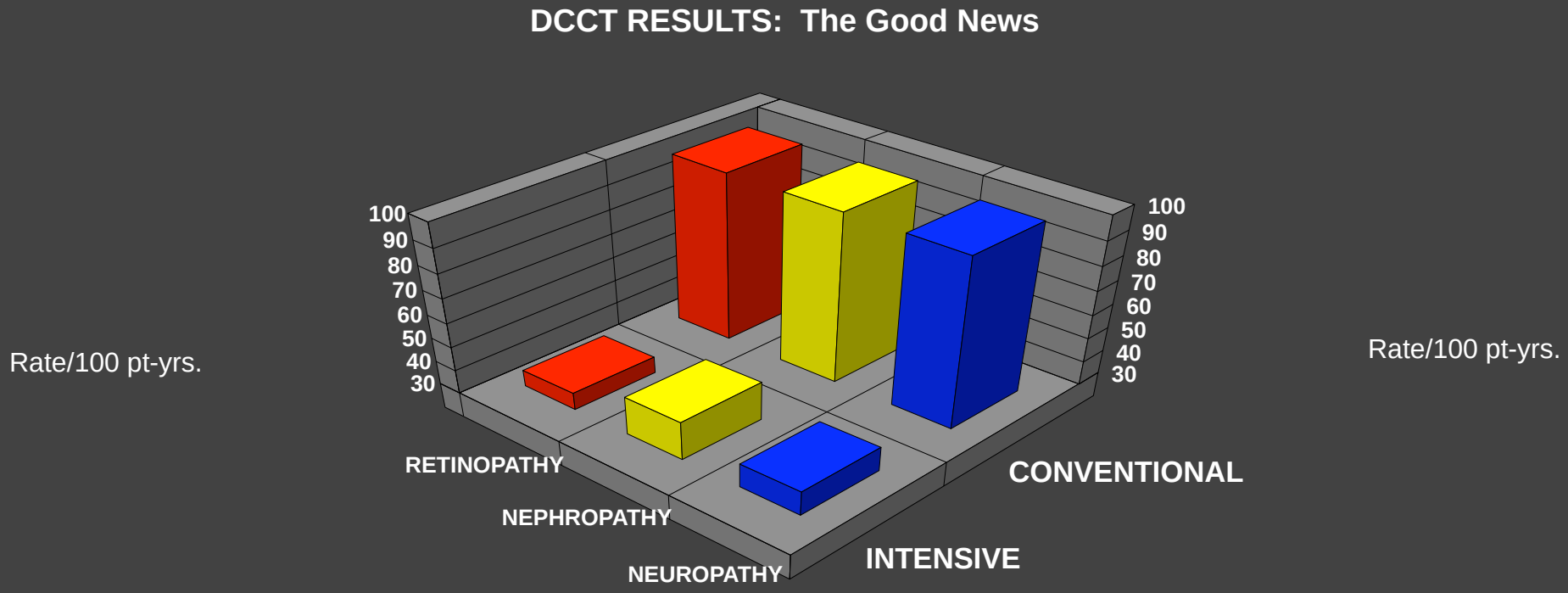
from T. Hostetter

The Diabetes Control And Complications Trial (DCCT) 1993



Does long-term normalization of blood glucose levels in type 1 diabetes reduce the risk of development or progression of microvascular complications?

The Benefits of “Tight Control”: The DCCT

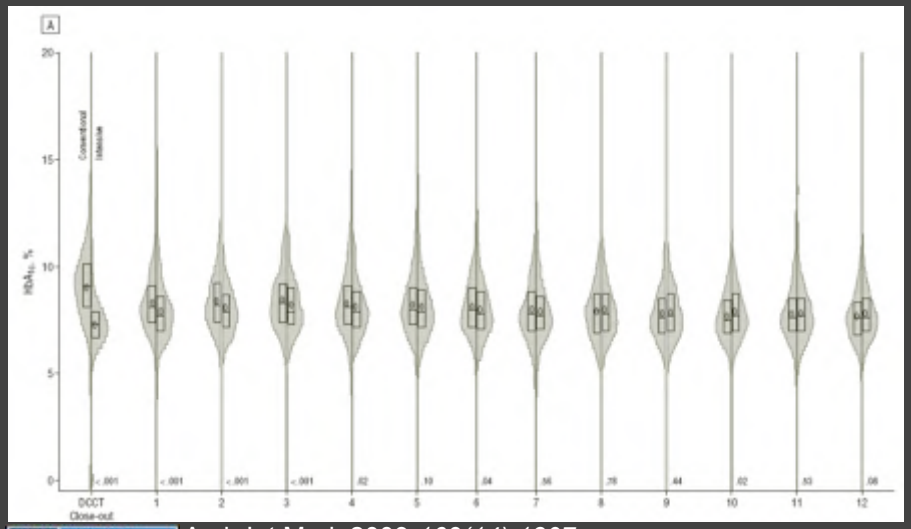


Intensive metabolic control dramatically reduced the risk of developing or worsening microvascular complications in type 1 diabetes.

The **United Kingdom Prospective Diabetes Study** (**UKPDS**), demonstrated very similar results in individuals with type 2 diabetes.

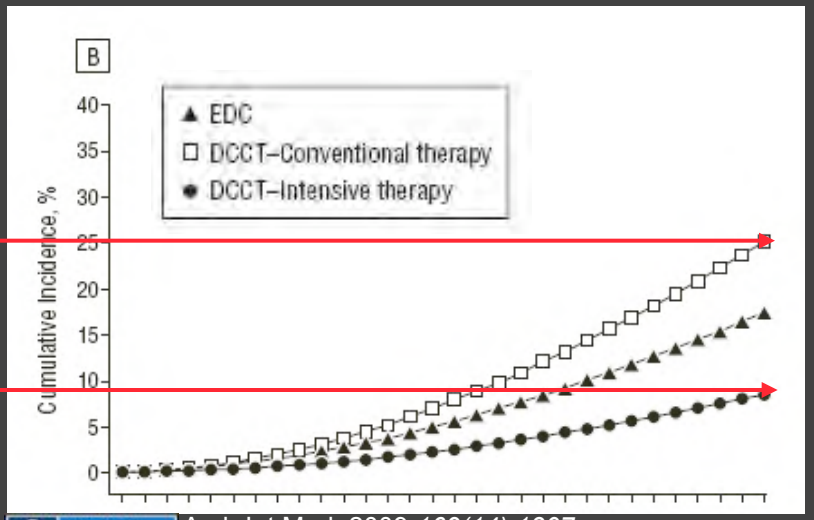
Intensive insulin Rx prevents diabetic nephropathy for years after (EDIC)

HbA1c levels after end of DCCT



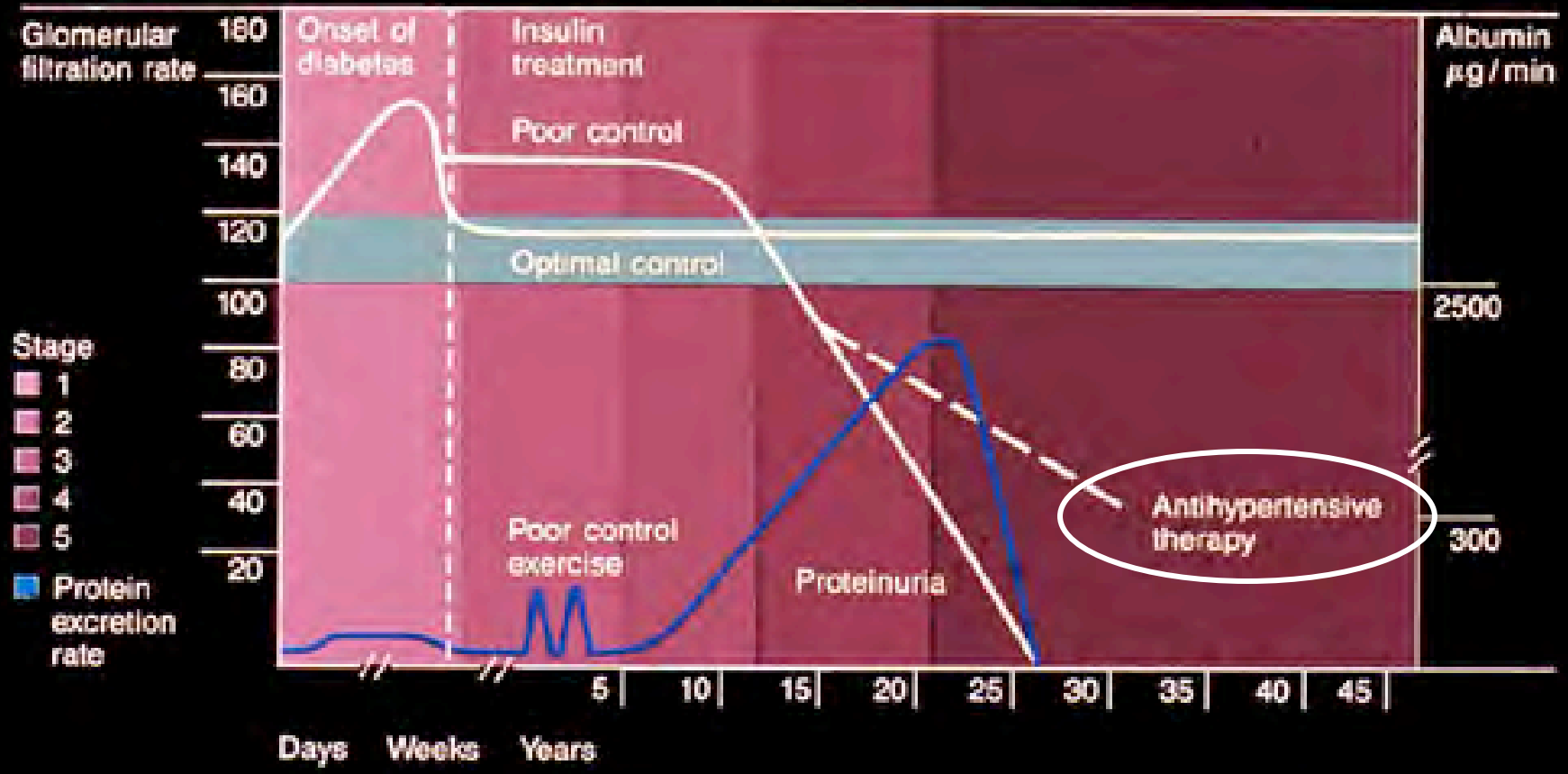
PD-INEL Arch Int Med; 2009;*169(14):1307*

Cumulative incidence of nephropathy



PD-INEL Arch Int Med; 2009;*169(14):1307*

The stages of diabetic nephropathy



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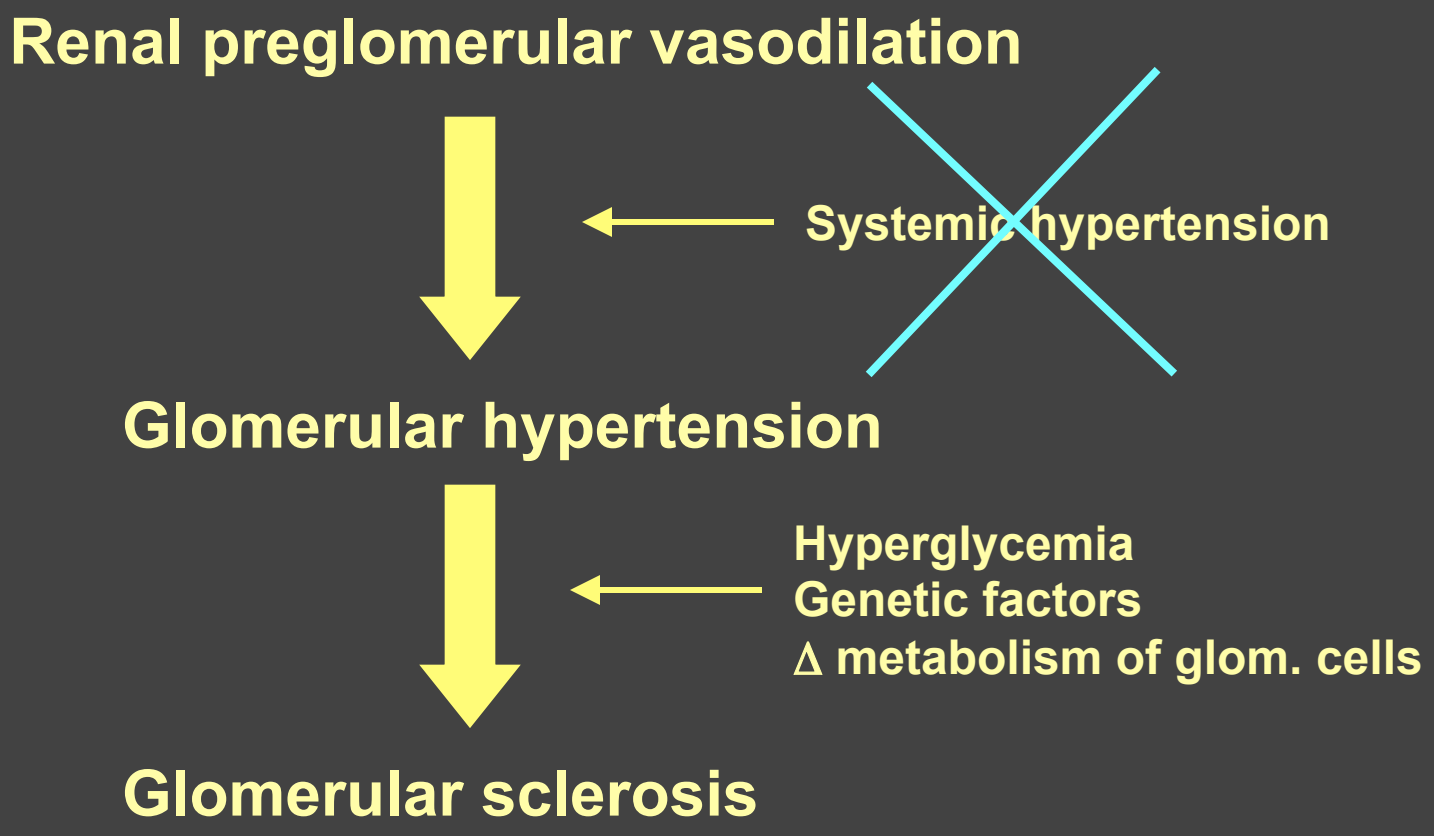
PD-INEL American Diabetes Association

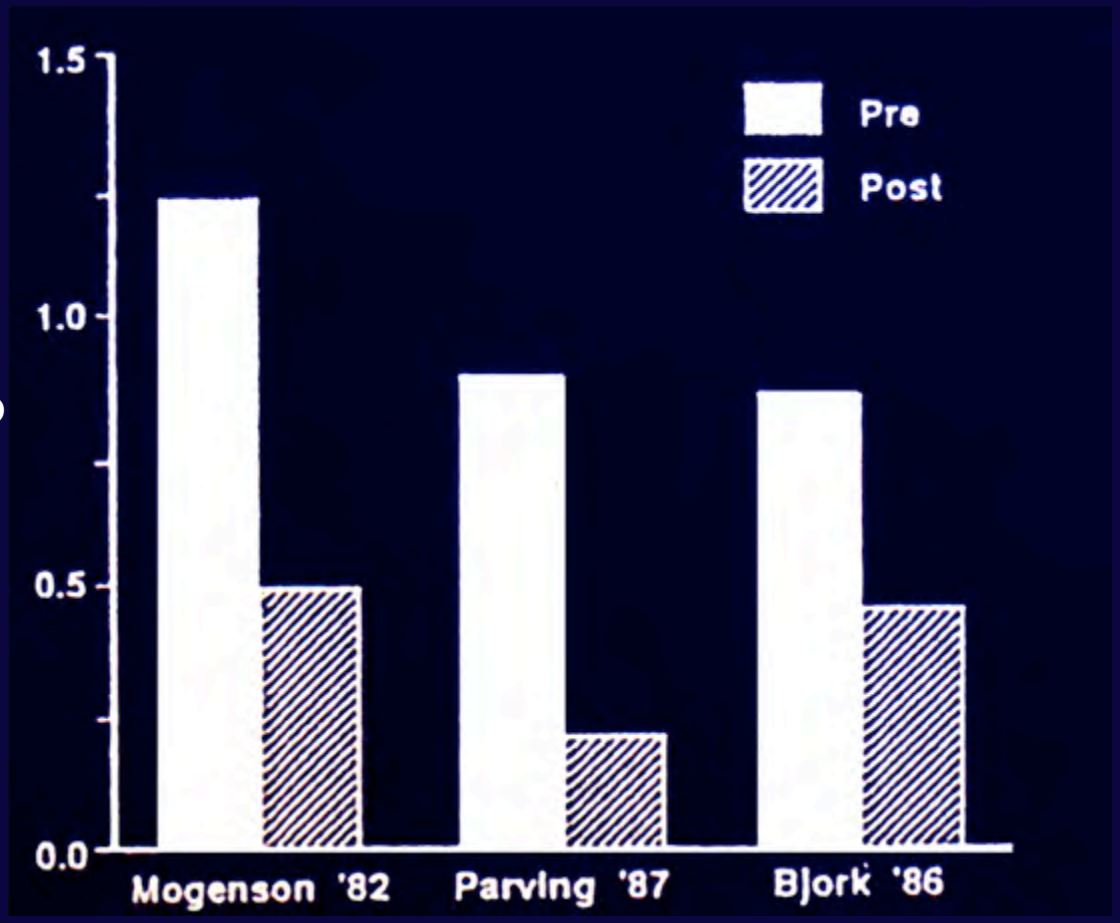
Treatment of DM nephropathy: Hypertension control



from T. Hostetter

Effect of antihypertensives on progression of DM nephropathy

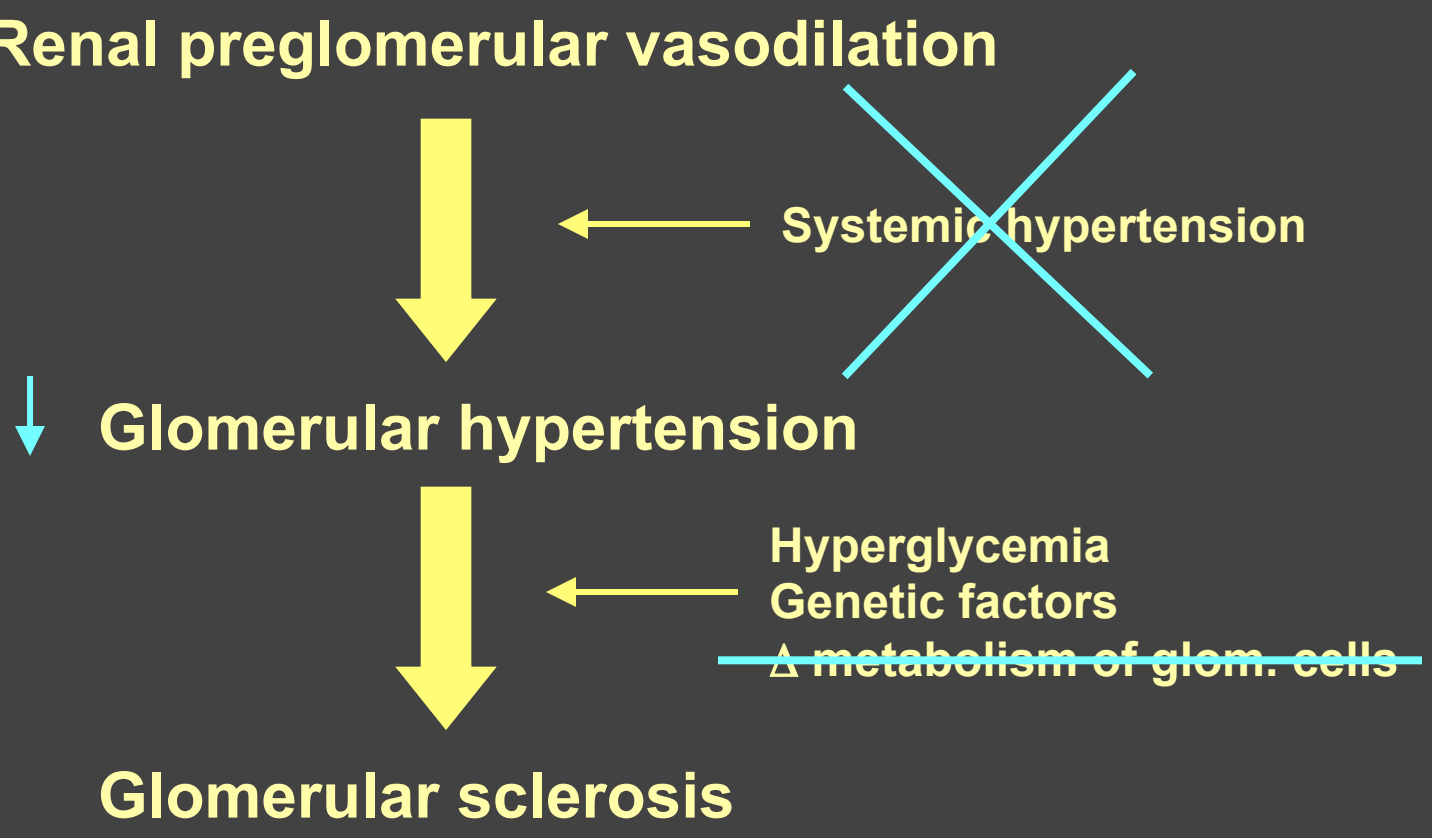
Rate of decline
In GFR (ml/min/mo



	Mogenson '82	Parving '87	Bjork '86
MAP post Rx (mmHg)	111	99	114

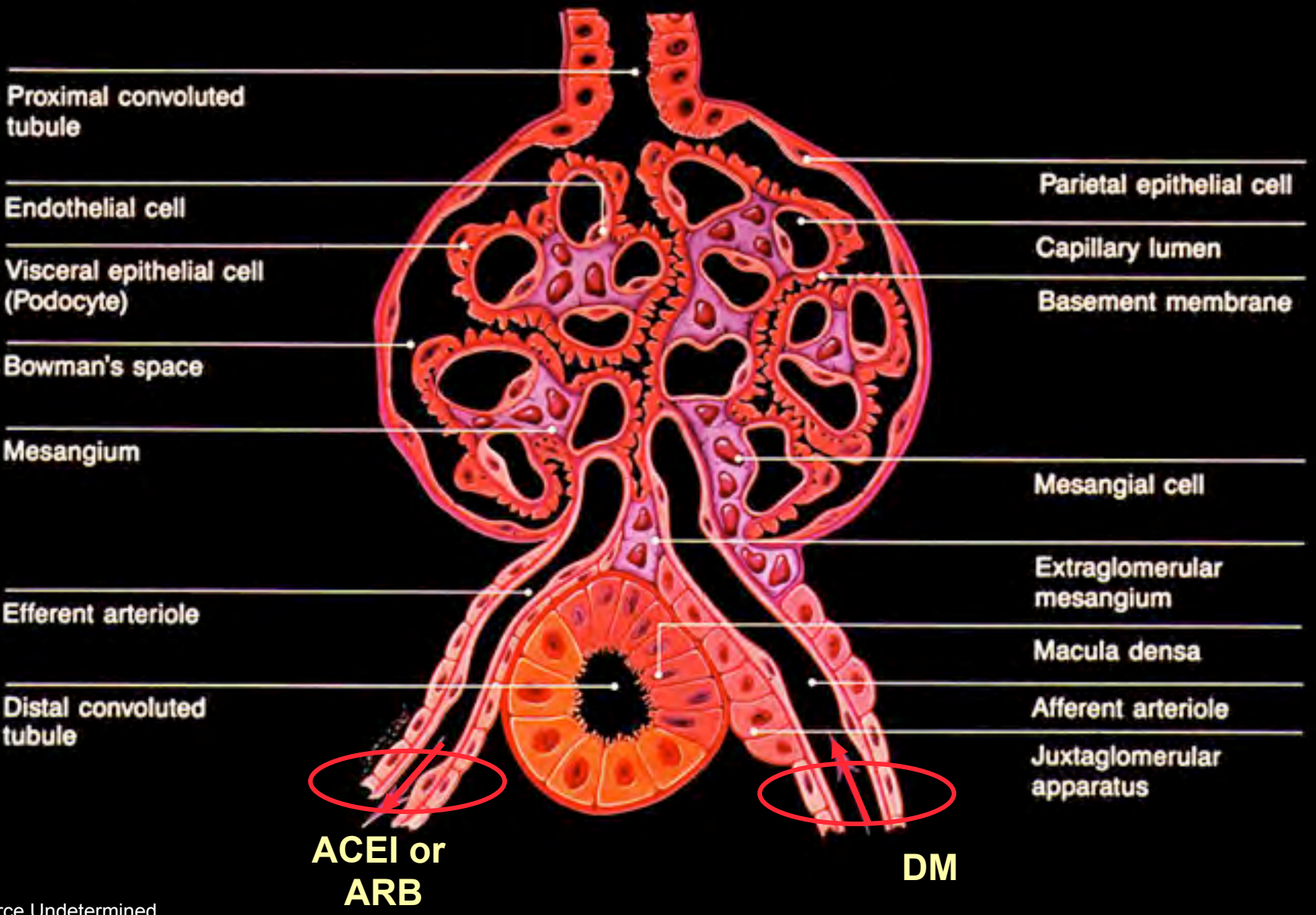
PD-INEL Source Undetermined

Treatment of DM nephropathy: Effect of ACEIs and ARBs



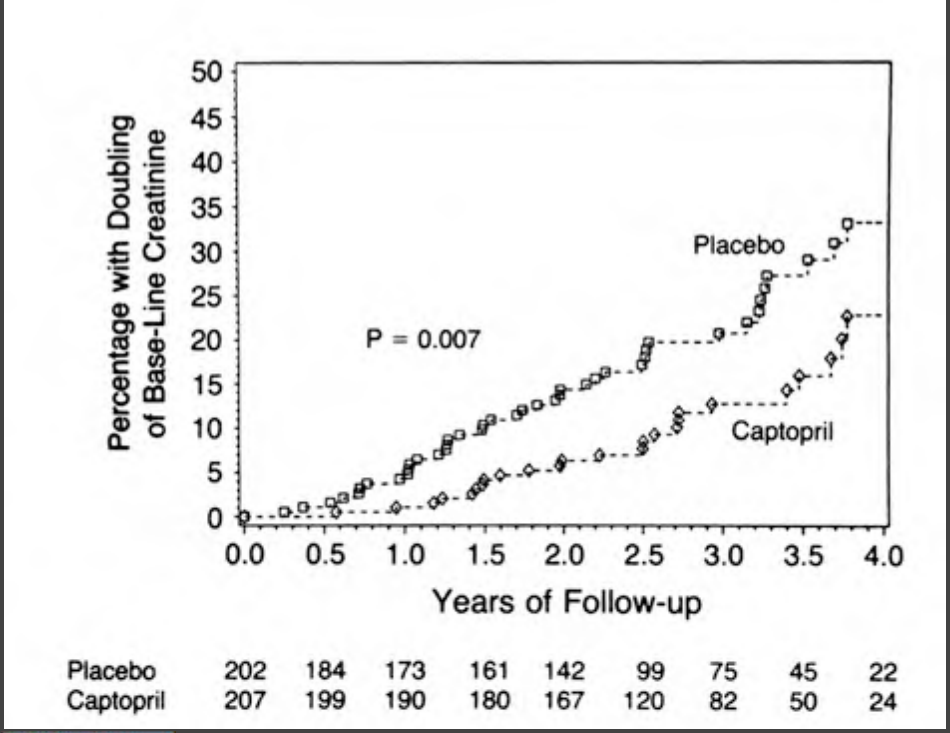
from T. Hostetter

The normal glomerulus

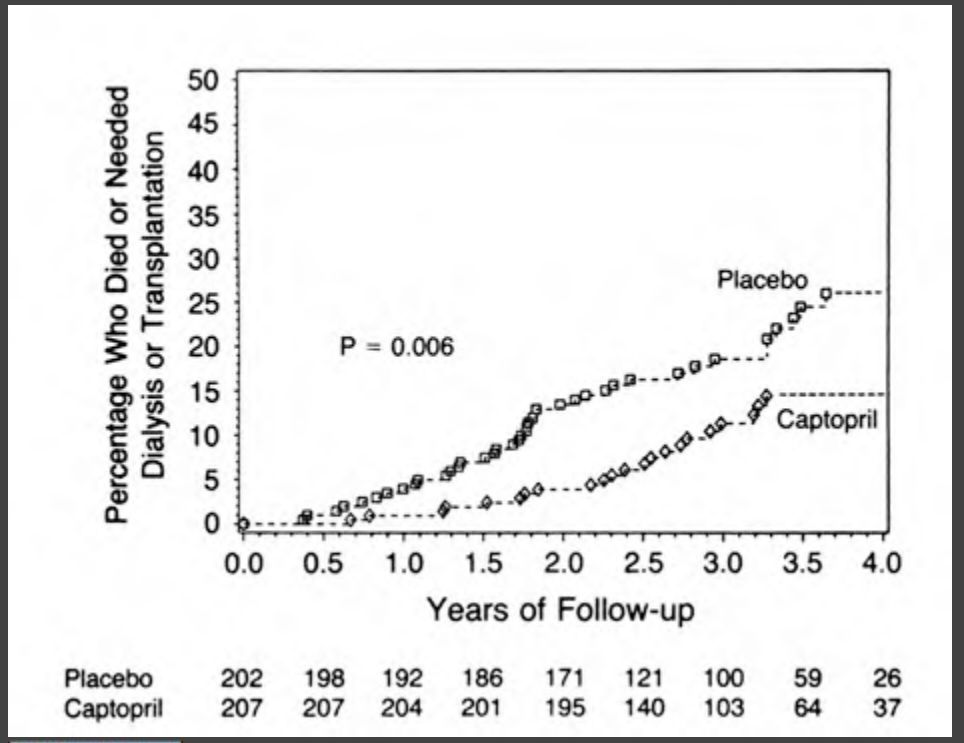


PD-INEL Source Undetermined

Delaying nephropathy with ACE inhibitors



PD-INEL Lewis et al., NEJM 329:1456, 1993



PD-INEL Lewis et al., NEJM 329:1456, 1993

Delay of diabetic nephropathy in type 2 patients with ARBs

RENAAL	Reduction of endpoints in non-insulin-dependent diabetes mellitus with the angiotensin II receptor antagonist losartan
IDNT	Irbesartan diabetic nephropathy trial
IRMA-II	irbesartan in patients with type II diabetes and microalbuminuria

ARB = angiotensin receptor blocker

NEJM, 2001

Delay of diabetic nephropathy in type 2 patients with ARBs

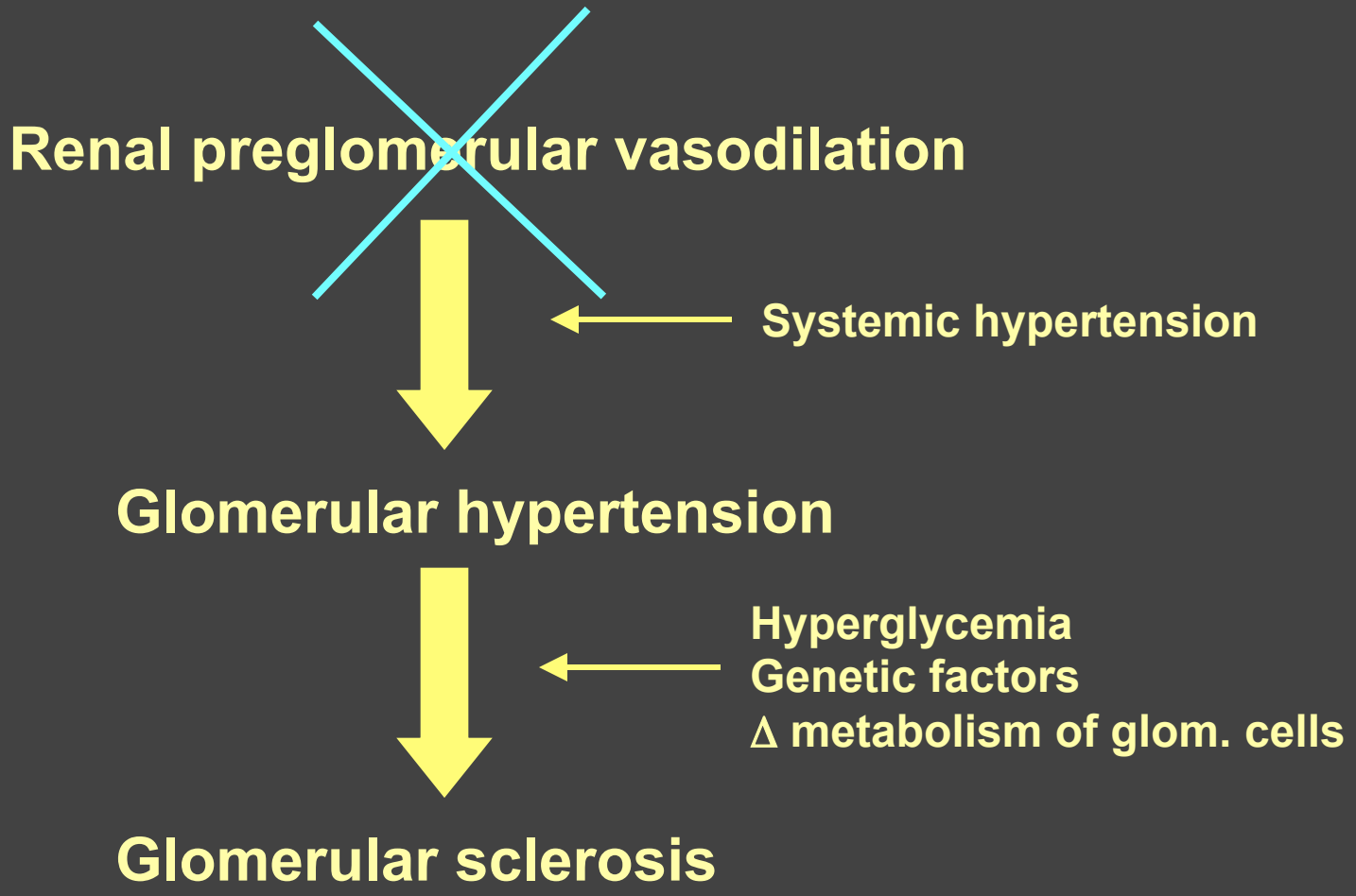
RENAAL and IDNT--

- •pts with established overt nephropathy
- •Age = 60 (IDNT)
- •virtually all pts hypertensive; groups had similar BPs
- •endpoints = 2x serum creatinine, ESRD, death
- •20-33% reduction in endpoints in ARB treated pts vs control or amlodipine-treated pts

IRMA-II

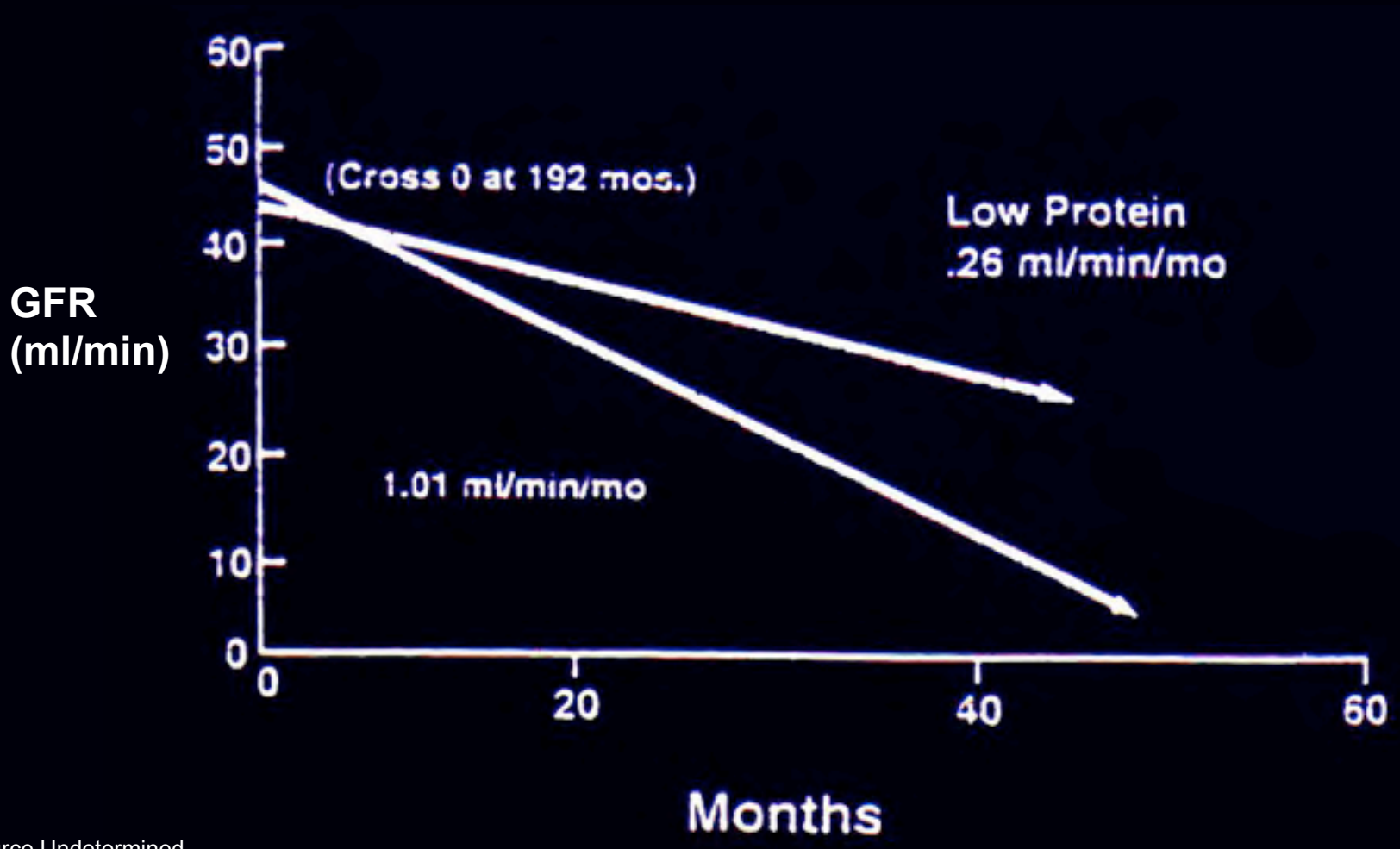
- • reduction in proteinuria and rate of progression to overt nephropathy in type 2 pts with microalbuminuria

Treatment of DM nephropathy: Effect of dietary protein restriction



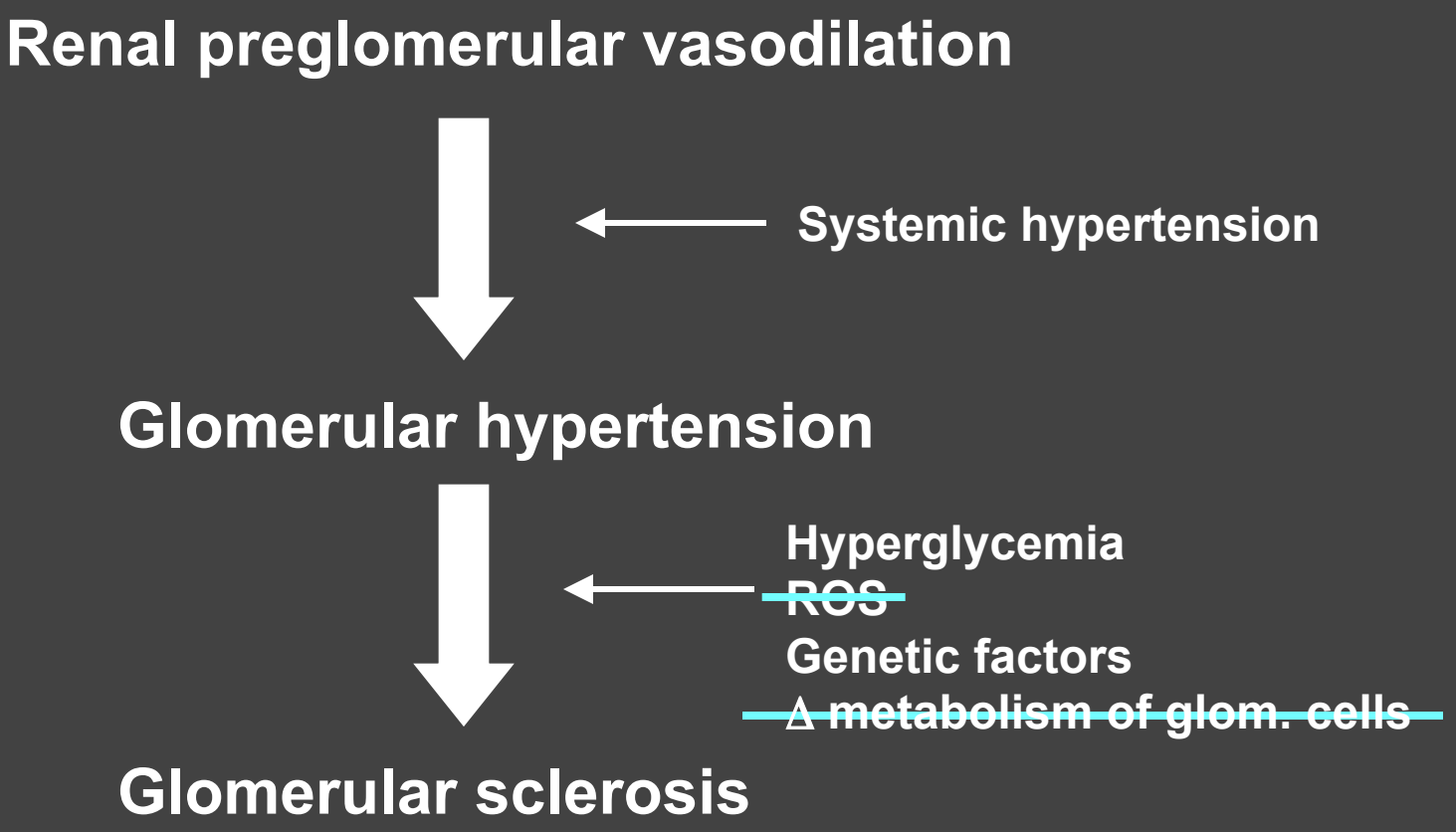
from T. Hostetter

Effect of dietary protein restriction on progression of DM nephropathy



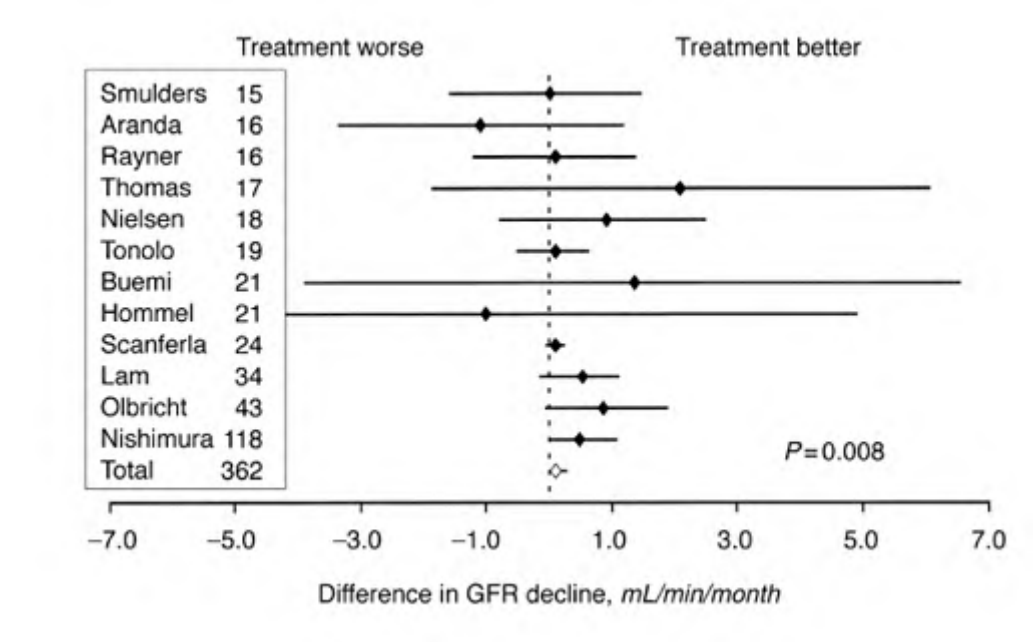
PD-INEL Source Undetermined

Treatment of DM nephropathy: Effect of statins

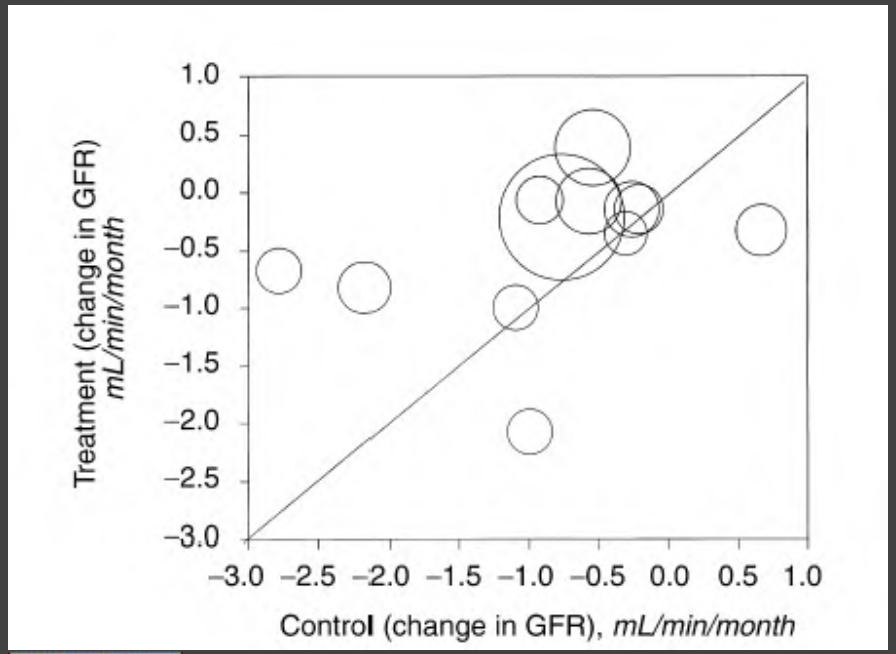


from T. Hostetter

Effects of lipid lowering on progression of diabetic nephropathy

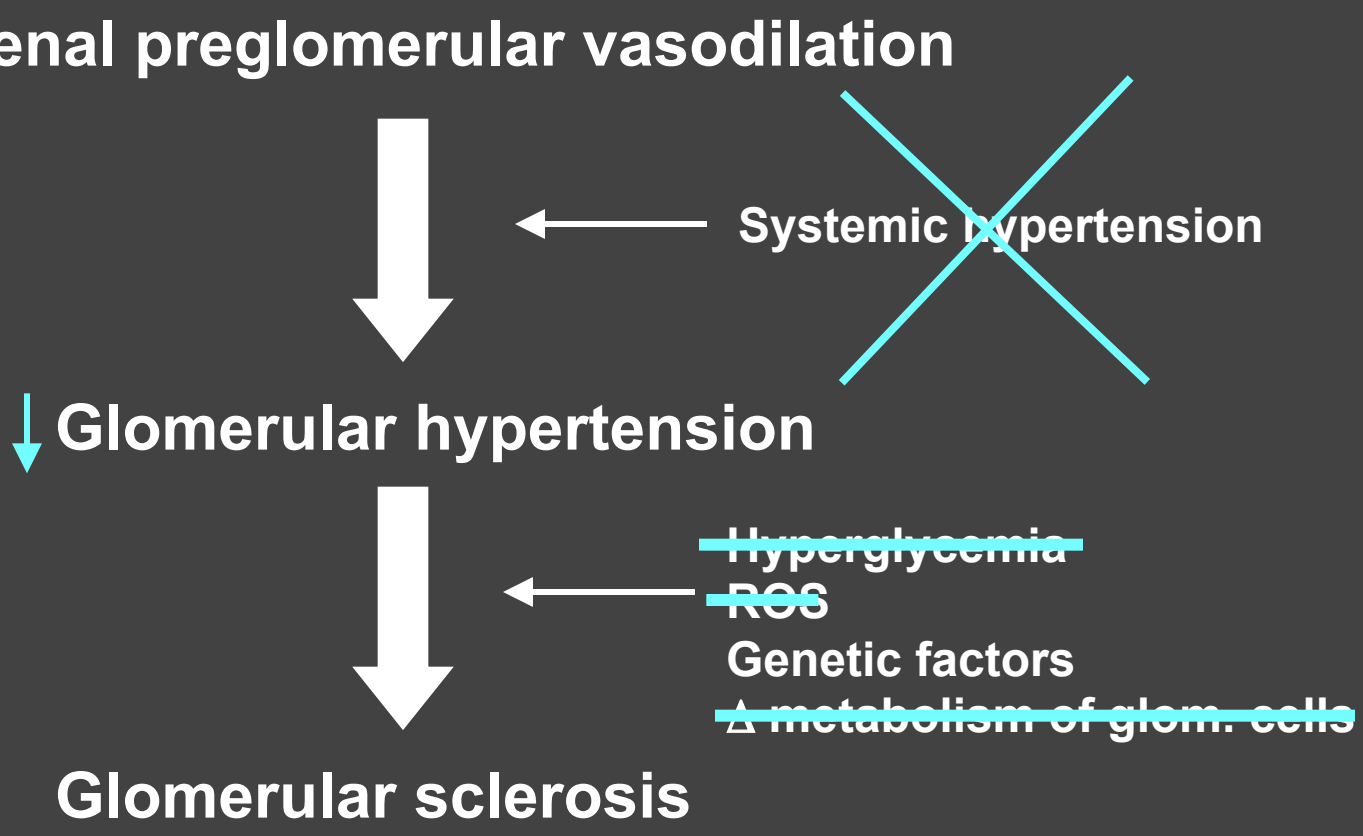


PD-INEL Fried, et al., Kidney Int, 2001; 59:260



PD-INEL Fried, et al., Kidney Int, 2001; 59:260

Treatment of DM nephropathy: All together!



from T. Hostetter

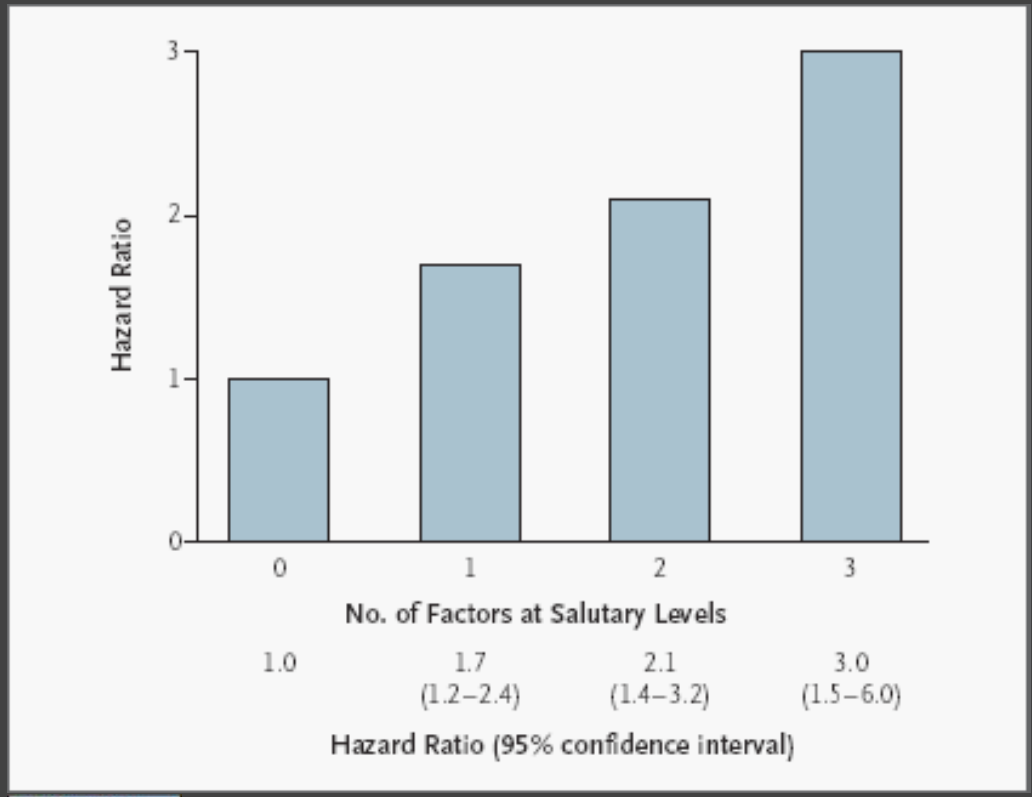
Remission of microalbuminuria

Table 3. Results of the Cox Regression Analysis of Regression of Microalbuminuria with the Use of Time-Dependent Factors.*

Factor	Adjusted Hazard Ratio (95% CI)	P Value†
Nonmodifiable		
Age (≤26 vs. >26 yr)	1.6 (1.2–2.2)	0.004
Incidence cohort (vs. prevalence cohort)‡	1.8 (1.2–2.6)	0.003
Modifiable		
Lipid status§		0.002
Cholesterol <198 mg/dl, triglycerides <145 mg/dl	2.4 (1.4–4.0)	
Cholesterol <198 mg/dl, triglycerides ≥145 mg/dl	1.9 (1.0–3.8)	
Cholesterol ≥198 mg/dl, triglycerides <145 mg/dl	2.1 (1.2–3.5)	
Cholesterol ≥198 mg/dl, triglycerides ≥145 mg/dl¶	1.0	
Glycosylated hemoglobin		0.02
<8.0 %	1.9 (1.2–2.9)	
8.0–8.9 %	1.5 (1.0–2.3)	
9.0–9.9 %	1.2 (0.8–1.9)	
≥10.0 %¶	1.0	
Systolic blood pressure‖		0.02
<115 mm Hg	1.4 (1.0–1.9)	
≥115 mm Hg¶**	1.0	

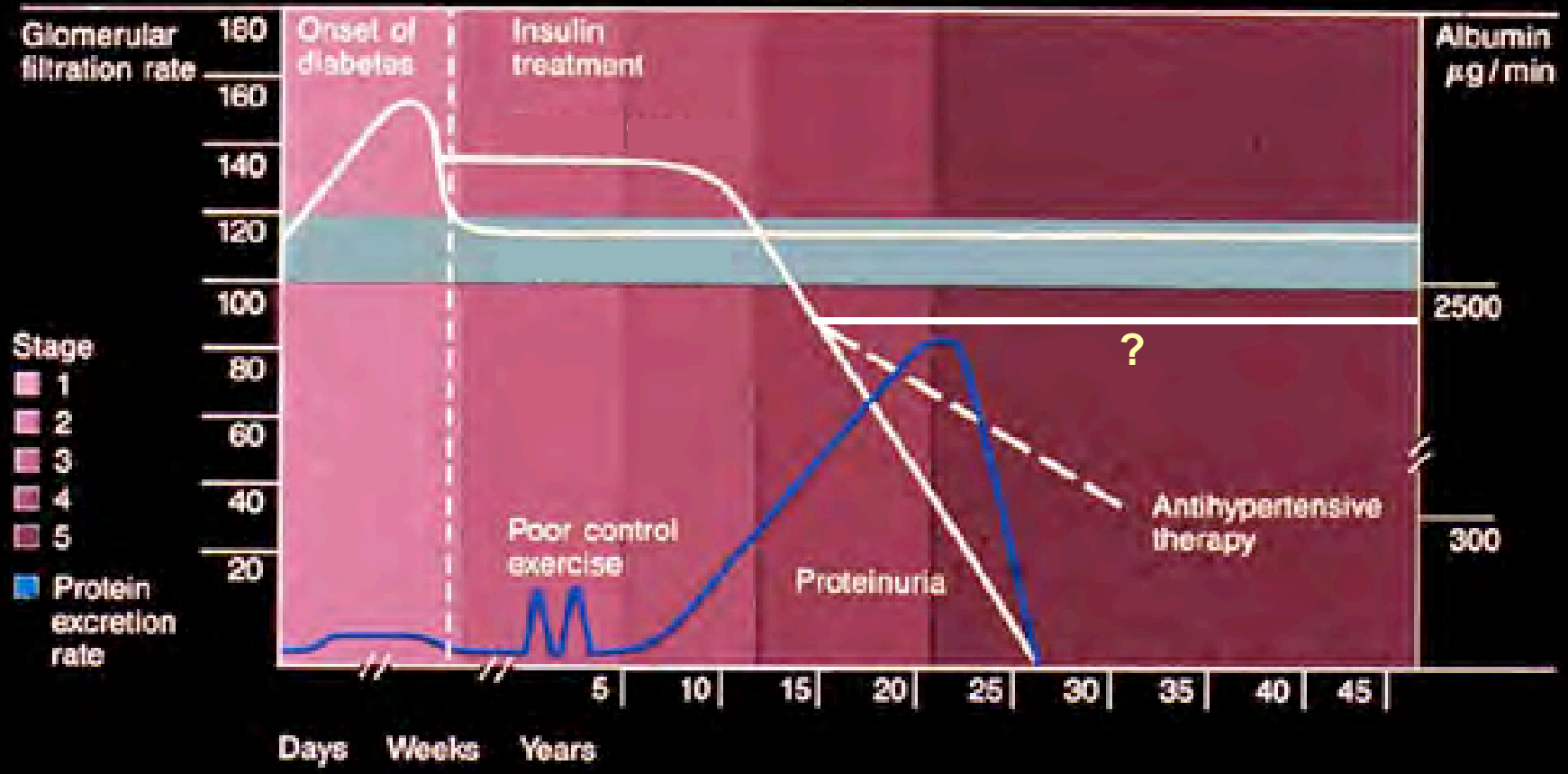
PD-INEL NEJM 348: 2265, 2003

Likelihood of regression



PD-INEL NEJM 348: 2265, 2003

The stages of diabetic nephropathy



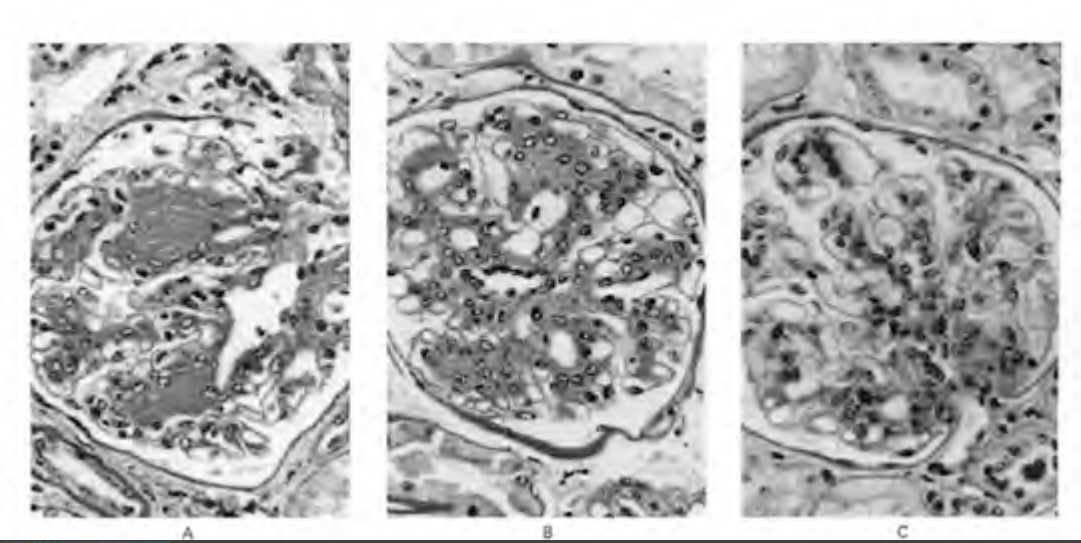
Adapted with permission from the American Diabetes Association, Inc., from Mogensen CE, Vittingus E: The stages in diabetic renal disease. *Diabetes* 1983; 32 (suppl 2): 64-68 and also with permission from Hostetter TH: Diabetic nephropathy. In Brenner BM, Rector FC Jr (eds): The Kidney. 3d ed., Philadelphia, PA: WB Saunders Co; 1986: chap 31.

PD-INEL American Diabetes Association

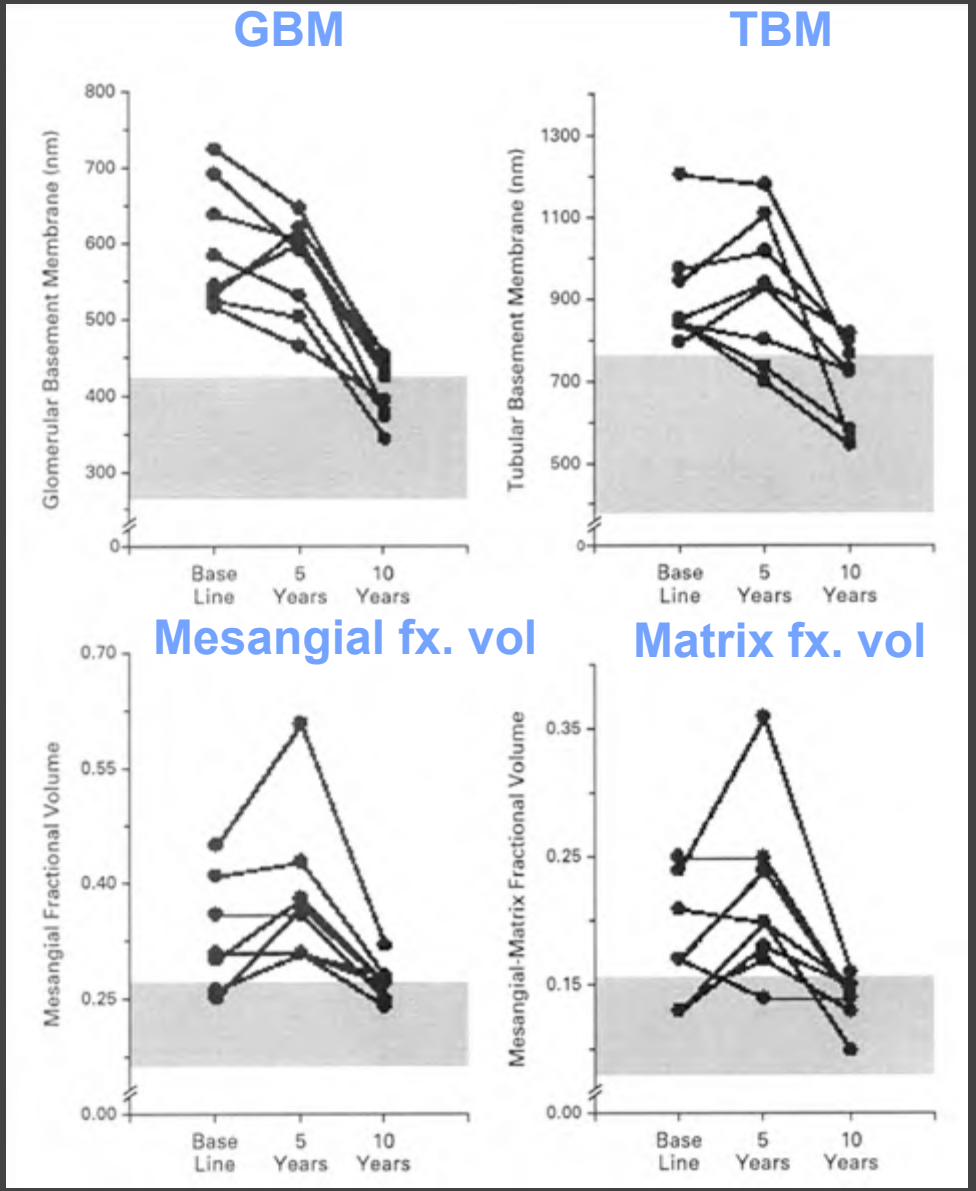
Remittive effect of pancreas Tx on DM nephropathy

time after Tx

0 yr | 5 yr | 10 yr

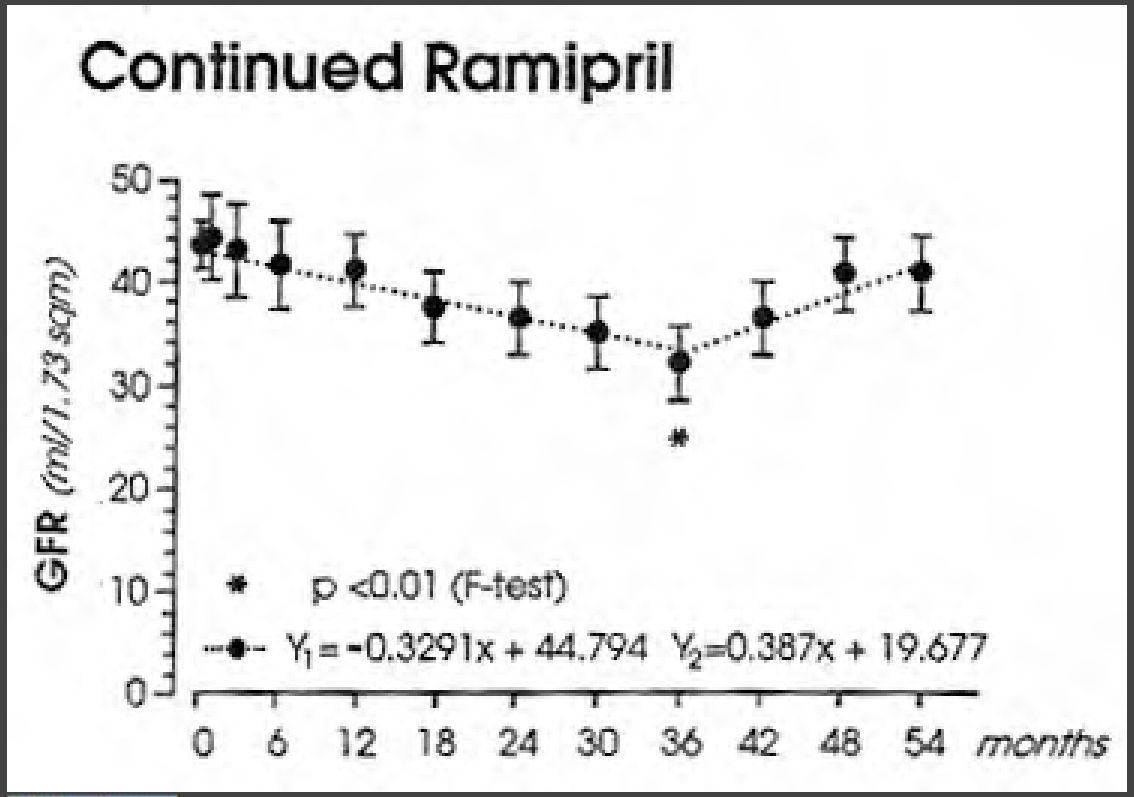


PD-INEL Fioretto, et al. N Engl J Med. 1998, 339:69



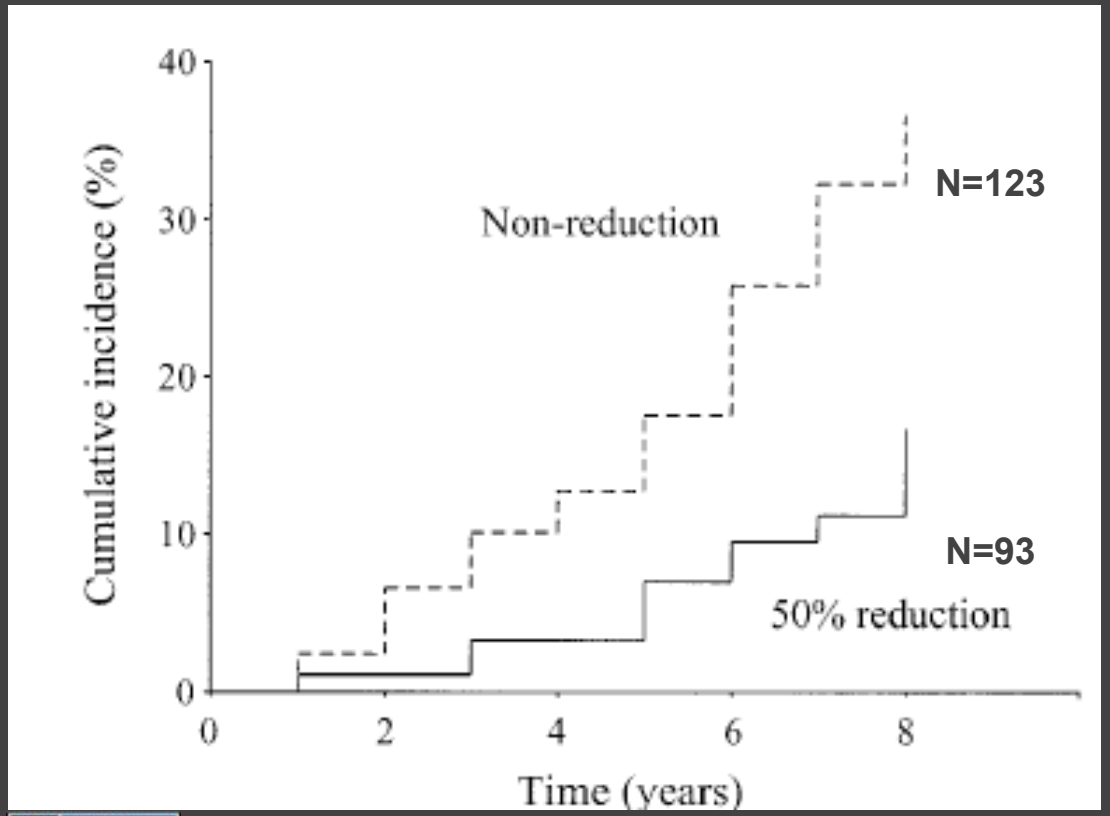
PD-INEL Fioretto, et al. N Engl J Med. 1998, 339:69

Remittive effect of long term ACEI on chronic nephropathies



PD-INEL Ruggenenti, JASN10:997, 99

Remission of microalbuminuria results in fewer cardiovascular and kidney events



PD-INEL Araki, et al., Diabetes. 2007 Jun;56:1727

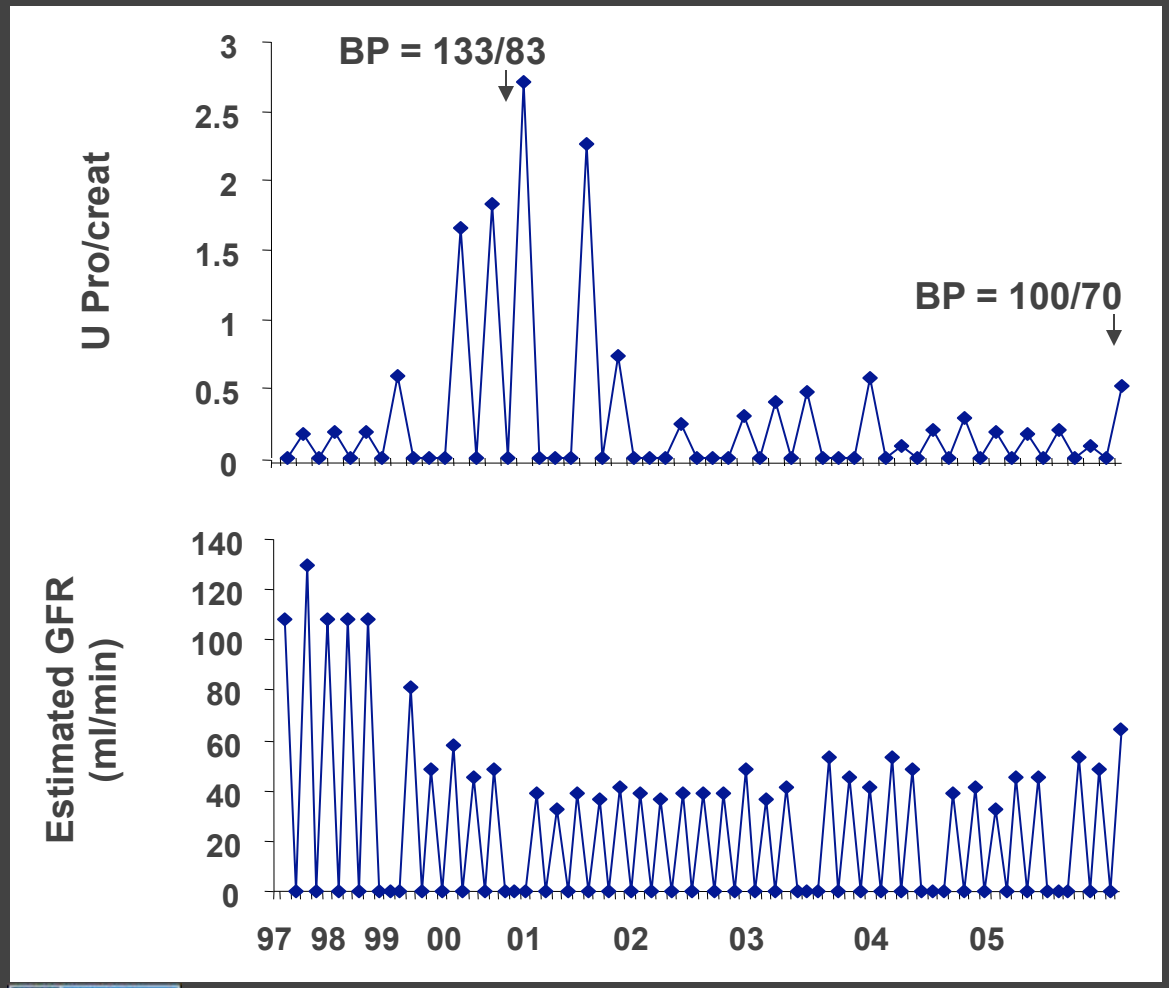
TABLE 3
The risk of death from and hospitalization for renal and cardiovascular events, evaluated using the pooled logistic regression analysis

	Crude risk (95% CI)	Adjusted risk (95% CI)	
		Model 1	Model 2
Reduction of albuminuria			
50% reduction	0.38 (0.16–0.91)	0.47 (0.17–0.98)	0.41 (0.15–0.96)
Nonreduction	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Stage of diabetic nephropathy			
Remission	0.30 (0.09–0.98)	0.27 (0.08–0.91)	0.25 (0.07–0.87)
No change	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Progression	2.31 (1.06–5.07)	2.45 (1.06–5.65)	2.55 (1.04–6.30)

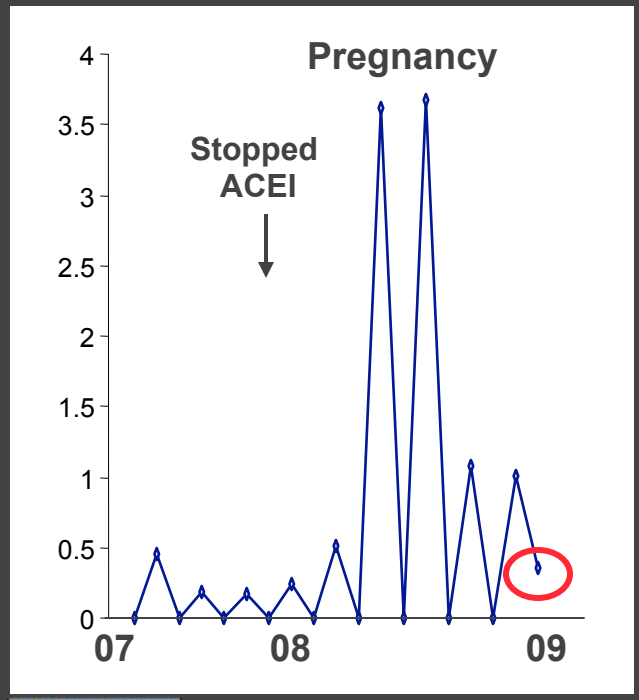
Model 1 adjusted for sex and age, initial AER levels, and a history of cardiovascular disease. Model 2 adjusted for sex, age, initial AER levels, a history of cardiovascular disease, current smoking, A1C, total and HDL cholesterol, triglyceride, systolic and diastolic blood pressure, BMI, and the use of ACE inhibitors, angiotensin receptor blockers, or lipid lowering-drugs. ref., referent.

PD-INEL Araki, et al., Diabetes. 2007 Jun;56:1727

Clinical course — M.W. (34 yo female with type 1 DM for 33.5 yrs)



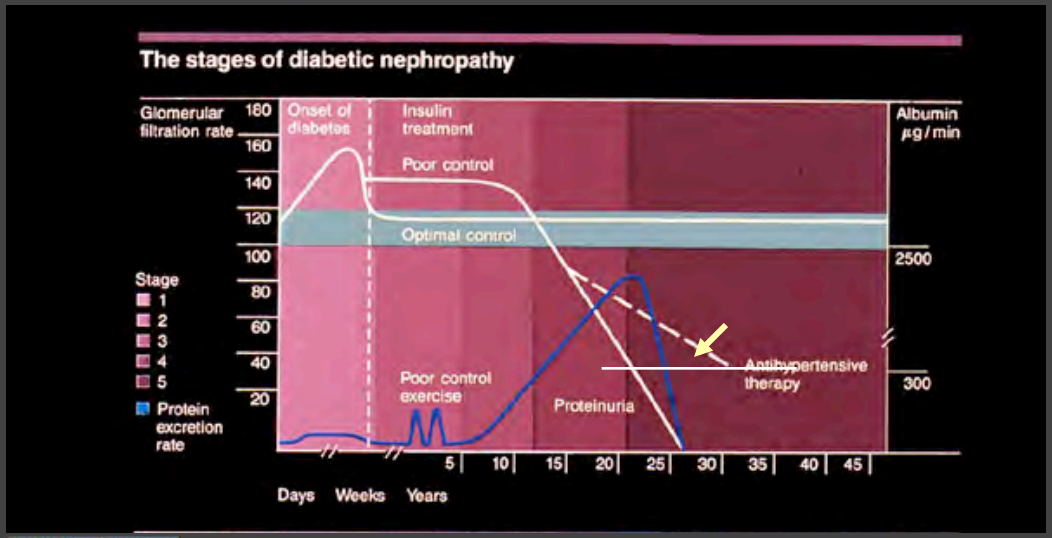
PD-INEL Source Undetermined



PD-INEL Source Undetermined

Last eGFR = 47 ml/min

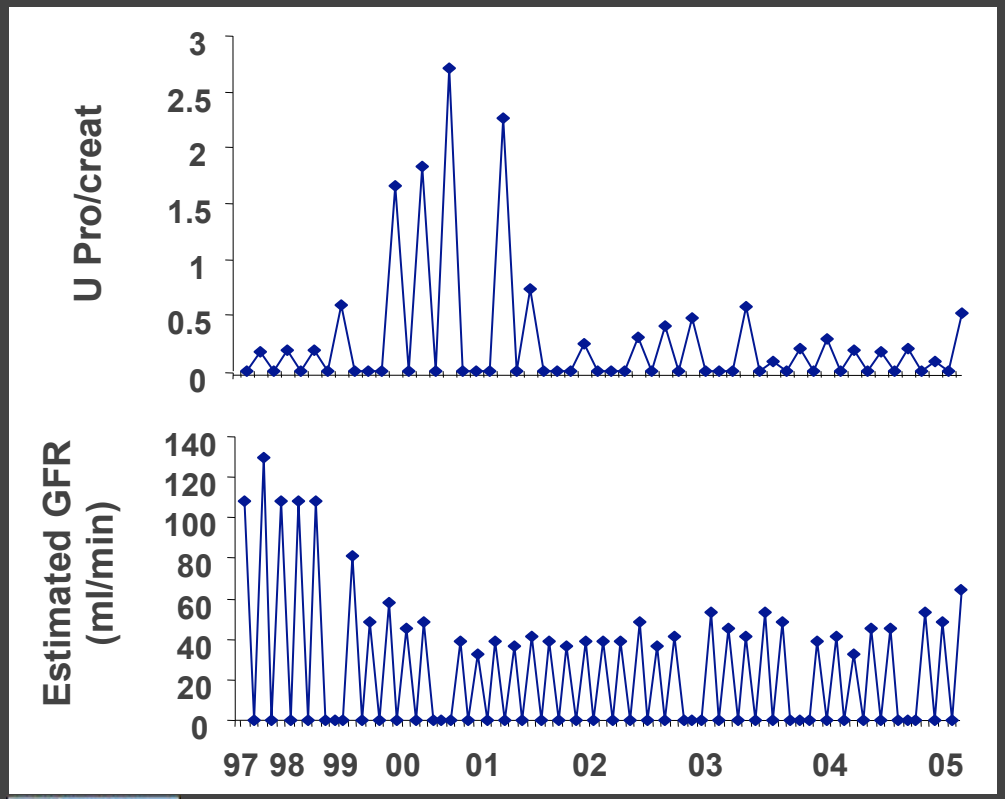
Diabetic Nephropathy: "You can't cure it so you have to endure it"



PD-INEL American Diabetes Association

With current treatment, we can keep patients stable or in remission for years…..

But can we do better?



PD-INEL Source Undetermined

Management of Diabetic Nephropathy-Dx

- Screen for microalbuminuria **and eGFR** (1x/yr).
- Identify high risk patients.
- Monitor BP, blood glucose closely at home.
- Monitor for macrovascular disease.

Management of Diabetic Nephropathy-Rx

- Normalize BP. Target <130/80.
- Treat with ACE inhibitors or ARBs.
- Treat hyperlipidemia and hyperglycemia aggressively.
- Moderate protein restriction (0.8- 1.0 gm/kg/day).
- Treat cardiovascular disease aggressively.
- Refer to nephrologist early in course of azotemia.

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 5: American Diabetes Association
Slide 6: U.S. Renal Data System, 2009, http://www.usrds.org/
Slide 7: U.S. Renal Data System, 2009, http://www.usrds.org/
Slide 8: U.S. Renal Data System, 2009, http://www.usrds.org/
Slide 9: CalorieLab, http://calorielab.com/index.html
Slide 10: U.S. Renal Data System, 2009, http://www.usrds.org/
Slide 11: U.S. Renal Data System, 2009, http://www.usrds.org/
Slide 12: American Diabetes Association
Slide 14: American Diabetes Association
Slide 15: American Diabetes Association
Slide 16: U.S. Renal Data System, 2009, http://www.usrds.org/
Slide 17: American Diabetes Association
Slide 18: Standards of Medical Care in Diabetes—2010 DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010
Slide 20: Diabetes Care, 23:S69, 2000
Slide 21: American Diabetes Association
Slide 22: Source Undetermined
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Slide 35: American Diabetes Association
Slide 39: Arch Int Med; 2009*;169(14):1307*
Slide 40: American Diabetes Association
Slide 42: Source Undetermined
Slide 44: Source Undetermined
Slide 45: Lewis et al., NEJM 329:1456, 1993
Slide 49: Source Undetermined
Slide 51: Fried, et al., Kidney Int, 2001; 59:260
Slide 53: NEJM 348: 2265, 2003
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Slide 55: Fioretto, et al. N Engl J Med. 1998, 339:69
Slide 56: Ruggenenti, JASN10:997, 99
Slide 57: Araki, et al., Diabetes. 2007 Jun;56:1727
Slide 58: Source Undetermined
Slide 59: American Diabetes Association; Source Undetermined