Holtz Children's Hospital
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Sickle Cell Nephropathy

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CEHMOB: MG Workshop
Projeto Atenção Especializada para Doença Falciforme
Belo Horizonte, Brazil
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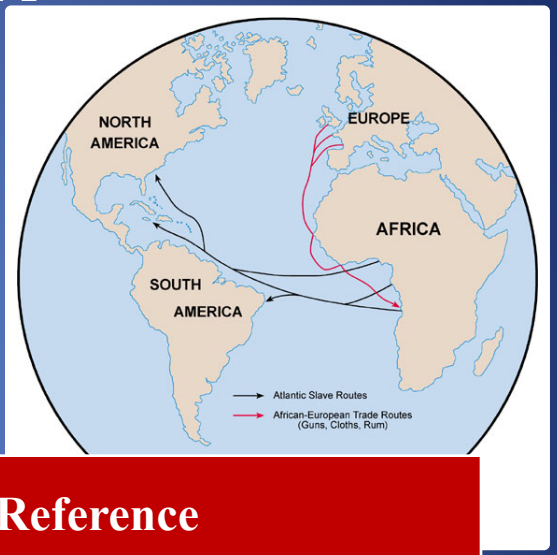
Objectives

- Introduction: The extent of the problem
- Kidney physiology
- Kidney pathology in sickle cell disease
- Diagnosis and progression
- Prevention
- Treatment

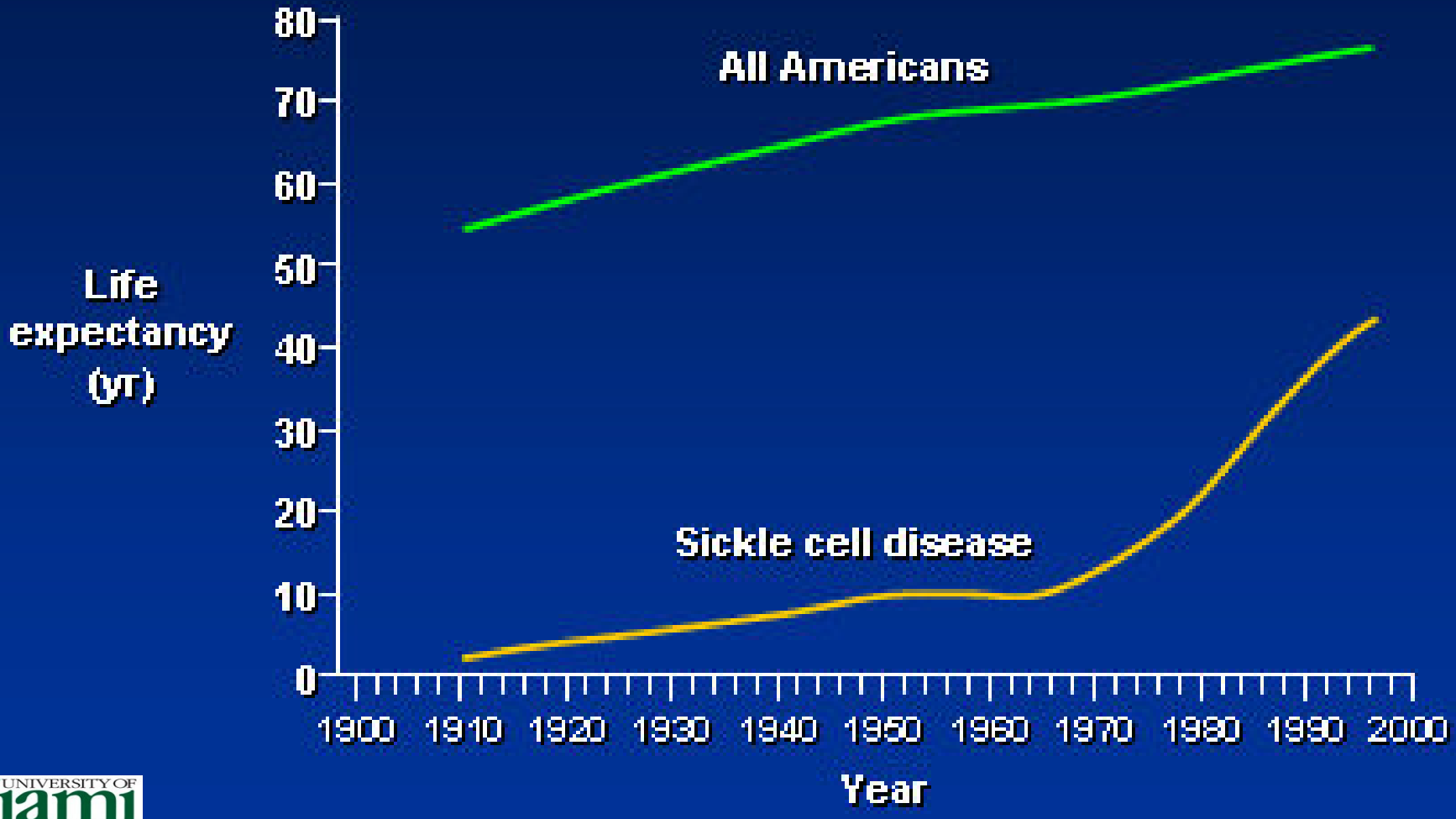
Sickle Cell Anemia: Global Problem

- 5% of the world's population carries a gene for hemoglobinopathy [WHO, 2011].
- 1 in 375 African-Americans and 1/1000-2000 Hispanics in the Eastern US has SCD.



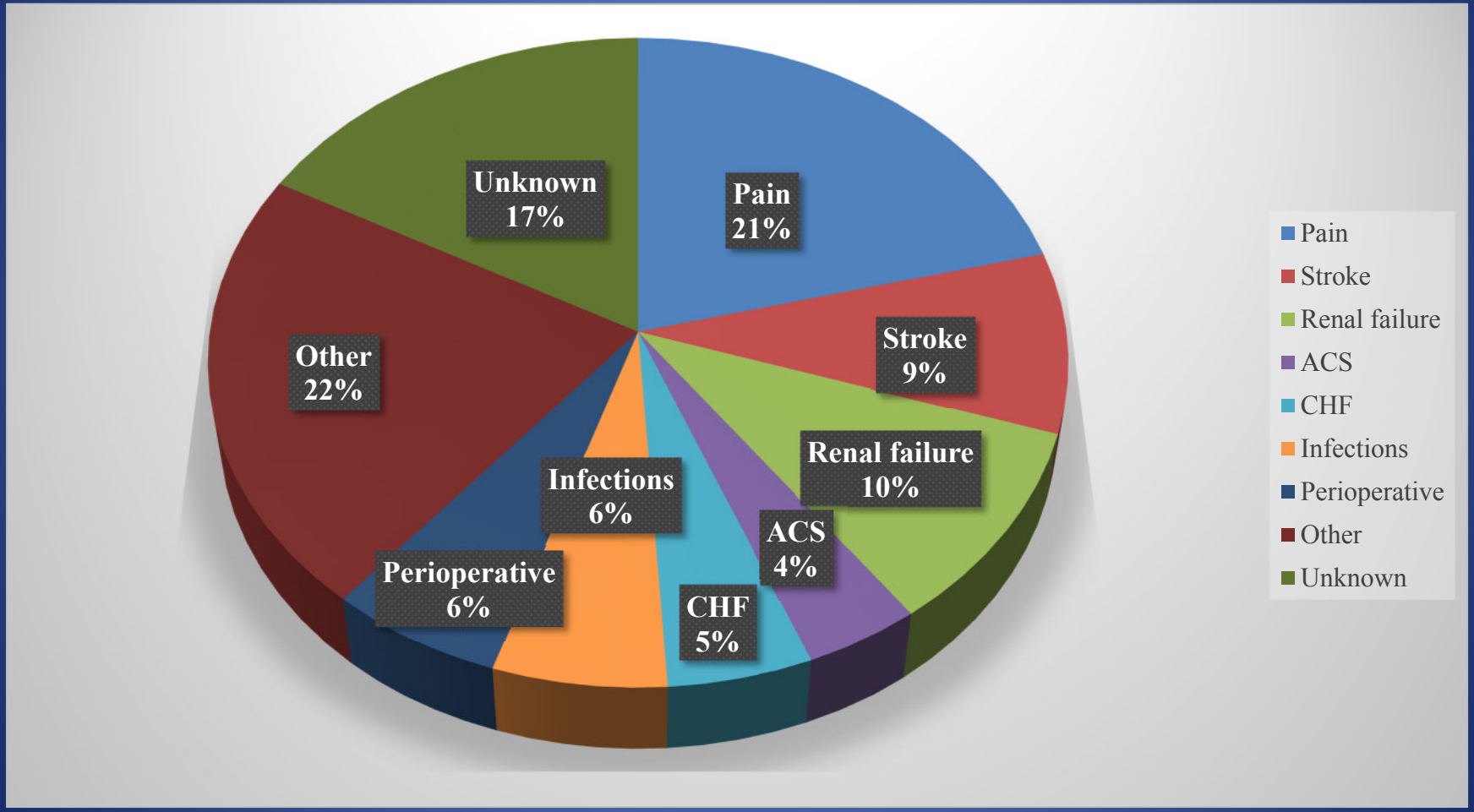
Country	Estimated affected population	Reference
USA	70-100,000	Hassell, *Am J Prev Med*, 2010
UK	12,000	Sharpe, Br J Haematol, 2011
Brazil	45,000	Salzano, *Am J Pediatr Hematol Oncol*, 1985 2000 Census Population
Nigeria	2% of children or 175,000 are born with SCD every year	World Health Organization

Increases in Life Expectancies of Patients With Sickle Cell Disease



Source: National Heart, Lung, and Blood Institute.

Mortality Causes,CSSCD



Platt, *N Engl J Med*, 1994

Disease category by system	No (%)	Causes of Death, 1999-2009
Sickle cell disease	5223 (100)	SCD without crisis 4196 (79.4%) SCD without crisis 1027 (19.6%)
Cardiovascular	1652 (31.6)	Congestive heart failure (326, 6%) Ischemic heart disease (252, 5%), Hypertension (214, 4%), arrhythmia (15, <1%)
Respiratory	1030 (19.7)	Pneumonia (331, 6%) Pulmonary embolism (279, 5 %) Pulmonary hypertension (161, 3%), ARDS (83, 2%) Pulmonary edema (58, 1 %), Asthma (36, <1%)
Renal	859 (16.4)	Chronic renal failure (369; 7%) Acute renal failure (144; 2%)
Infectious	755 (14.4)	Other septicemia (592; 11%), viral hepatitis (72, 1%) Streptococcal septicemia (36; <1%),HIV (26, <1%)
Neurological	624 (11.9)	CVA (462; 9%), anoxic brain damage(71,1%) Meningitis/encephalitis (8; <1%)
Gastrointestinal	483 (9.2)	Liver disease (342; 6.5%) Gallbladder, biliary tree and pancreas (40; <1%) Peptic ulcer disease (8; < 1%)
Malignancy	33 (0.63)	Breast, leukemia, kidney and bladder, prostate, MDS, colon
Congenital and perinatal	13 (0.25)	Prematurity, congenital &chromosomal abnormalities
Pregnancy and childbirth	3 (0.06)	Miscarriage, preeclampsia/ eclampsia, infections, vascular causes

Hamideh & Alvarez, *Pediatr Blood Cancer*, 2013

SCA-Related Renal Failure Starts at Young Age and Is Associated with Mortality

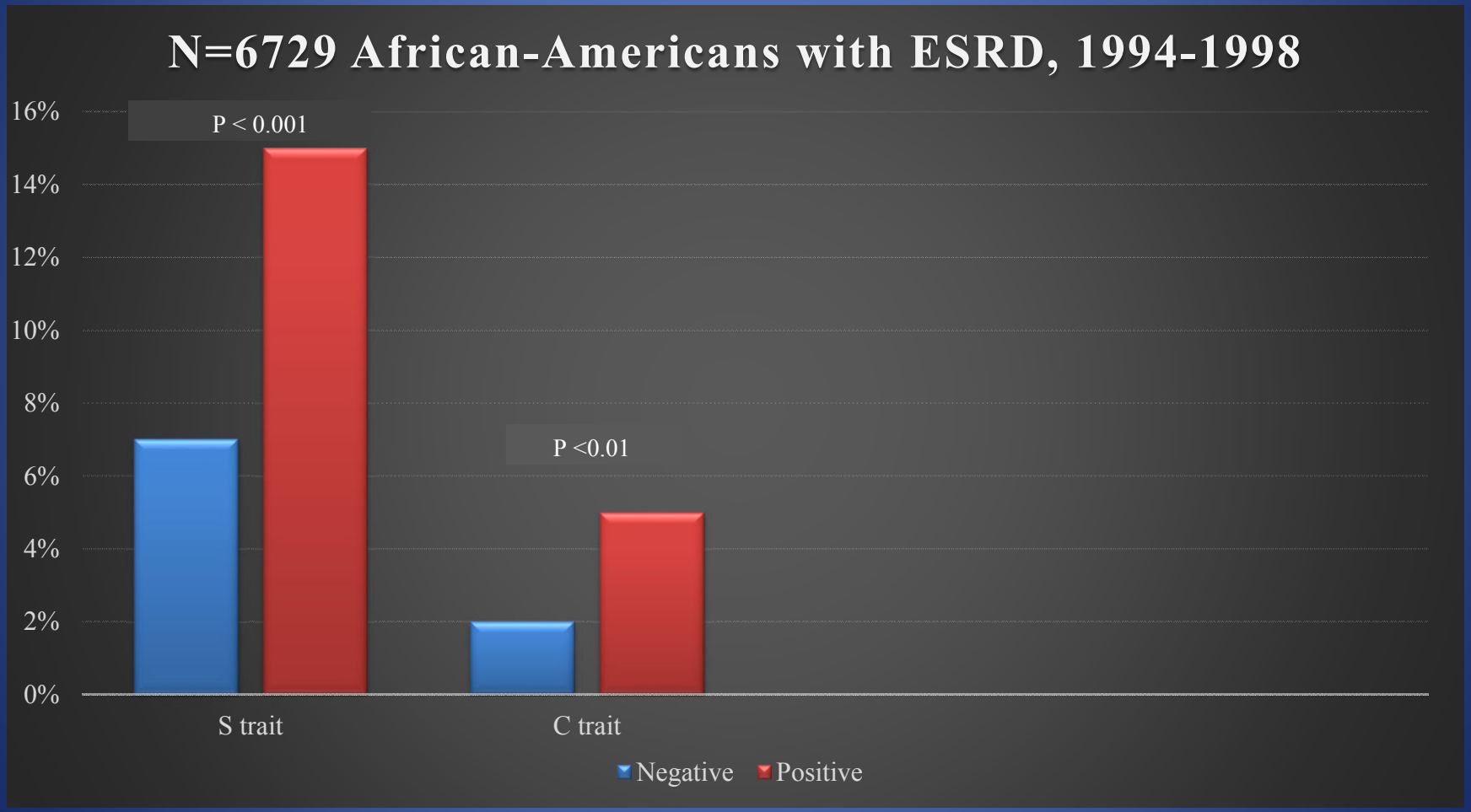
- USC Cohort (N=934); 25 years follow-up.
- 4% (N=36) Hb SS developed renal failure at median age of 23-37 and 2.4% of Hb SC at 50

  Powars, *Ann Intern Med*, 1991
- ESRD associated with SCD carries 2.8 x mortality risk compared to non-SCD causes
- 26% die during the first year [McClellan, *Br J Haematol*, 2012] ; median survival 4 years [Powars, 1991].

Do Race and Age Contribute to CKD?

- African-Americans ages 25-44 are 20x more likely to have ESRD related to hypertension than Caucasians.
- 20% of African-Americans will be affected by CKD, especially those over age 60 (43%) [Flessner, Jackson Heart Study, *Am J Kidney Dis*, 2009].
- CKD was the most common cause of death in the individuals > 60 years of age in the Jamaican cohort [Serjeant, *Int J Lab Med*, 2009].

End Stage Kidney Disease among African-Americans with AS and AC

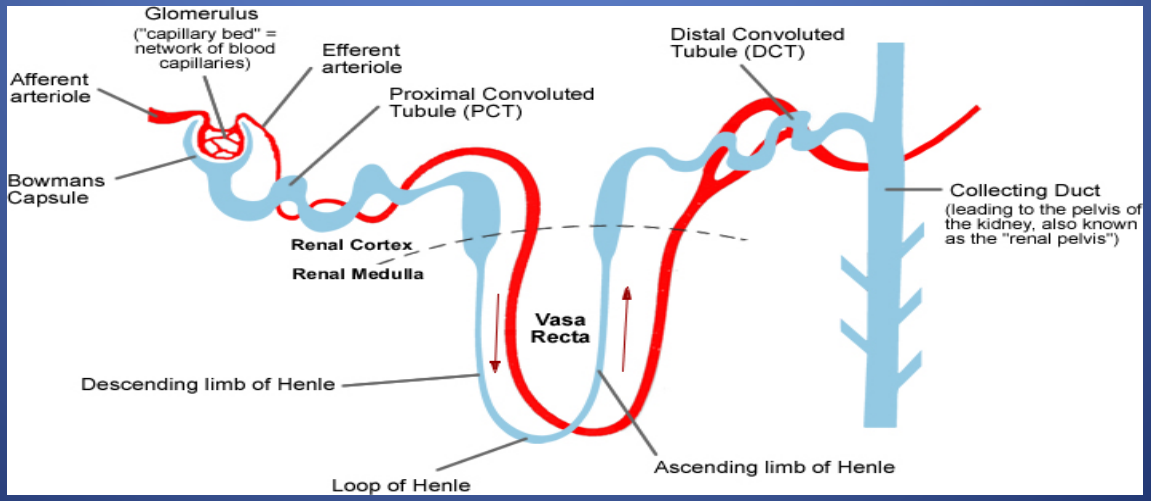


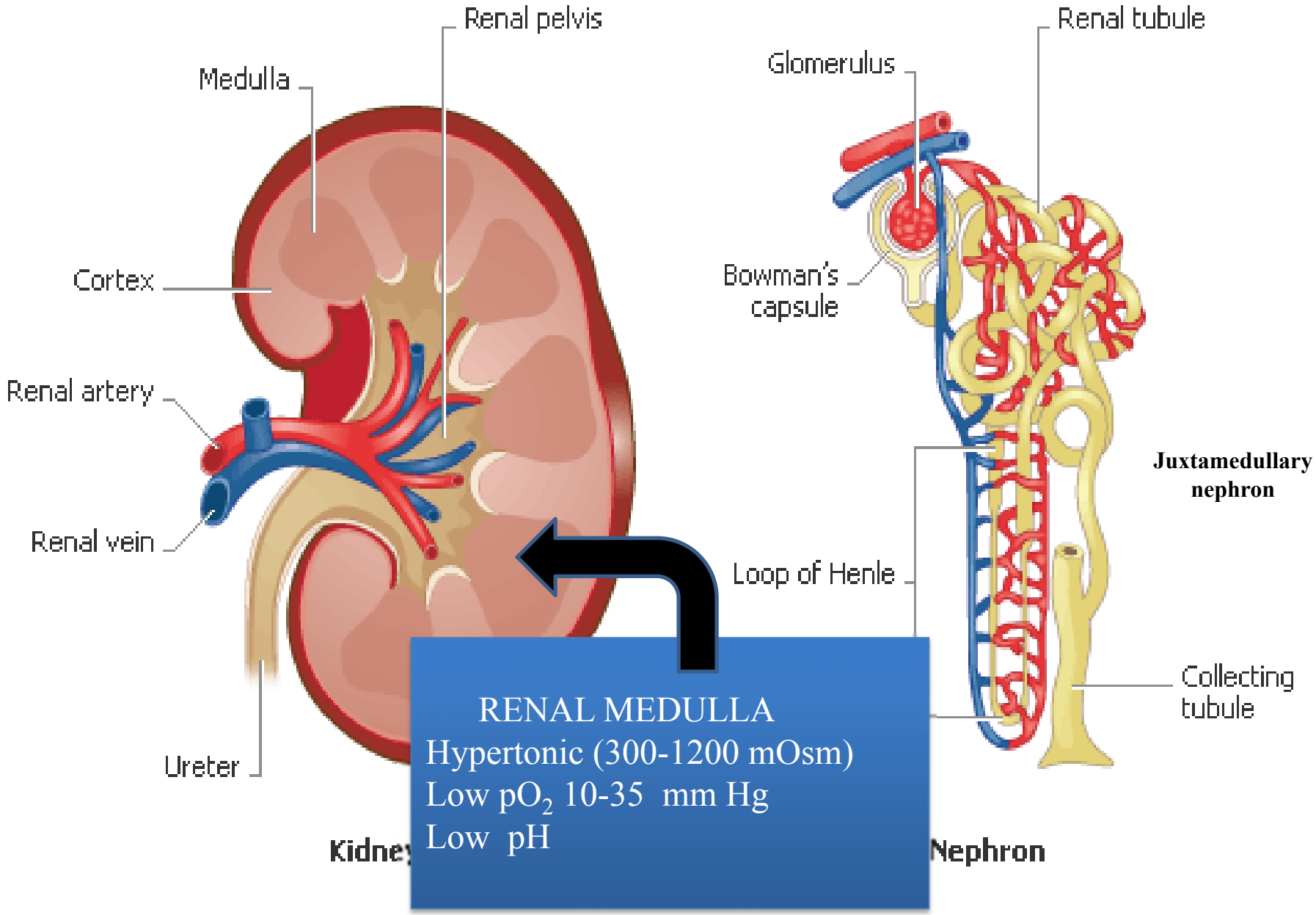
Derebail, *JASN*, 2010

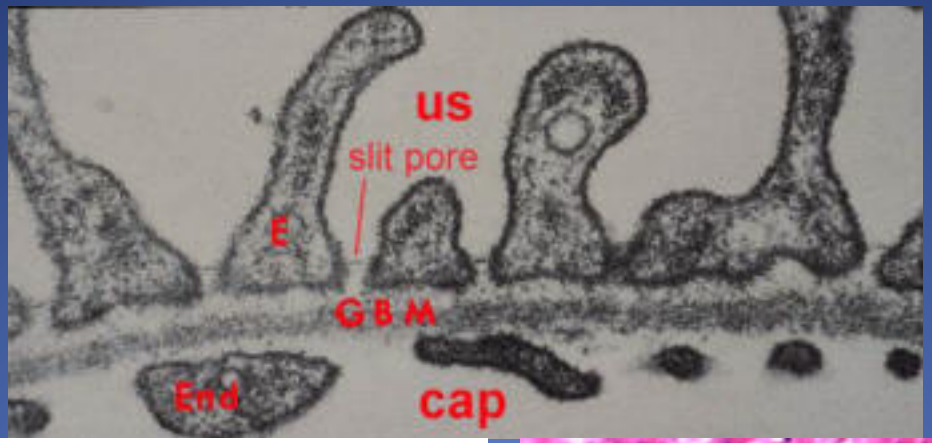
KIDNEY PHYSIOLOGY

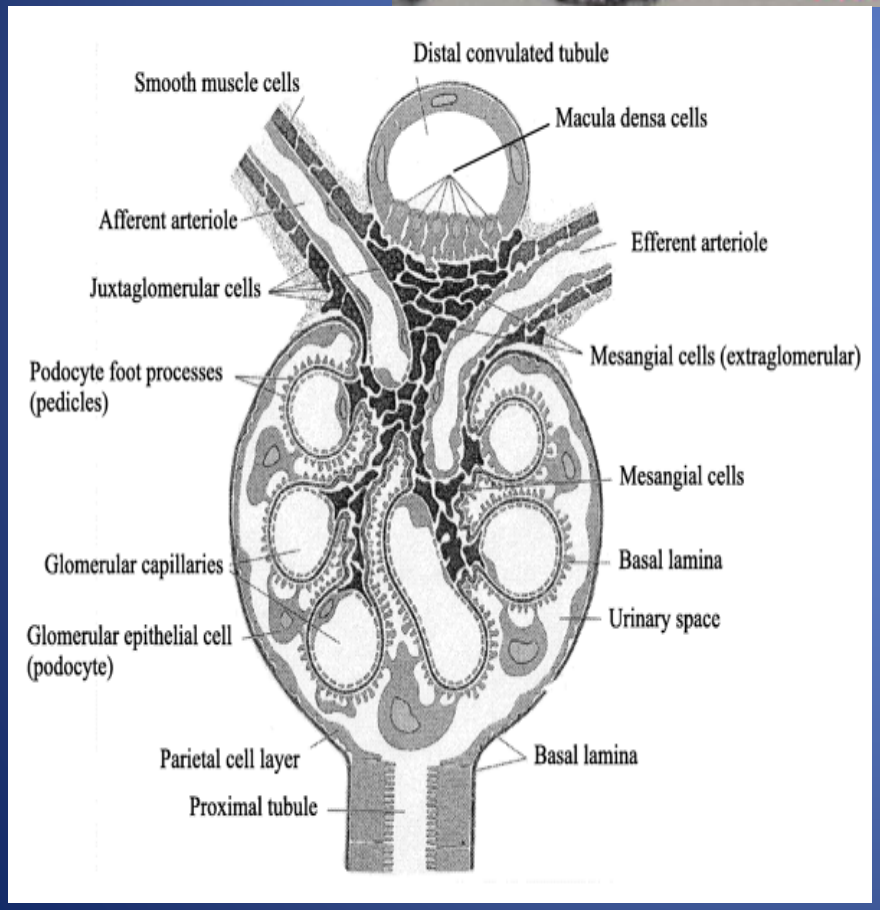
Normal Kidney Physiology

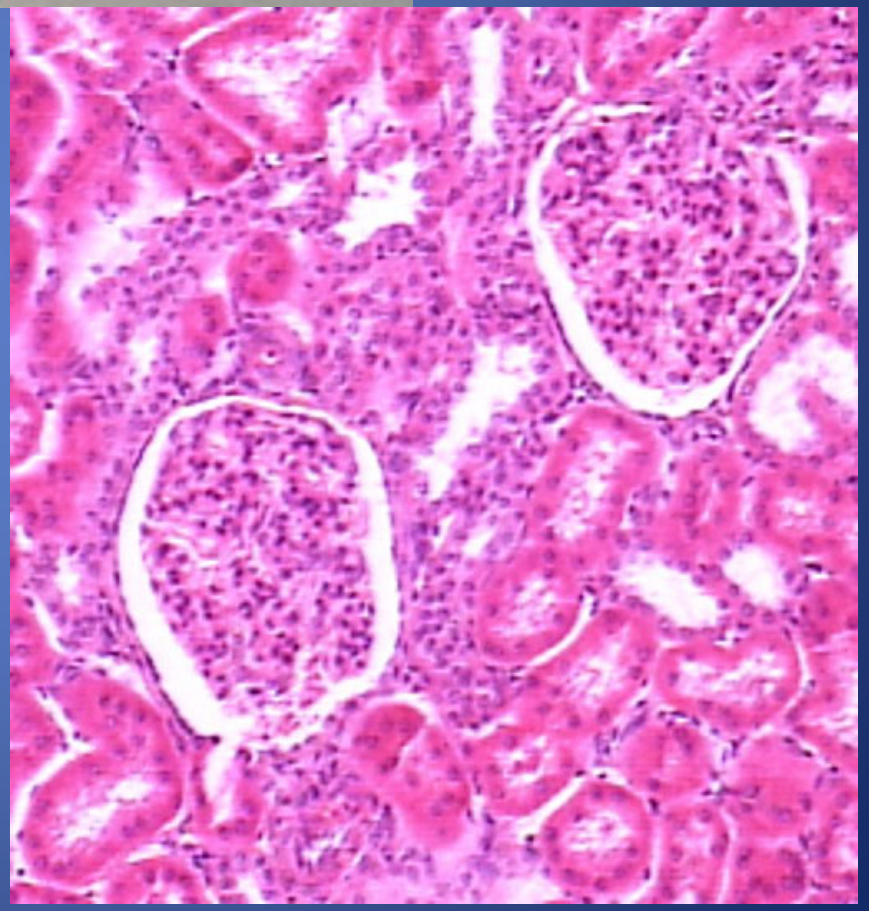
- Blood enters the kidney outer surface (cortex)
- Blood enters the afferent arterioles through each glomerulus and exits through the efferent arteriole.
- Water and ions are filtered to the Bowman's capsule and blood cells and proteins are retained.
- Some blood goes to the vasa recta which supply the renal medulla.
- There is a cortico-medullary solute gradient which is critical for water and solute reabsorption, with the highest concentration in the medulla.




Renal pelvis
Medulla
Cortex
Renal artery
Renal vein
Ureter
Kidney
Renal tubule
Glomerulus
Bowman's capsule
Juxtamedullary nephron
Loop of Henle
Collecting tubule
Nephron
RENAL MEDULLA
Hypertonic (300-1200 mOsm)
Low pO_2 10-35 mm Hg
Low pH


us
slit pore
E
GBM
End
cap

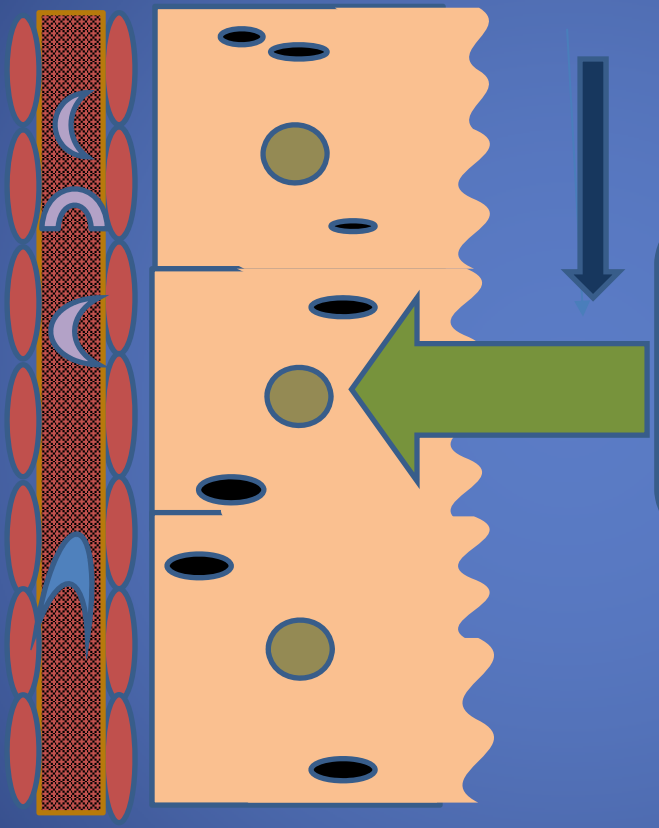

Distal convulated tubule
Smooth muscle cells
Macula densa cells
Afferent arteriole
Efferent arteriole
Juxtaglomerular cells
Mesangial cells (extraglomerular)
Podocyte foot processes
(pedicles)
Mesangial cells
Glomerular capillaries
Basal lamina
Urinary space
Glomerular epithelial cell
(podocyte)
Parietal cell layer
Basal lamina
Proximal tubule



GFR=Renal Plasma Flow x Filtrate Fraction

Increase GFR by ↑ PF	Increase GFR by ↑ FF
• Increased cardiac output - anemia • Dilate afferent arteriole - compensatory to nephron damage or loss	• Increased glomerular pressure • Vasoconstrict efferent arteriole -mediated by angiotensin II

Filtrate Reabsorption in the Renal Tubules and Vasa Recta



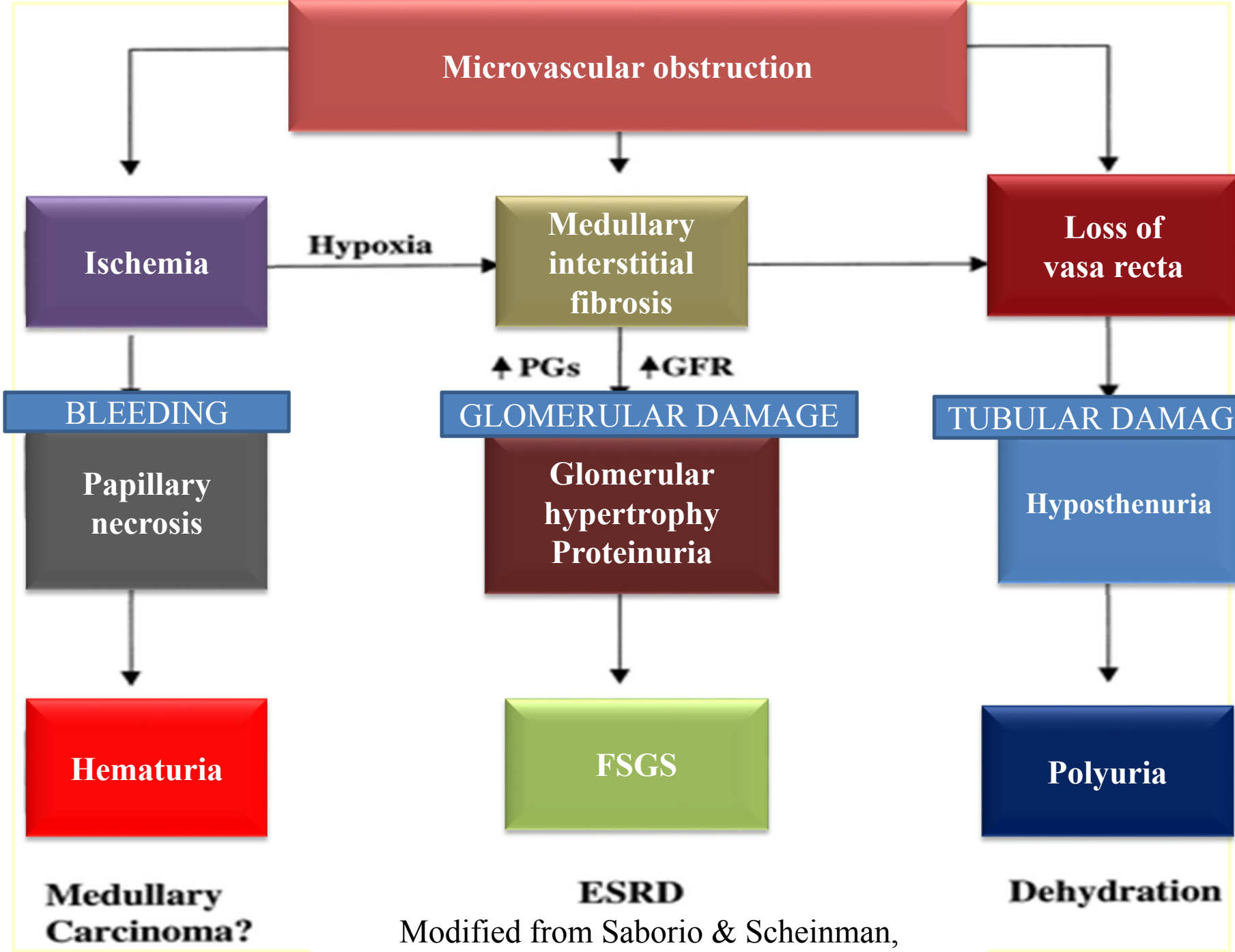
Na Cl
Other solutes
Water

The ultrafiltrate contains electrolytes, glucose, phosphate, urea, creatinine, peptides, and proteins<68 K MW.

99% of the water is reabsorbed in the tubules, most of it in the proximal tubules and return to the bloodstream.

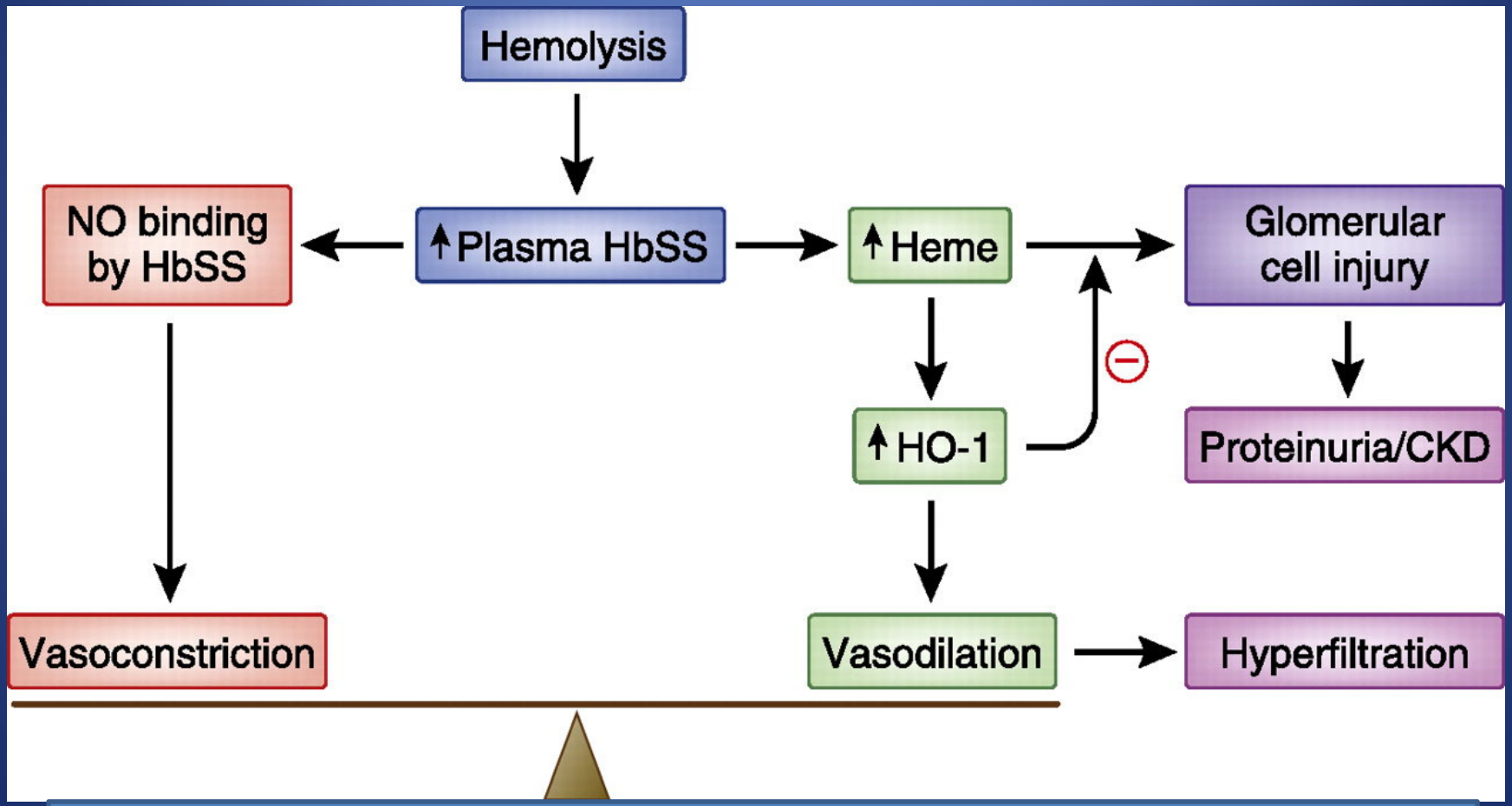
KIDNEY PATHOLOGY IN SCD

Fig. 1. *Microradioangiograph of a kidney from a control subject, showing normal vasa recta* (left) *and from a patient with sickle cell anemia, with the absence of the vasa recta* (right).



Modified from Saborio & Scheinman,
J Am Soc Nephrol, 1999

Hemolysis



Nath & Katusic, *JASN*, 2012; 23: 781-784

Proximal Tubular Dysfunction

- ↑ Reabsorption of phosphorus and β2-microglobulin
- ↑ Secretion of uric acid and creatinine, reflective of excessive proximal tubular functioning.

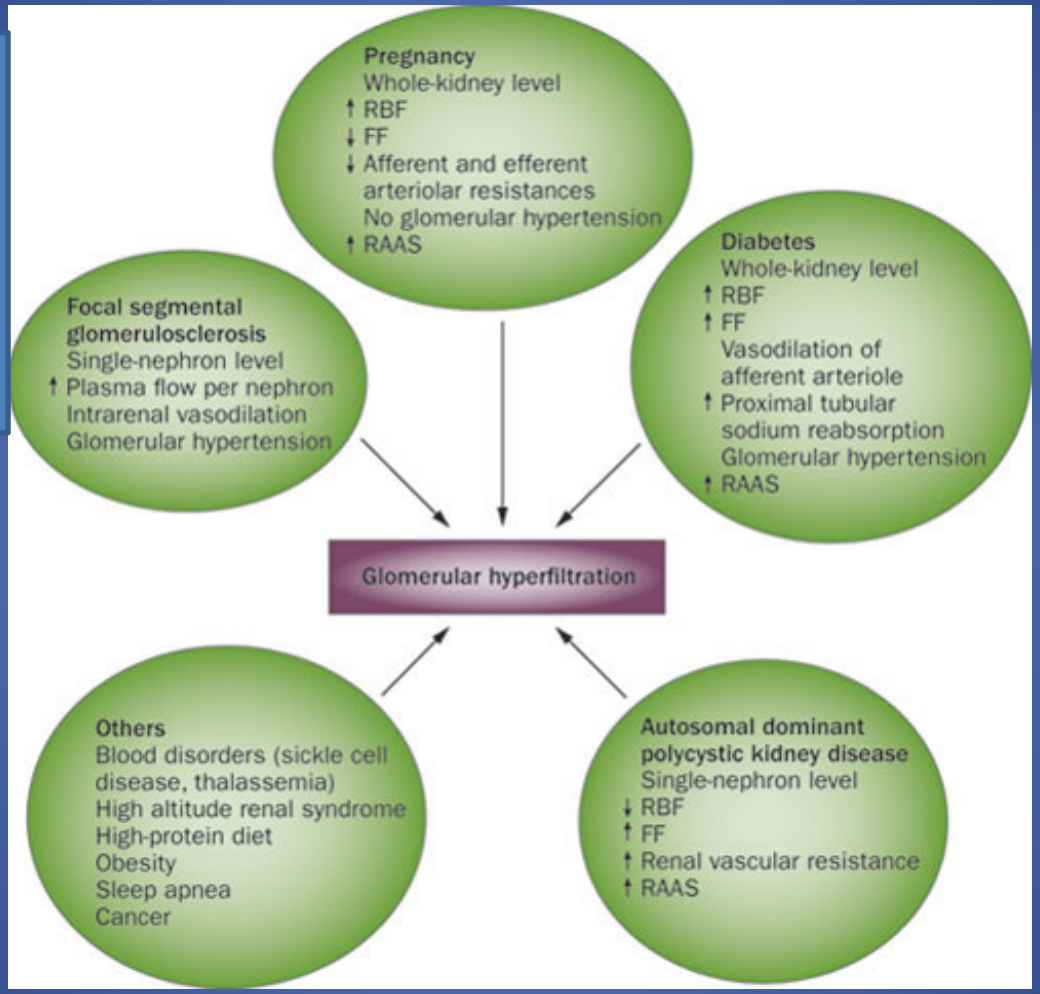
Distal Tubular Dysfunction

- Impaired free-water reabsorption and urine concentration.
- Inability to maintain a hydrogen ion gradient (incomplete distal RTA) and an electrochemical gradient (leading to ↑ K).

Ability to dilute urine remains intact due to sparing of the superficial loops of Henle, which are supplied by peritubular capillaries rather than by the vasa rectae.

Disorders Associated with Hyperfiltration

DEFINITION:
GFR of more than 2 SD above the mean GFR of healthy individuals



Helal, I. *et al.* (2012) Glomerular hyperfiltration: definitions, mechanisms and clinical implications *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2012.19

nature REVIEWS NEPHROLOGY

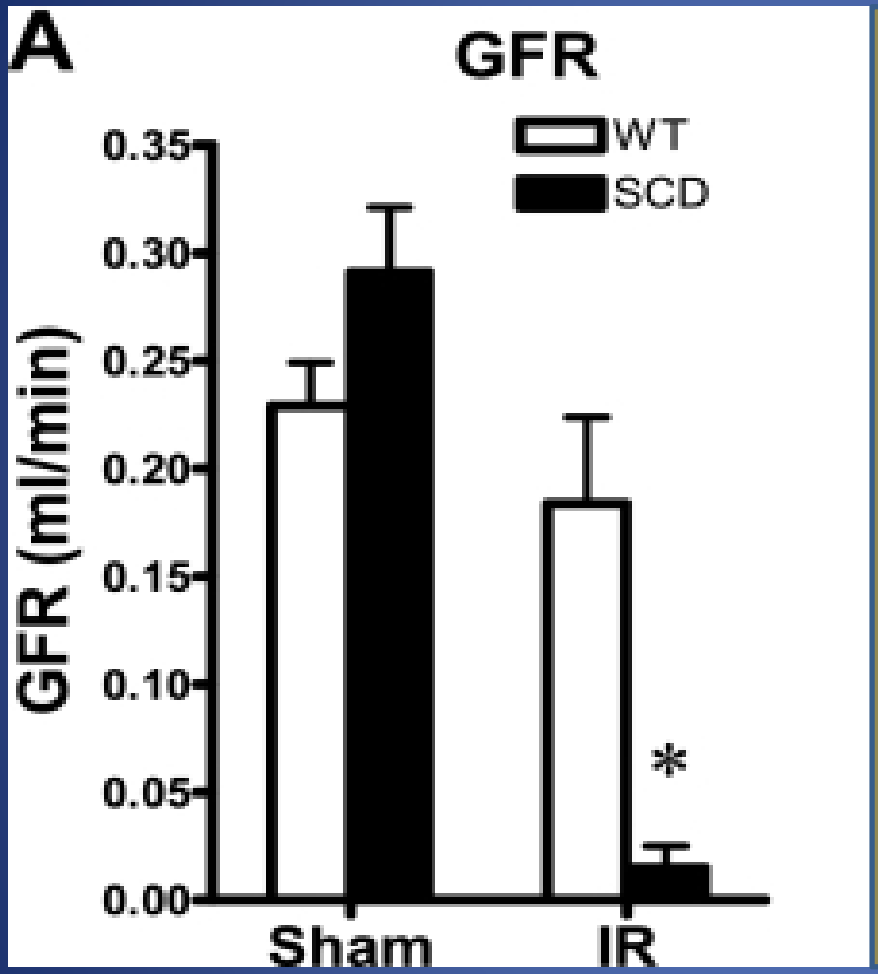
Glomerular Hyperfiltration in Adults with SCA

- When renal mass is reduced, the remaining nephrons undergo functional and structural hypertrophy with increased GFR.
- Hyperfiltration ⟶ proteinuria and glomerular sclerosis.

Brenner BM. *Kidney Int* 1983; 23: 647–655
Hostetter, TH, *J Am Soc Nephrol* 2001; 12: 1315–1325.
Becker A, *Pediatr Nephrol* 2011; 26: 2099-2109

Author, Year	N	Age Range	GFR SCA	GFR Controls	GFR Method
Hatch, 1970	10	17-27	146 (102-165)	117 (106-131)	Inulin
Guasch, 1997	12	18-65	108±7	98±4	Inulin
Allon, 1988	19	18-32	119±5	97±5	Inulin
Schmitt, 1998	14	26.6±1.3	146±9	120±2.8	Inulin
Thompson, 2007	65	18-23	137 (21-210)	105 (89-123)	^{51}Cr-EDTA

GFR Experiments in Mice



GFR was reduced in wild-type (WT) and SCD mice following bilateral renal **ischemia-reperfusion** (IR) for 22.5 min or after sham ischemia.

Juncos JJ and Nath KA. *Am J Physiol Renal Physiol* 2010; 298(4): F982-99.

DIAGNOSIS OF SICKLE CELL NEPHROPATHY

Albuminuria, a Sign of Glomerular Injury

- Urine albumin/creatinine ≥ 30 mg/g creatinine
- Hyperfiltration will promote glomerular damage.
- Albuminuria may appear due to changes in the glomerular filtration permselectivity.
- Eventually cumulative damage will lead to fibrosis and ESRD in some patients.

Becker AM. *Pediatr Nephrol* 2011; 26: 2099-2109.
Sharpe CC, Thein SL. *Br J Haematol* 2011; 155:287-297.

CKD Stages

Stage	GFR
1	>90 ml/min/m^2 with albuminuria
2	60-89 ml/min/m^2
3	30-59 ml/min/m^2
4	15-29 ml/min/m^2
5	<15 ml/min/m^2

Not All Renal Disease in SCD May Be Due to Sickle Cell Nephropathy

- Lupus nephritis
- Hepatitis C
- HIV
- Other genetic factors

---CKD is 2.5-5 x more common in people of African descent

-- Co-inheritance with *MYH9* and *APOL1*

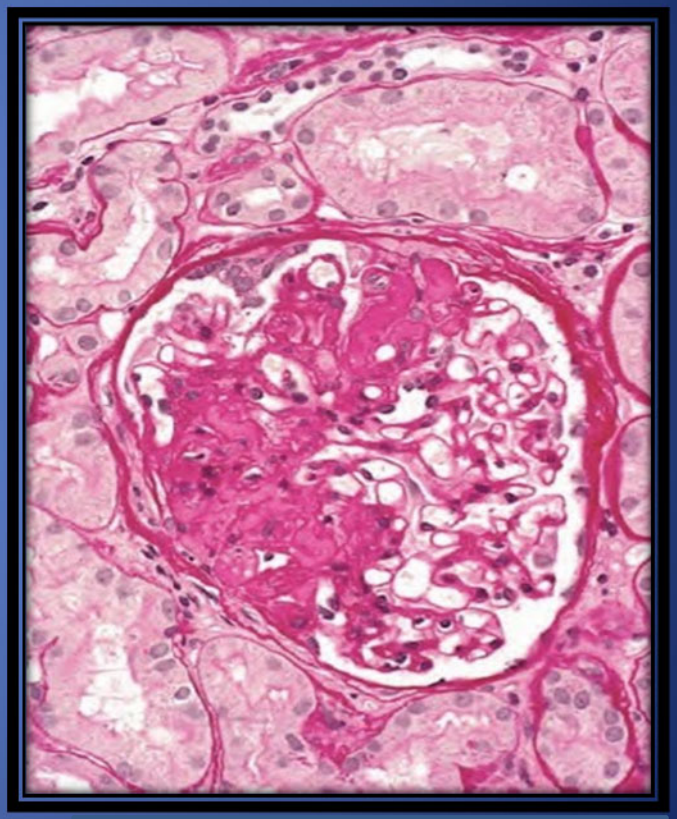
Work up for proteinuria

- Immunology for lupus nephritis
- Autoantibodies
- Double-stranded DNA antibodies
- Complement levels
- Virus serology: HIV, hepatitis B & C, parvo B 19 if nephrotic or history of red cell aplasia
- Myeloma screening (>40 years of age)
- Renal ultrasound
- Consider kidney biopsy if other causes are suspected or for acute onset nephrotic syndrome

Renal Biopsy Findings

- Glomerular hypertrophy with distended capillaries
- Abundant hemosiderin granules in proximal tubular epithelial cells

Pathology	Description	Prevalence
Focal segmental glomerulosclerosis (FSGS)	Adhesions between tuft and Bowman capsule with hyalinosis, lipid vacuolation and foam cells	39%
Membranoproliferative glomerulonephritis (MPGN)	Mesangial cellular proliferation and mesangial expansion with interposition and duplication of peripheral glomerular basement membrane	28%
Sickle cell thrombotic microangiopathy (TMA)	Capillary wall thickening with basement membrane changes including capillary thrombi	17%
Early sickle cell disease glomerulopathy	Glomerular hypertrophy with enlarged glomeruli and dilated and congested capillaries	17%



Maigne, G, et al.
Medicine 2010 Jan; 89(1): 18-27

Recommendations from US Expert Panel, NIH, 2012 [Draft]

- Beginning at age 10, screen all people with SCD for proteinuria using standard urine dipsticks. When negative, repeat annually.
- If albuminuria is found, order 24 hour urine, refer to nephrologist, and initiate ACE inhibitor.
- All patients should be screened for hypertension annually. If BP >140/90, screen for renal disease and initiate lifestyle modification and/or medication to lower BP.
- In the setting of acute elevation of creatinine >0.7 mg/dL in children or >1.0 mg/dL in adults, monitor renal function daily and fluid intake and output. Avoid nephrotoxic drugs and imaging agents.

OUR CLINICAL DATA

Prevalence and Risk Factors for Albuminuria in Children with SCD

- 120 children
- MA screening by random urine samples
- 16 % (19/120) had MA (mean 80 ± 62 mg/g)
- 17% SS group and 18% SC group
- 19% of children ≥10 years had MA, as compared to 8% of children <10 years (P = 0.018)
- MA was associated with history of acute chest syndrome and worse anemia.
- Children on chronic transfusions before age 9 had less chance of having MA (P = 0.03).

Alvarez O, Montane B, Lopez G, Wilkinson J, Miller T
Pediatr Blood Cancer 2006; 47(1):71-76

Serum Creatinine and Serum Cystatin C

- Serum creatinine is generally low in SCD due to increased tubular secretion.
- Serum cystatin C (MW 13 kDa) is an inhibitor of cysteine proteases which is produced by all nucleated cells, filtered and not secreted by the kidney.
- Normal serum cystatin is 0.55-1.06 mg/L

Alvarez, Zilleruelo, Wright, Montane, Lopez-Mitnik.
Pediatr Nephrol 2006 Apr;21(4):533-537

Cystatin C and Creatinine

GFR/Serum tests	Normal albumin N=11	Micro albuminuria N=5	Macro albuminuria N=4	*P*
Serum cystatin C mg/L	0.78	0.84	1.25	0.004
Cystatin GFR	103	94	63	0.03
Serum creatinine mg/dL	0.55	0.56	0.7	0.37
Creatinine clearance	163	144	133	0.54

Factors Affecting Serum Cystatin C

- 4.3% lower for every 20 years of age
- 9.2% lower for female gender
- 1.9% lower in blacks

Data from MDRD Study, AASK, Collaborative Study Group, Nephro Test Cohort
Stevens, *Kidney Int* ,2009 Mar; 75 (6): 652-660

- Thyroid function

Ye, *Endocr Pract*, 2013; 19(3): 397-403

- Oral corticosteroids

Shigemura, *Clin Chem Lab Med,* 2012; 50 (8): 1367-1371

Progression of SCN in Children is Variable

- 4/38 patients with albuminuria (10.5%) had PD during mean follow-up of 20 ±12 months.
- PD was associated with worse anemia and hemolysis.
- Nephrotic-range proteinuria was associated with decreased GFR.

Alvarez, Lopez-Mitnik, Zilleruelo.
Pediatr Blood Cancer 2008; 50(6): 1236-9.

Factors which Might Contribute to CKD Progression

- Not all of patients with Stage 1 CKD will progress.

- **Environmental factors**
  Exposure to opioids
  NSAIDS

- **Genetic factors**
  CAR haplotype [Powars, *Ann Int Med*, 1991]
  Low Hb F; Hb F >20% is protective
  Absence of α globin deletion [Guasch, *JASN*, 1999]
  Genetic susceptibility for CKD among African-Americans
  Co-inheritance with CKD-related genes (*MYH9*, *APOL1*)
  [Friedman and Pollack, *J Clin Invest*, 2011; Ashley-Koch , *Br J Haematol*, 2011]

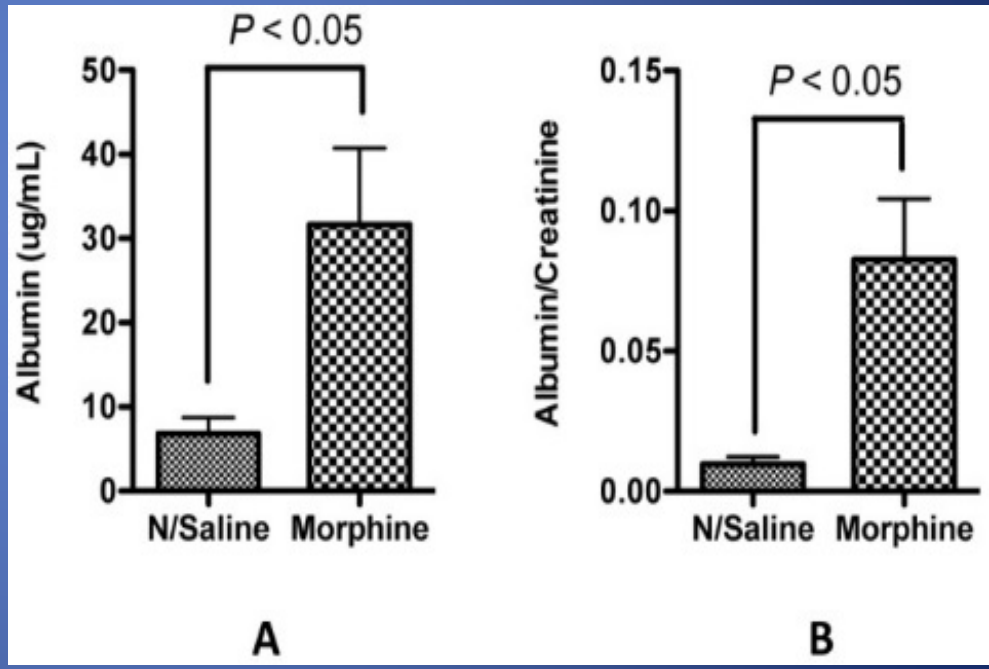
Non-steroidal Anti-inflammatory Drugs (NSAIDs) Effect on GFR (N=19 SS, 8 controls)

- Baseline GFR and renal plasma flow (RPF) were higher in SS than in controls.
- Indomethacin and sulindac lower GFR by 16% and 14%.
- Therefore, the data suggested supranormal GFR was prostaglandin-mediated.

Allon, et al. *Kidney Int*, 1988 Oct; 34 (4):500-6.

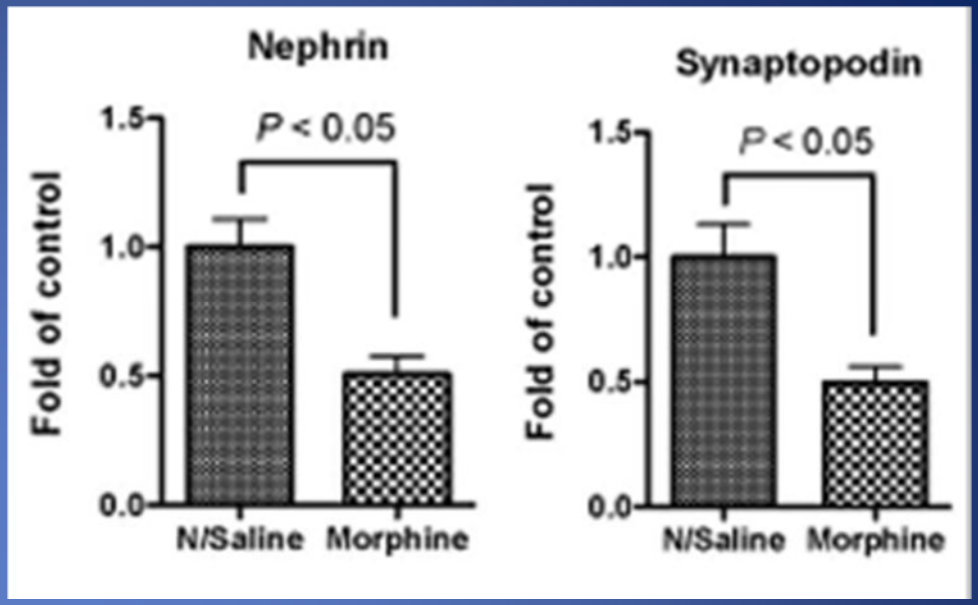
Morphine Induces Albuminuria by Compromising Podocyte Integrity

- Mice were administered either normal saline or subcutaneous 75 mg slow-release morphine for 72 hr.
- Urine samples were collected and kidneys were subsequently isolated for immunohistochemical studies and Western blot.
- Morphine-receiving mice displayed a significant increase in albuminuria.



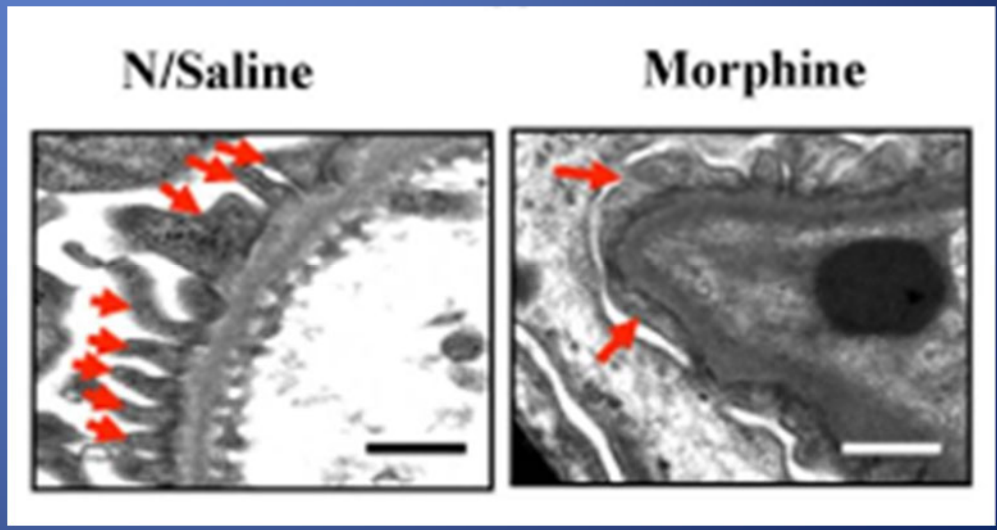
Lan, *PLoS One*, 2013

- The expression of synaptopodin, a molecular marker for podocyte integrity, and the slit diaphragm constituting molecules (SDCM), such as nephrin, podocin, and CD2-associated protein, were decreased in morphine-treated podocytes.

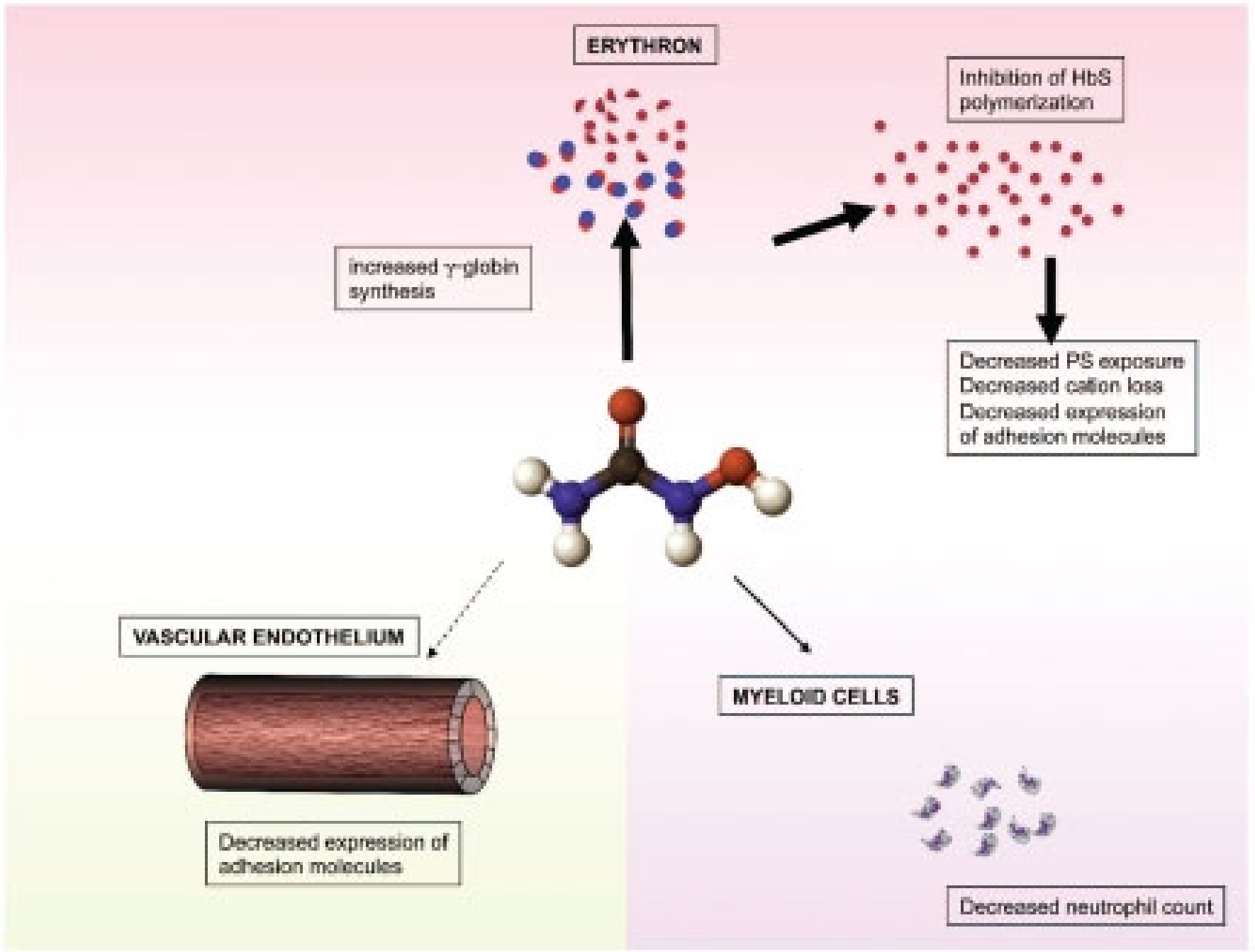


- Morphine modulated podocyte expression of SDCM through opiate mu (MOR) and kappa (KOR) receptors.

- EM showed that foot processes fused in morphine-treated mice.



DOES HYDROXYUREA PREVENT RENAL DISEASE OR RENAL DISEASE PROGRESSION?


ERYTHRON
Inhibition of HbS polymerization
increased γ-globin synthesis
Decreased PS exposure
Decreased cation loss
Decreased expression of adhesion molecules
VASCULAR ENDOTHELIUM
MYELOID CELLS
Decreased expression of adhesion molecules
Decreased neutrophil count

Event Rates per 100 Person-years [Exact 95% Confidence Limits for Events].

Cause of Death According to Cumulative Hydroxyurea Exposure. (129 deaths)

Event	Never 321 Person-Years	<5 yrs 1152 Person Years	5-<10 yrs 593 Person-Years	10-<15 yrs 506 Person-Years	≥15 yrs 337 Person-Years
Death	4.98 [2.85, 8.09]	6.77 [5.35, 8.45]	4.39 [2.87, 6.44]	1.78 [0.81, 3.38]	0 [0, 1.09]
Stroke	0 [0, 1.15]	1.04 [0.54, 1.82]	0.51 [0.10, 1.48]	0 [0, 0.73]	0.89 [0.18, 2.60]
Renal Disease	**2.80 [1.28, 5.32]**	**2.34 [1.54, 3.41]**	**1.69 [0.81, 3.11]**	**0.99 [0.32, 2.31]**	**0.30 [0.01, 1.65]**
Hepatic Disease	1.56 [0.52, 3.64]	0.78 [0.36, 1.48]	0.51 [0.10, 1.48]	0.20 [0.01, 1.10]	0 [0, 1.09]
Malignancy	0 [0, 1.15]	0.09 [0, 0.48]	0.34 [0.04, 1.22]	0 [0, 0.73]	0 [0, 1.09]
Sepsis/Infection	0.94 [0.19, 2.73]	2.34 [1.54, 3.41]	2.53 [1.42, 4.18]	1.98 [0.95, 3.63]	0 [0, 1.09]

Steinberg M, et al
Multicenter Study of Hydroxyurea (MSH) 17.5 years
Am J Hematol 2010 Jun;85(6):403-8

Hydroxyurea and Albuminuria in Adults with Sickle Cell Disease

- Cross-sectional study of 149 adult patients
- The prevalence of albuminuria was lower among patients on hydroxyurea (34.7%) versus not on hydroxyurea (55.4%); P = 0.01
- Median albumin excretion (17.9 versus 40.5 mg/g; P = 0.04) was lower.
- Hydroxyurea users were less than one-third as likely to exhibit albuminuria.

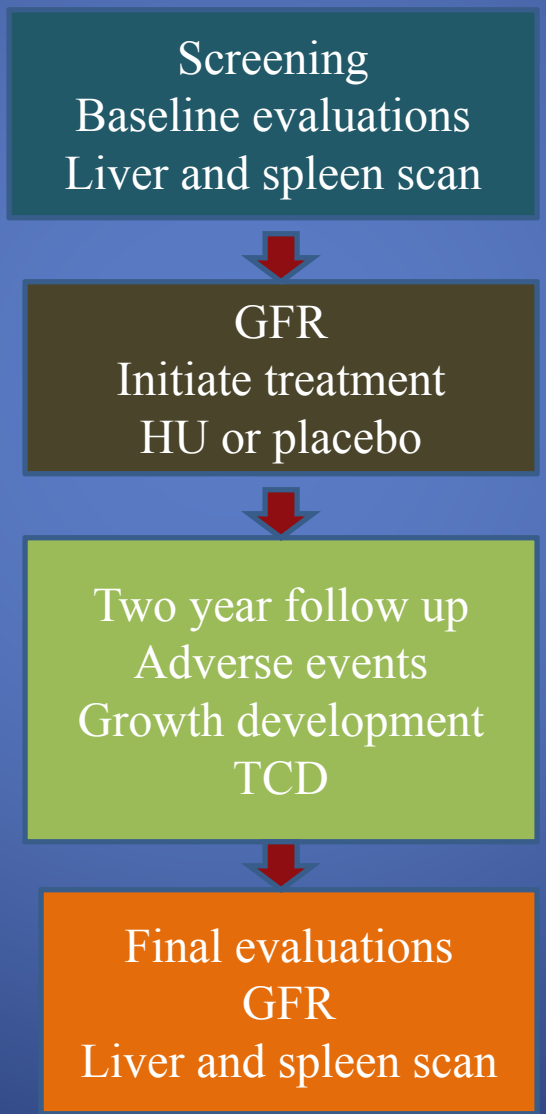
Laurin LP, et al. *Nephrol Dial Transplant*. 2013 Sep 30. [Epub ahead of print]

BABY HUG

- Multi-center double-blind randomized placebo-controlled trial of 193 infants with Hb SS and $S\beta^0$ ages 9-18 months at the time of enrollment.
- Children were *not* selected based on severity.
- The primary endpoints of the study was to evaluate whether the use of hydroxyurea at fixed dose 20 mg/kg/day preserves spleen and kidney function.

Wang W, et al, *The Lancet*, 2011; 377: 1663-72

Study Flow



GFR was measured by DTPA clearance analyzing plasma samples at 1,2,4 hrs after a single dose of 0.05 µCi/kg

Urine Concentration after Overnight Water Deprivation at 1 Year of Age

Parameters	N	Hydroxyurea	N	Placebo	*P*
Urine pH	96	6.47±0.98	97	6.57±0.98	0.47
Urine SG	96	1.011±0.005	97	1.012±0.006	0.09
Serum osmolality	93	286.13±5.56	94	286.45±5.89	0.70
Urine osmolality	94	403.22±151.6	97	408.32±152.4	0.82
Hypoosmolar **Normoosmolar** **Hyperosmolar** **>292 mOsm/kg** **>500 mOsm/kg**	21 2 71 29	22% 2% 76% 30%	20 4 73 26	21% 4% 74% 27%	0.91

Renal Parameters at Baseline (mean age, 13 months)

Parameters	N	Hydroxyurea	N	Placebo	P-value
Serum creatinine	83	0.25±0.09	90	0.23±0.07	0.07
Serum cystatin C	64	0.91±0.17	71	0.90±0.14	0.59
Cystatin GFR	64	96.4±23.5	71	96.5±17.0	0.99
Schwartz GFR	82	190±61	89	198±49	0.37
Bedside Schwartz	82	142±46	89	141±36	0.37
CKiD Schwartz	60	99±21	69	105±18	0.08
DTPA-GFR	86	126±39	90	124±30	0.65

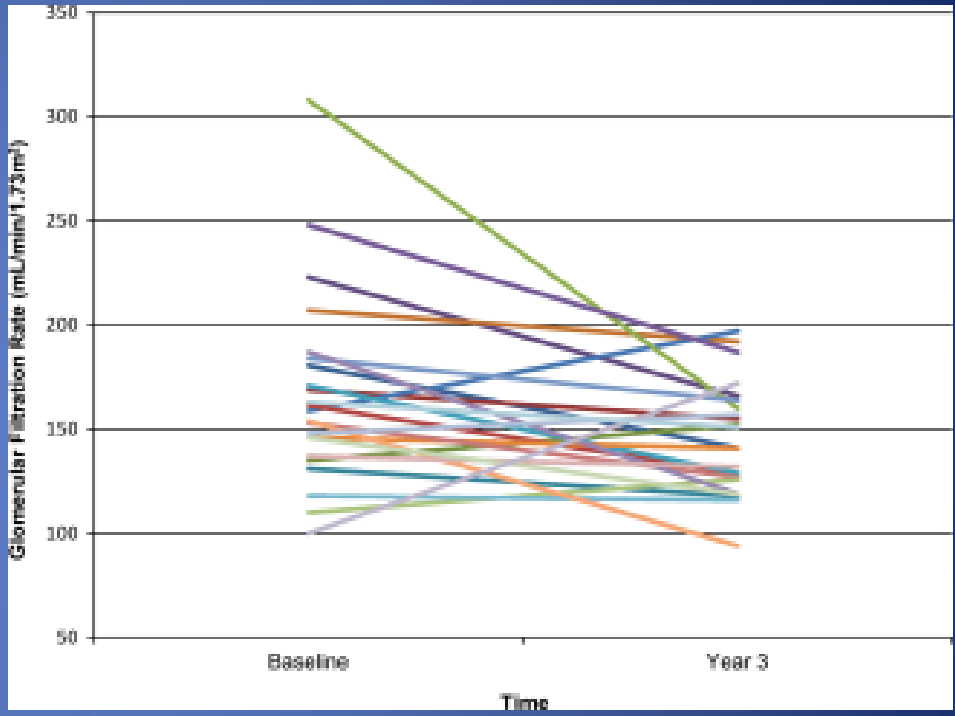
Data at 3 Years of Age and after 18-24 Months of Treatment

Parameter	N	Hydroxyurea	N	Placebo	P-value
Serum creatinine	79	0.27/0.07	84	0.25/0.07	0.38
Serum cystatin C	57	0.92/0.13	59	0.90/0.16	0.36
Cystatin GFR	57	93.75/15	59	96.34/17	0.12
Schwartz GFR	79	216/66	80	234/90	0.45
Bedside Schwartz GFR	79	161/49	80	174/68	0.45
CKiD Schwartz	53	112/23	57	120/27	0.39
DTPA-GFR	74	146/44	66	146/48	0.93
Urine specific gravity	86	1.012/0.004	83	1.011/0.004	**0.03**
Urine osmolality **>500 mOsm/kg H_2O**	83 42	495/110 50%	85 29	452/92 34%	**0.007** **0.03**
Bilat renal volume (ml)	81	91.83/24	78	97.65/21	**0.007**
Renal length, left kidney (cm)	82	7.36/0.8	80	7.40/0.6	**0.03**

Adapted from Alvarez et al,
Pediatr Blood & Cancer, 2012, Oct; 59 (4): 668-74

Hydroxyurea Study of Long-Term Effects (HUSTLE)

- 23 children with SCA
- Median age 7.5 (2.5-14 years)
- Hydroxyurea at MTD x 3 years
- ^{99m}TcDTPA GFR decreased from 167±46 to 145± 27(P=0.016)



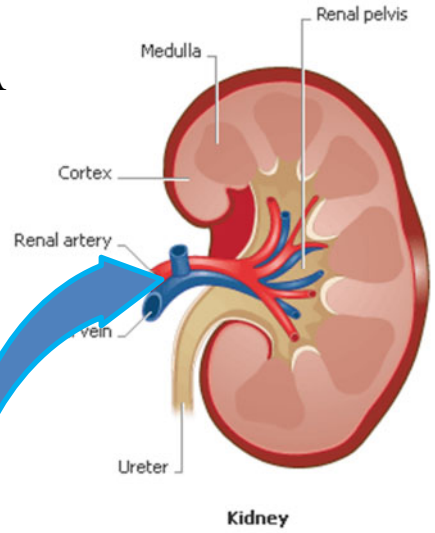
- GFR decrease was associated with higher HbF (mean 11.2% ±6.2) and lower LDH.

Aygun, *Am J Hematol*, 2013

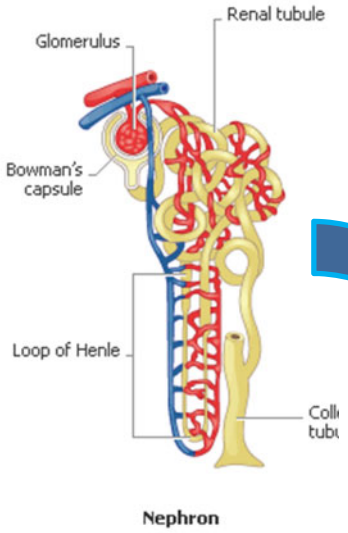
TREATMENT OPTIONS

Angiotensin blockade

TUBULAR DYSFUNCTION
HYPOSTHENURIA
ENURESIS



Kidney



Nephron

GLOMERULAR DYSFUNCTION
MICROALBUMINURIA
PROTEINURIA
STAGE I CHRONIC
RENAL DISEASE

INCREASED GFR

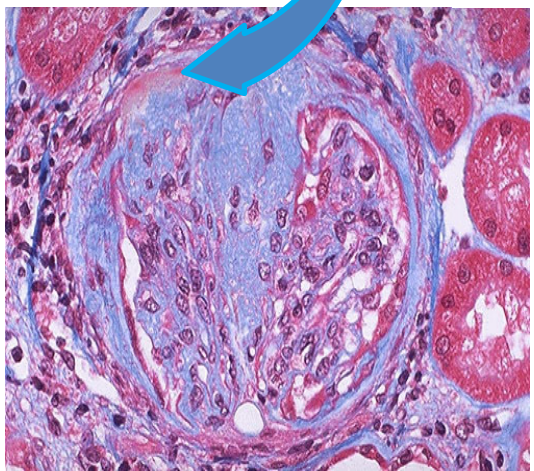
DECREASE GFR

ISCHEMIA-REPERFUSION INJURY
NEPHRON LOSS

SICKLING IN HYPOXIC AND ACIDIC RENAL ENVIRONMENT

FSGS
RENAL FAILURE
DEATH

Sickle-cell directed therapies



ACE Inhibitors

- Most data comes from diabetic patients
- Enalapril 5-10 mg reduced proteinuria by half after 2 weeks of treatment in 10 patients with SCD [Falk, *N Engl J Med*,1992].
- Enalapril decreased MA in 7 of 8 patients [Aoki & Saad, *Am J Med*, 1995].
- Captopril decreased MA in 22 pts treated for 6 months compared to placebo [Foucan, *Am J Med*, 1998].

Other Treatment Options and Recommendations

- **Angiotensin receptor blocker**
- Alone or in combination with ACE inhibitor
- Use is under investigation in clinical trials

Other recommendations for CKD patients

- Avoid NSAIDS
- Frequent monitoring for hydroxyurea toxicity
- Recombinant erythropoietin avoiding Hb >10 g/dL
- Appropriate renal replacement (dialysis and transplant)

Current Drug Research in the US and France for SS and Sβ^0 with Albuminuria

- Phase II Losartan

  0.7 mg/kg ages 6-16

  50 mg ages 16-21 x 6 months

  Malik, Children's Hospital Medical Center, Cincinnati

- Irbesartan 300 mg vs. Ramipril 5 mg x 6 months in adults

  Lionnet, Hôpital Tenon, Paris

Kidney Transplant for ESRD-SCN

- Pre-transplant transfusion or exchange is recommended.
- Some recommend regular transfusions post-transplant to prevent SCN recurrence [Sharpe, *Br J Haematol*, 2011].
- The prognosis of individuals with SCN was better after transplantation (67% survival at 7 years vs. 83% for other African-Americans) when compared to dialysis (14% at 10 years) [Scheinman, *Nature Clin Practice*, 2009].

Kidney Transplantation

- Problems: Organ rejection and disease recurrence
- Graft survival at 12 and 24 months post-transplant is 89 ± 11% and 71 ± 18%, respectively.

Warady, Pediatr Transplant, 1998

- 10-year survival post transplant is >50%
- SCD patients were less likely to be listed for kidney transplant than the general population

Abbott, *Clin Nephrol* 2002;58(1):9-15

Schneinman, *Nat Clin Pract Nephrol* 2009; 5;78-88

- 52,000 people awaits kidney transplant in the US, but only 12,000 get transplanted [United Network of Organ Sharing]

Implantable Artificial Kidney Corporation

"Artificial Kidney Research and Development"

Shown without filters and covers installed

Implantable Artificial Kidney (IAK) Device

- 2 ¼ in high x ½ in thick x 4 in long device
- Implantable or extracorporeal
- Plan is to last 10 years or more
- It is in laboratory testing
- Plan is to be tested in pigs prior to human trials, expected for 2017

Where Do We Go From here?

- Follow-up of BABY HUG cohort is ongoing to evaluate whether long-term hydroxyurea use may show a protective effect on the kidney.
- Annual surveillance with renal function test including serum cystatin C and urine albumin, protein and creatinine for children 10 years and older.
- We need to better define what are the risk factors for SCN, so we may provide early diagnosis.
- Large longitudinal studies to investigate treatment strategies for SCN are certainly needed.

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