GENETICS AND (PEDIATRIC) NEPHROLOGY

PIECES OF A PUZZLE

WITH SPECIFIC EMPHASIS TO THE TRANSITION TO ADULT CARE

Categories of inherited renal diseases
Congenital or inherited?

Congenital

- Present at birth
- may be inherited

OR

- aquired
  - TORCH
- Sometimes difficult to distinguish
  - Categories may change
  - Ex CAKUT

Inherited

- Genetically determined
  - Autosomal (AD-AR)
  - X-linked (XD-XR)
  - Mitochondrial
- Original concept
  - „One gene – one enzyme”
- Diversity due to the
  - Severity of the mutation (point-, deletion-, nonsense-, frame-shift- etc)
  - Interplay of different genes (modifyer effect – ex nephronophtysis)
  - Regulatory elements, micro RNA-s, etc.

Categories of inherited renal diseases

The problem of transition into adult care

1. Diseases of the urinary tract („CAKUT")
   - Usually sporadic
   - Known genetic background mainly in a few, syndromic malformations (*HNF1b*, *PAX2*, *EYA1*, *SIX1*, and *SALL1)*
   - Subvesical obstruction, VUR, PU and UV stenosis
2. Tubulopathies and metabolic diseases
   - Cystinosis, Bartter syndrome(s), RTA, oxalosis,
3. Glomerular diseases
   - Alport sy, nail-patella syndrome
   - Congenital nephrosis
   - …aHUS…
4. Cystic diseases
   - ADPKD, ARPKD, nephronophtisis(es), tuberous sclerosis

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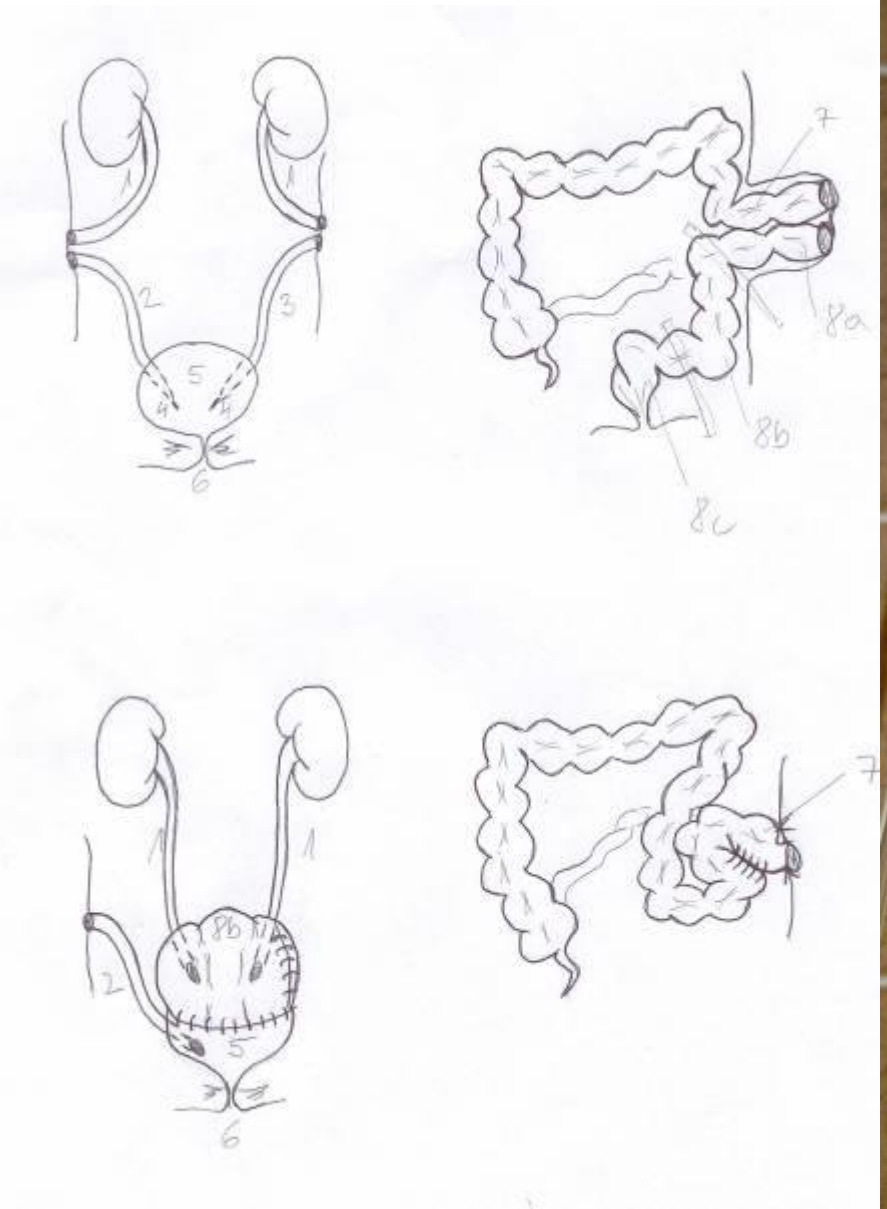
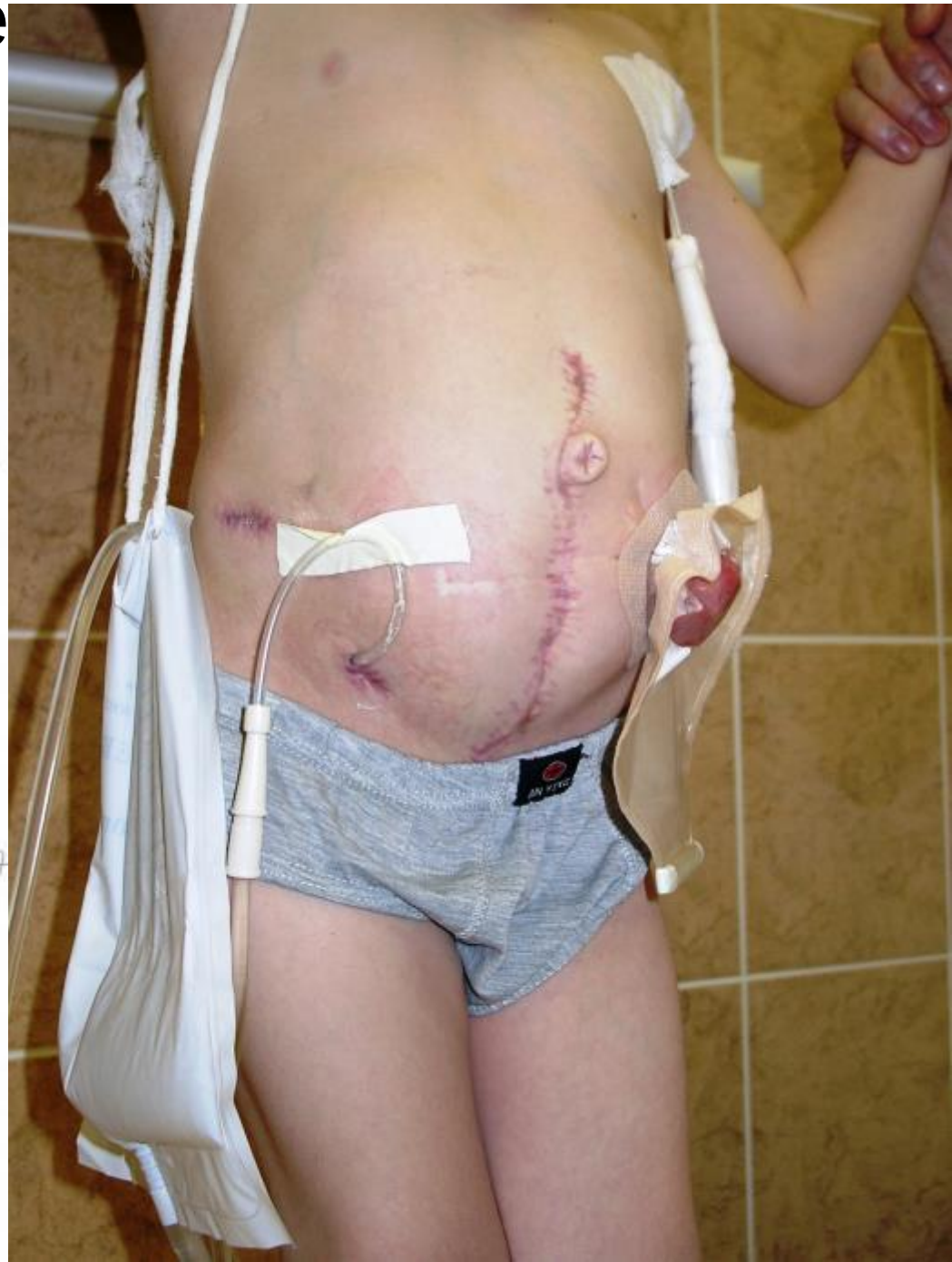
Diseases of the urinary tract („CAKUT”)

(Re)construction of the bladder and Tx





Sequence of kidney damage 1.

UTI

↓

Damage of the kidney

↓

Fibrosis

↓

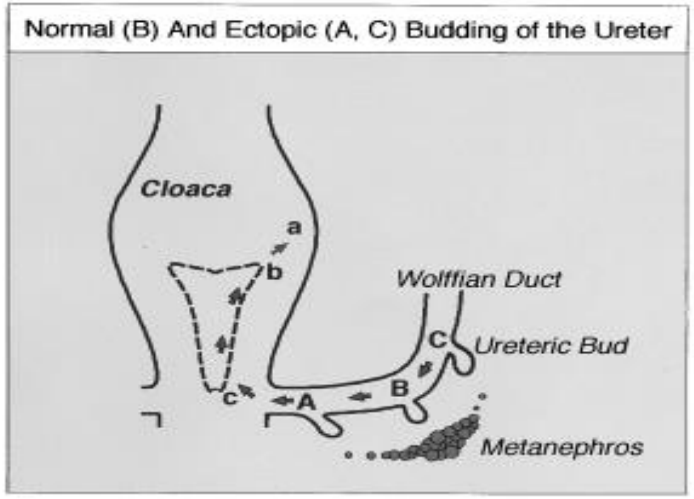
Loss of function

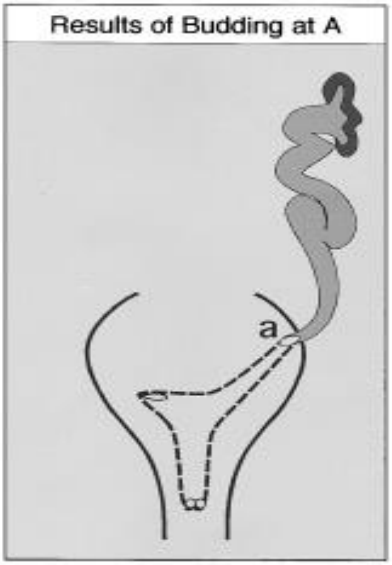
↓

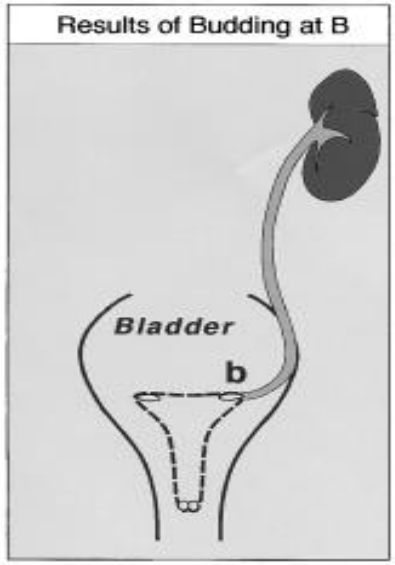
Renal insufficiency

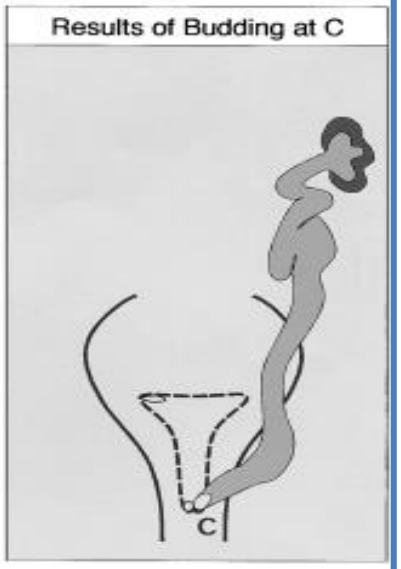
- Predisposing factors
  - Anatomic malformations
    - Subvesical obstruction
    - VUR
    - UV - stenosis
    - PU - stenosis
    - Meningomyelocele
    - Prune-Belly-syndrome
  - Immune deficiency
  - Bacterial virulence

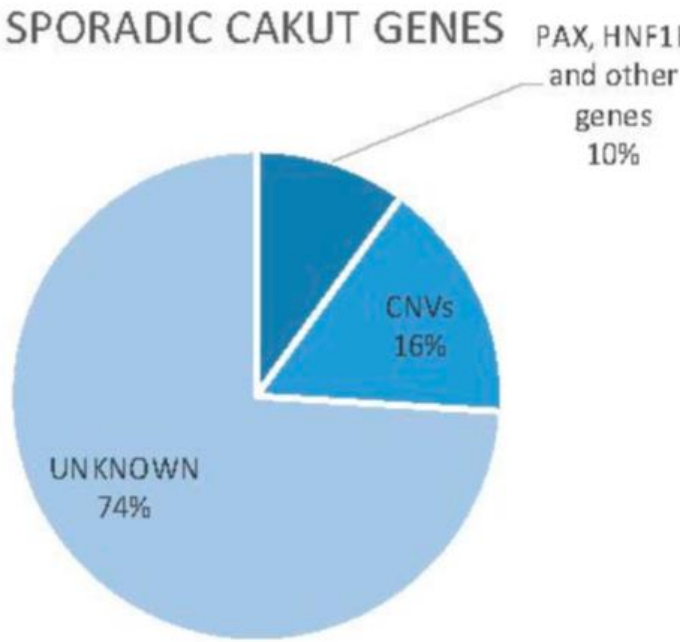
Ichikawa I et al: Paradigm shift from classic anatomic theories to contemporary cell biological views of CAKUT. *Kidney International* (2002) **61**, 889–898;











Valentina P. Capone et Al: Genetics of Congenital Anomalies of the Kidney and Urinary Tract: The Current State of Play
Int. J. Mol. Sci. **2017**, 18, 796

Sequence of kidney damage 2.

Primary bilateral kidney dysplasia

↓

Lower nephron number

↓ ↓

Urinary tract infection

↓

Parenchymal damage, hyperfiltration

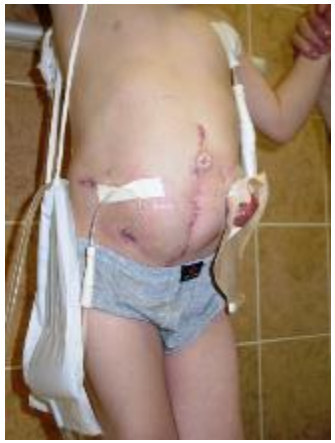
↓

Fibrosis

↓

Loss of function

ESRD



- Predisposing factors
  - Kidney hypoplasia - Lower nephron number
  - Anatomic malformations
    - Subvesical obstruction
    - VUR
    - UV - stenosis
    - PU - stenosis
    - Meningomyelocele
    - Prune-Belly-syndrome
  - Immune deficiency
  - Bacterial virulence
  - Vitious circle

Tubulopathies

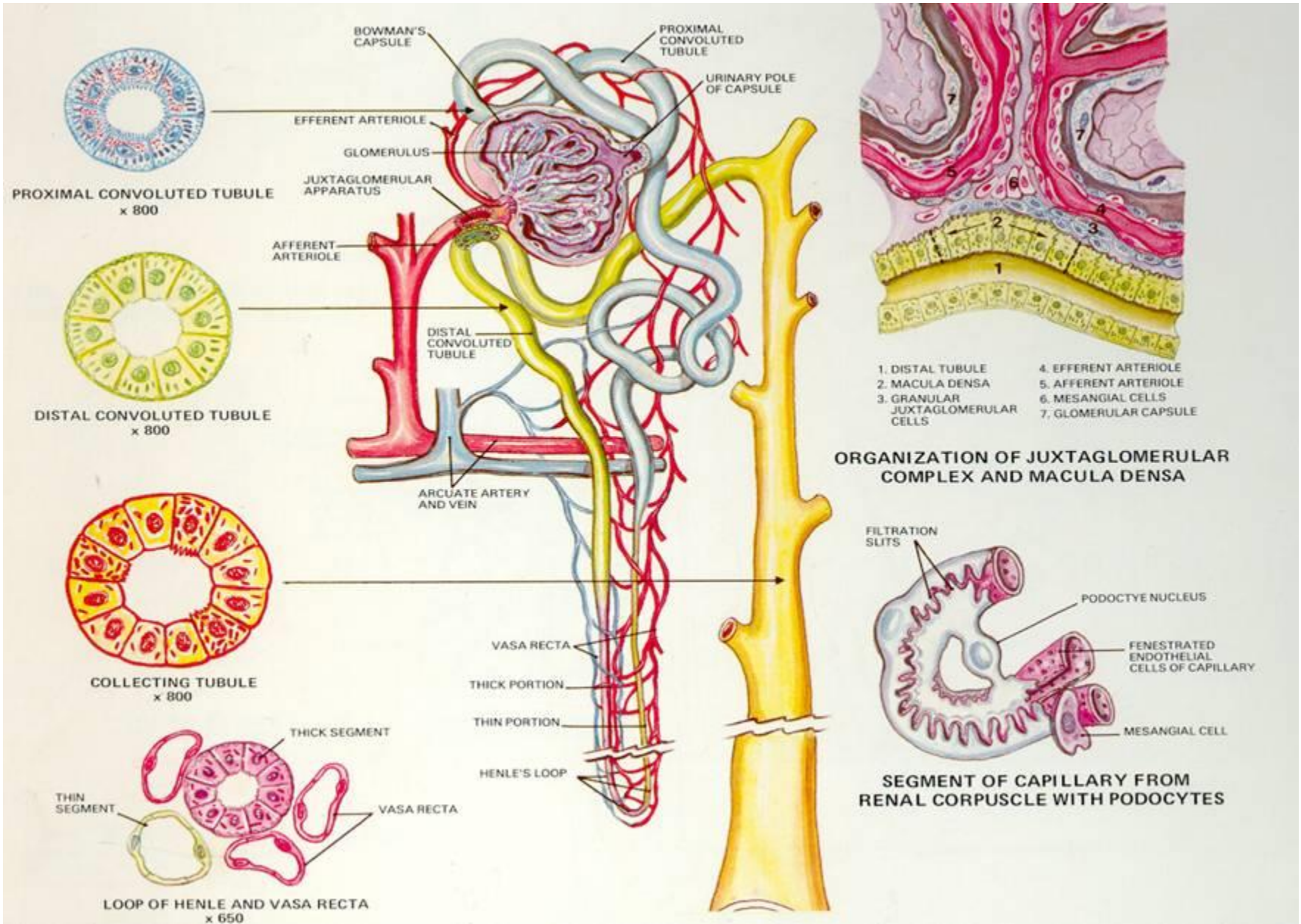
Fanconi syndrome

Fanconi syndrome

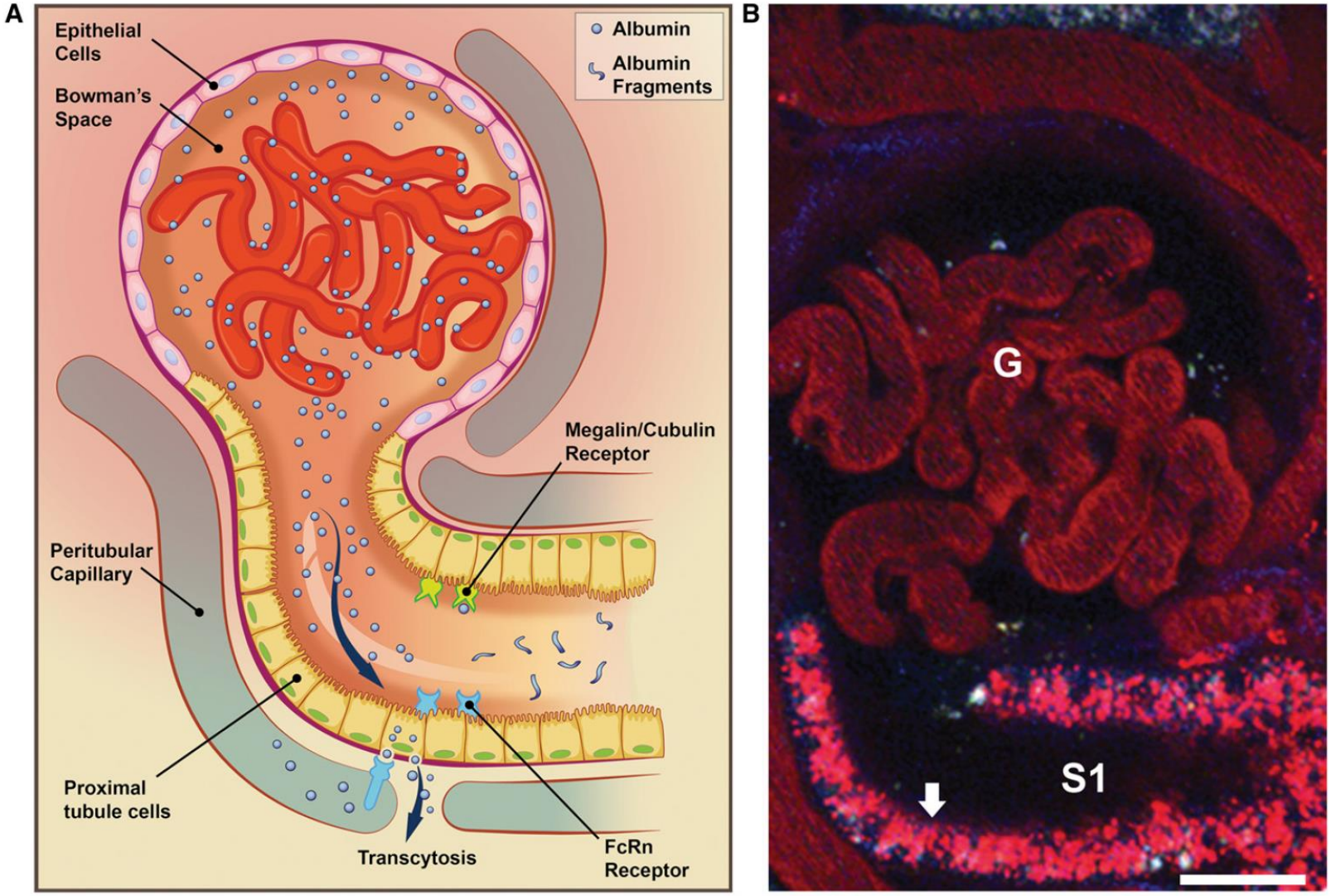
- Diagnosis of proximal tubular damage at the age of 6 mo
- ESRD at 8 years
- Successful kidney Tx at 9 years

- Diagnosis of cystinosis at 10 years

Structure of the kidney

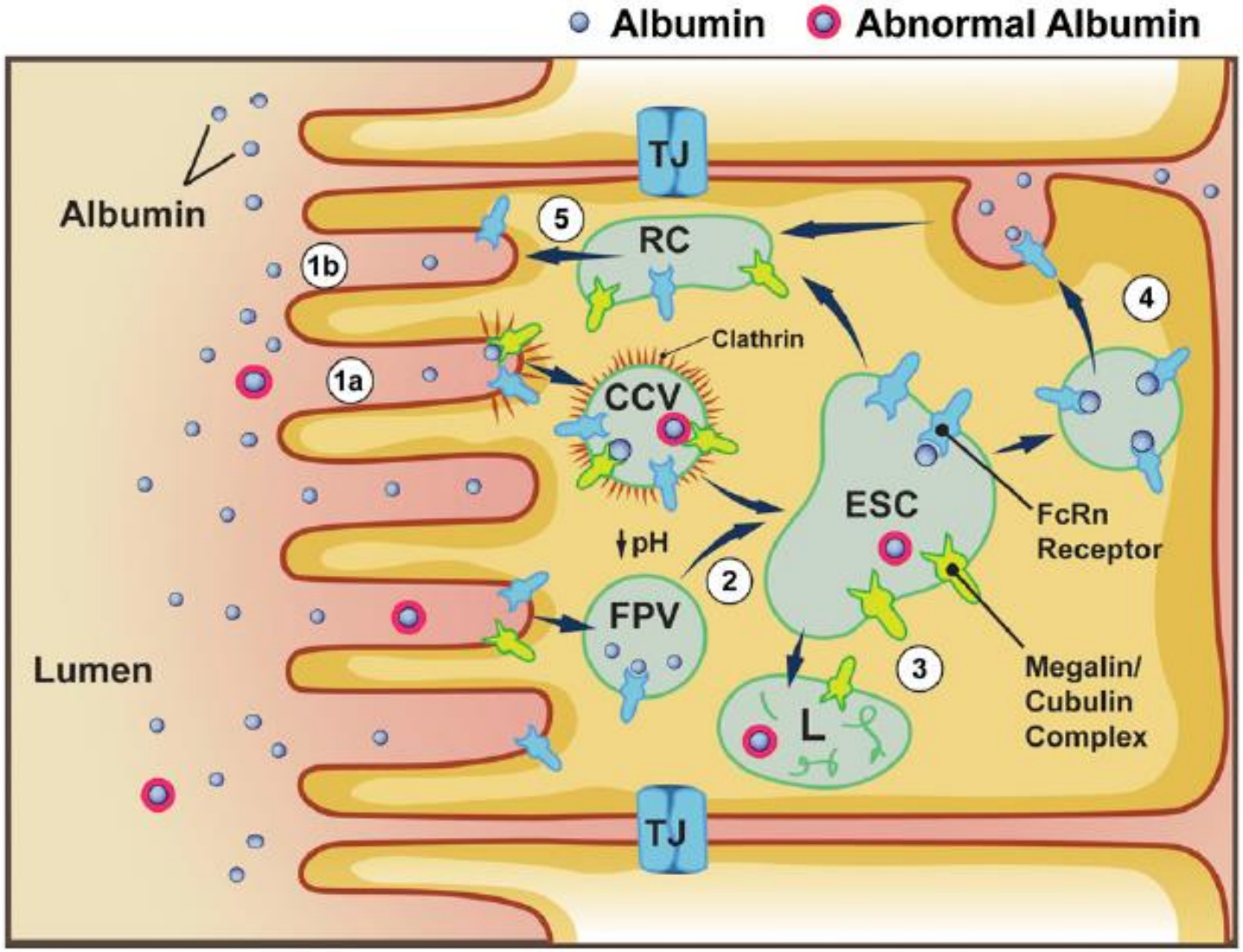


Albumin reabsorption in the kidney



Dickson EL: J Am Soc Nephrol , 2014; 25: 443–453,

Albumin reabsorption in the kidney



Dickson EL: J Am Soc Nephrol , 2014; 25: 443–453,

Fanconi syndrome

de Toni, Debré and Faconi
renal rickets+glycosuria+hypophosphatemia
=proximal tubular defect=

aminoaciduria
glycosuria
hyperphosphaturia-hypophosphatemia
bicarbonate loss
hypokalemia
proteinuria

Incidence: 1 - 100,000 Bretagne: 1 - 26,000

<u>Clinical manifestation:</u>

growth retardation, rickets, polyuria, dehydration + symptoms specific to the underlying disease

Fanconi syndrome. Etiology:

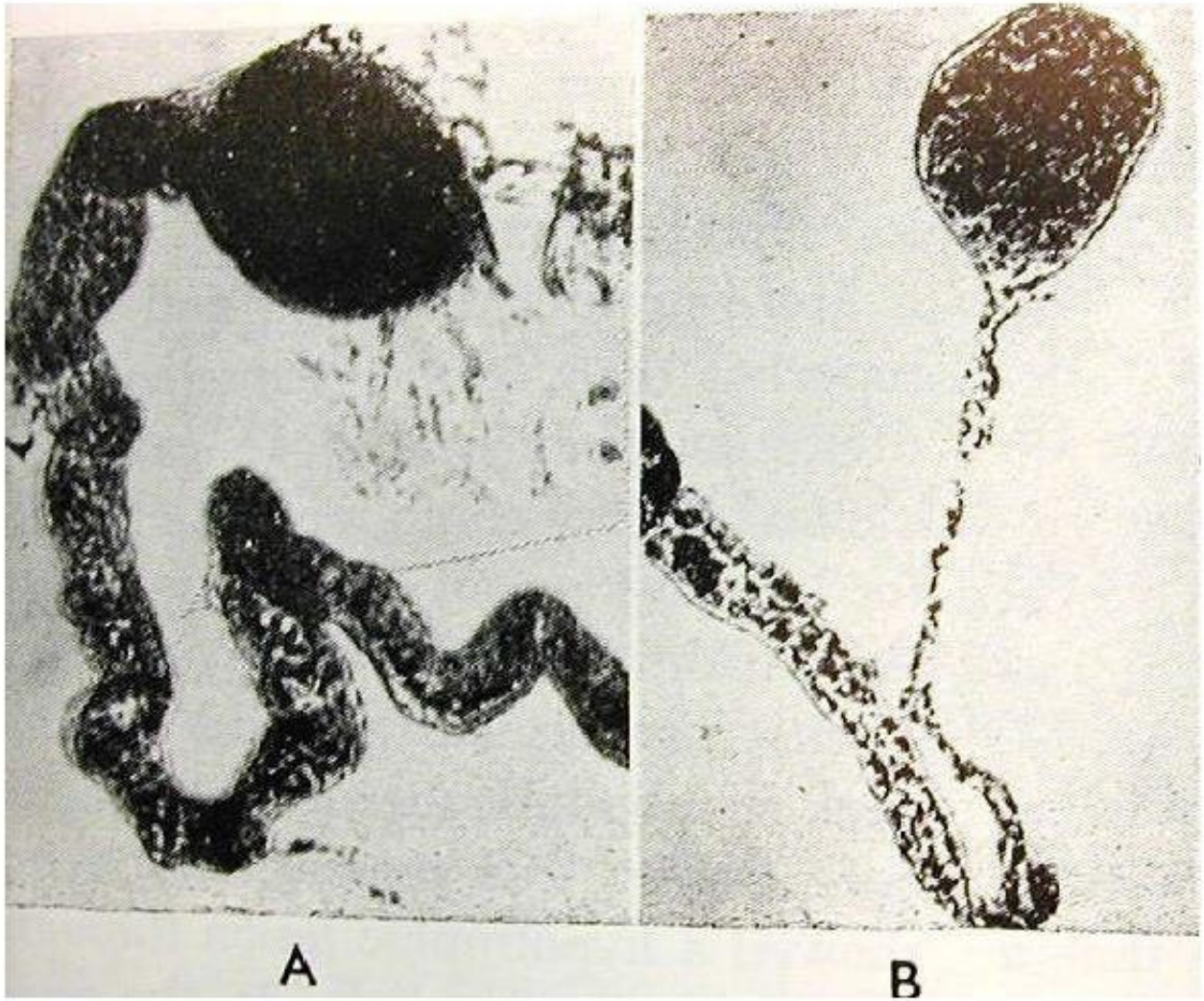
inherited

- **cystinosis**
- galactosemia
- fructose intolerance
- tyrosinemia
- Wilson’ s disease
- Lowe sy
- glycogenosis
- cytochrome-c oxidase def.
- idiopathic

acquired

- heavy metal
- Glue-solvent inhalation
- Azathioprine
- Gentamicin streptozocin induced
- Myeloma multiplex
- Sjögren sy
- Amyloidosis
- Cysplatin
- Iphosphamid
- Transplantation

"Swan-neck Deformity"

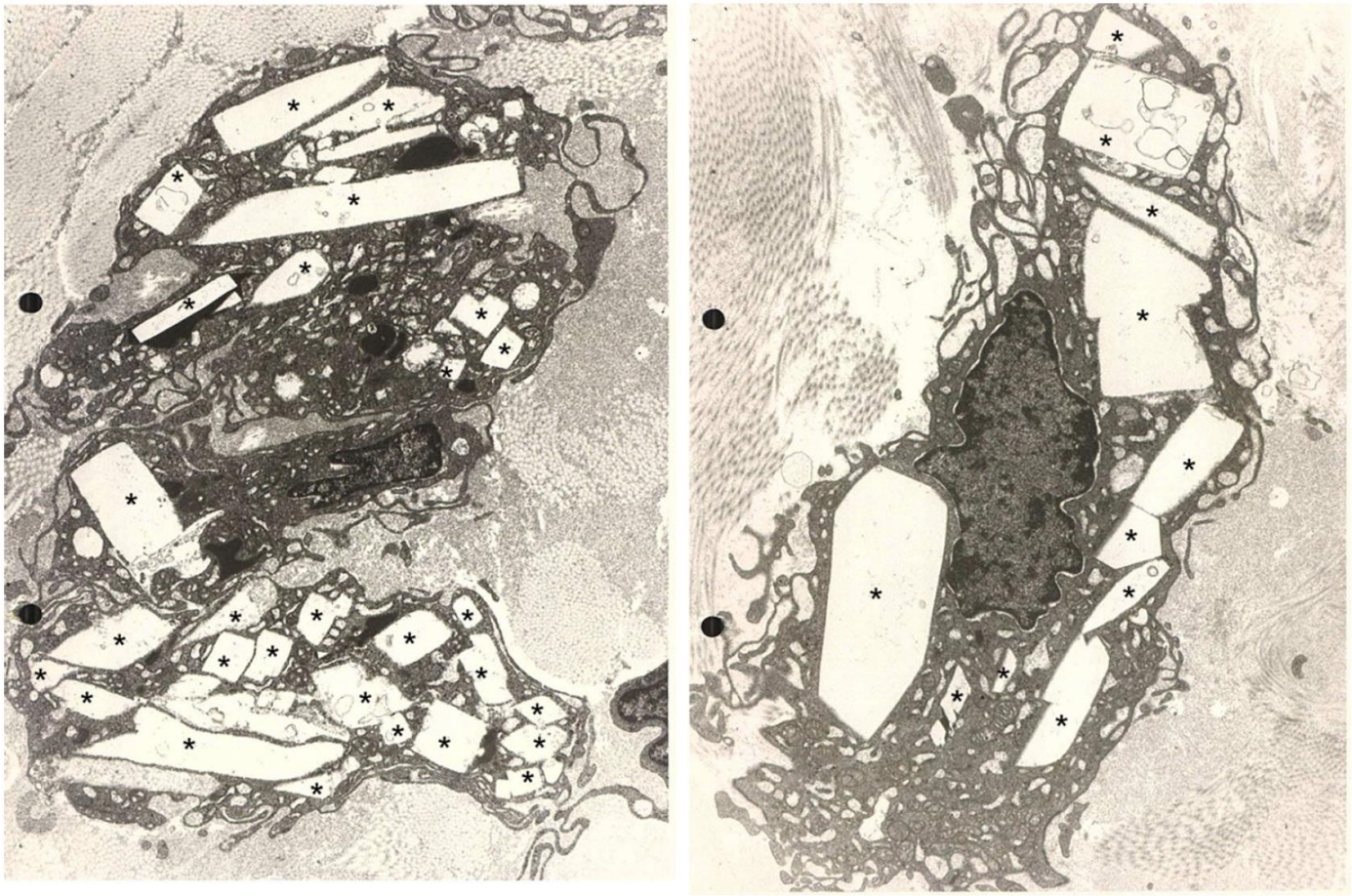


Cystinosis Tissue Repository Study of Atubular Glomeruli
http://www.slideshare.net/ringer21/cystinosis-tissue-repository-study-of-atubular-glomeruli

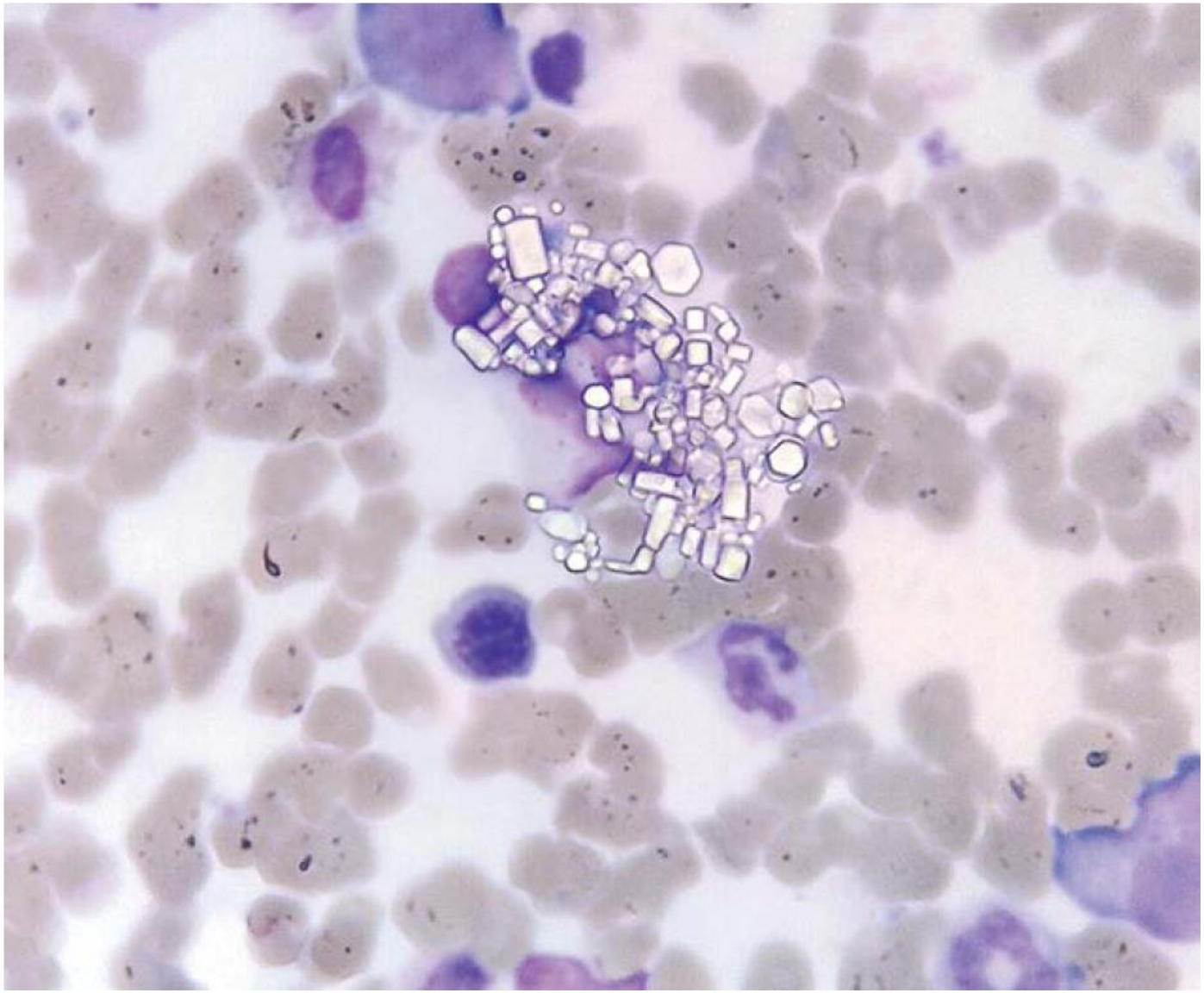
Cystin cristal deposition

Pediatr Nephrol (2015) 30:1349–1360

Fig. 2 Electron microscopy of fibroblasts obtained from conjunctival biopsy of the index patient. Fibroblasts can be seen to be packed with cystine crystals (*asterisks*)

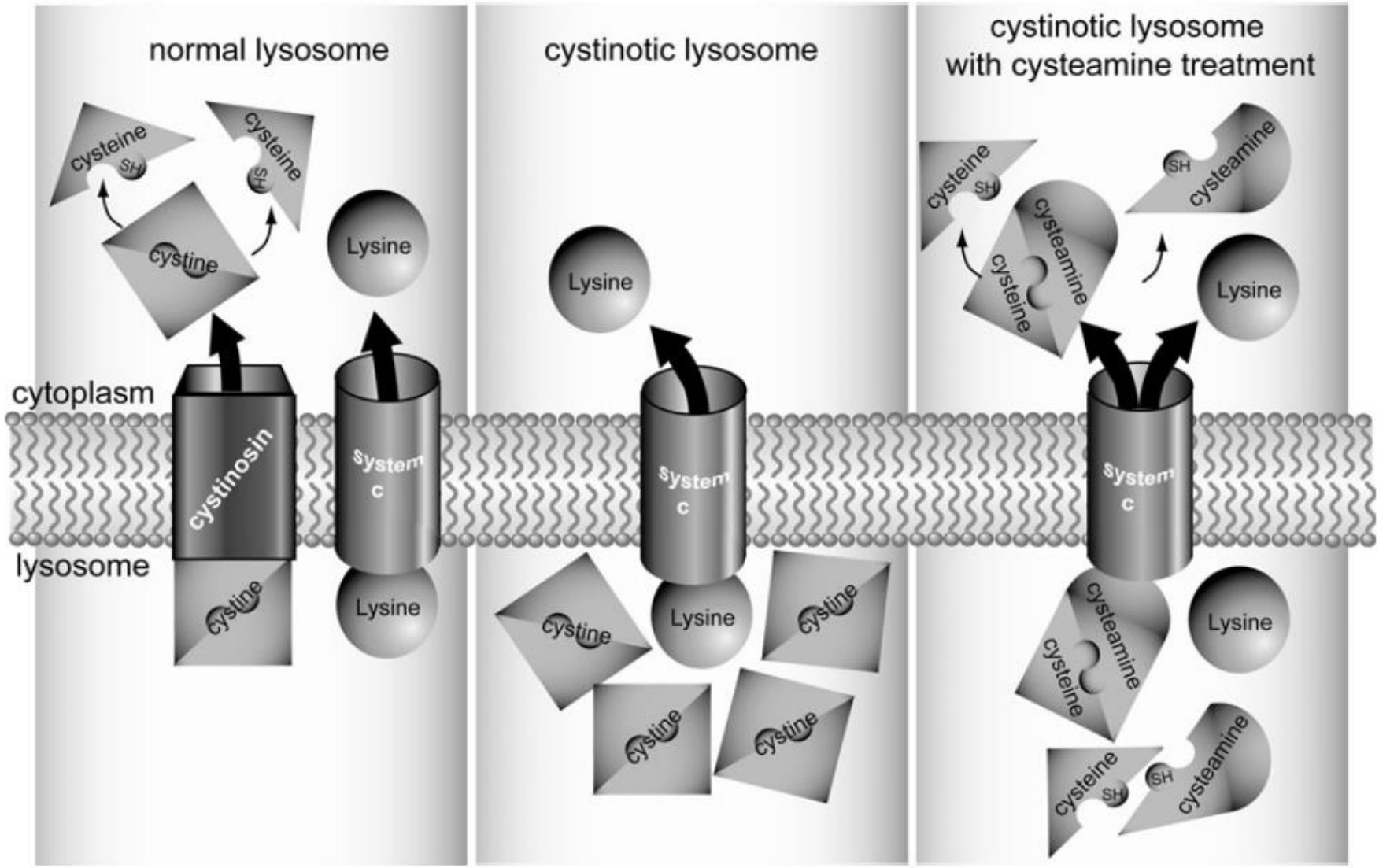


Cystin cristals in bone marrow

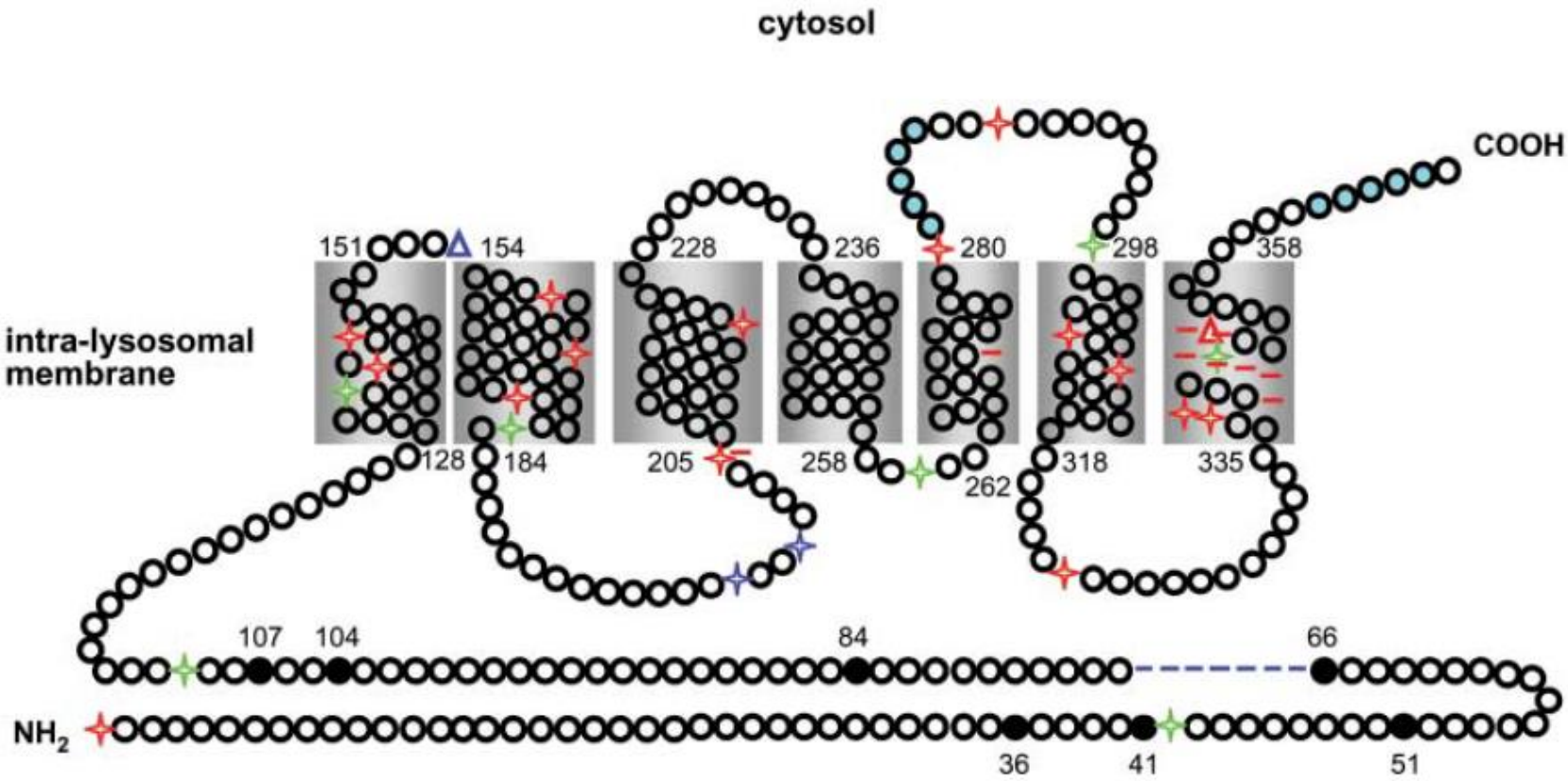


NEJM: DOI:10.1056/NEJMicm1415736

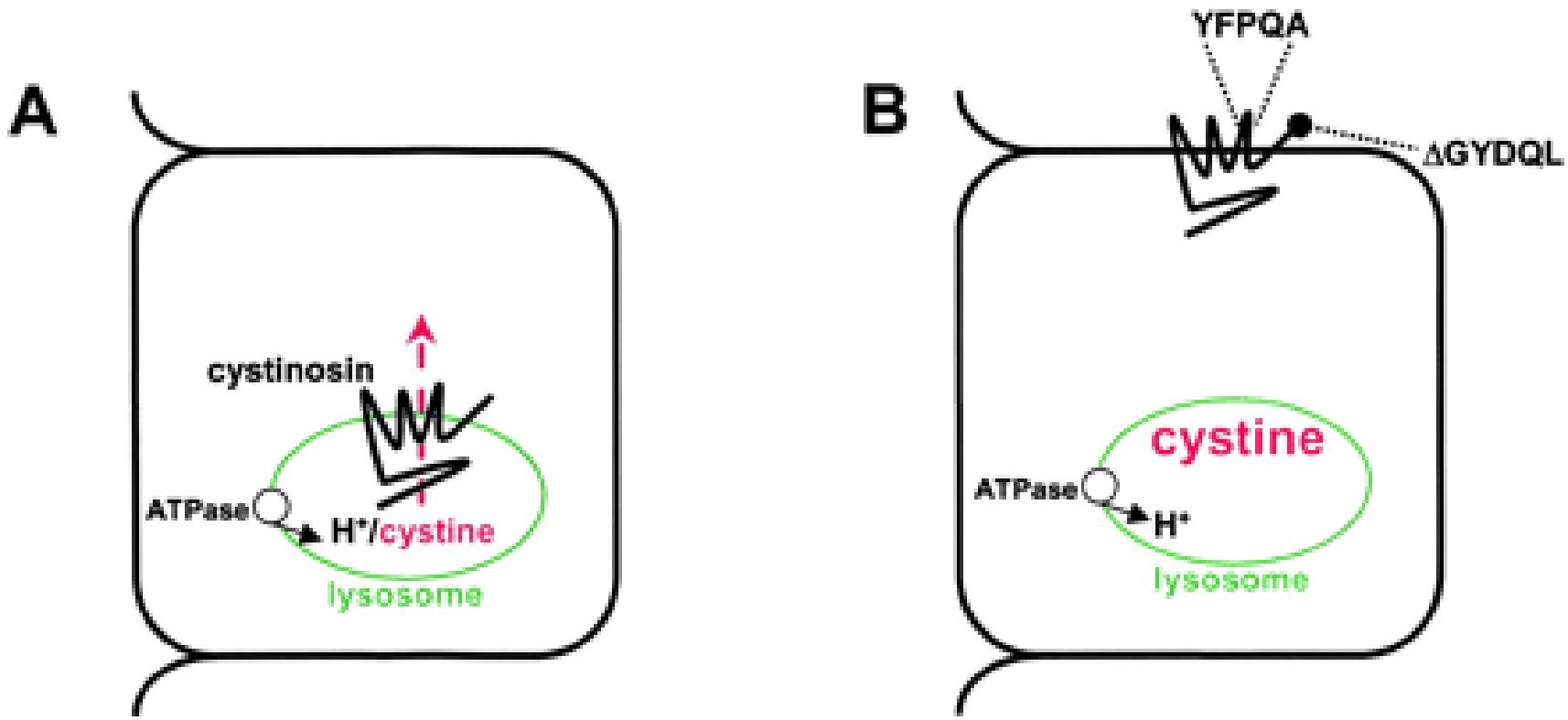
Pediatr Nephrol (2011) 26:205–215



Human Molecular Genetics, 2004, Vol. 13, No. 13



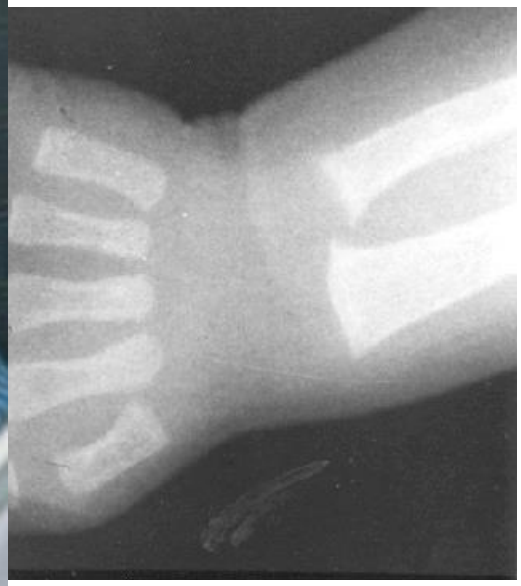
Renal Epithelial Traffic Jams and One-Way Streets



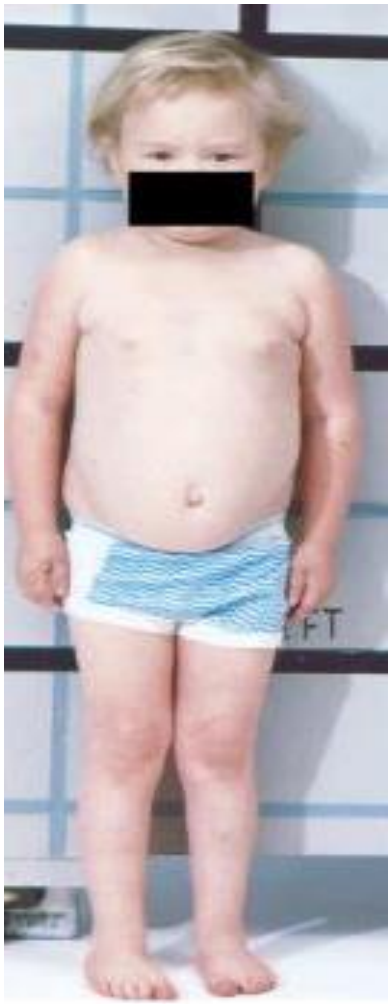
Mark A.J. Devonald and Fiona E. Karet . Am. Soc. Nephrol., Jun **2004**; **15**: 1370 - 1381.

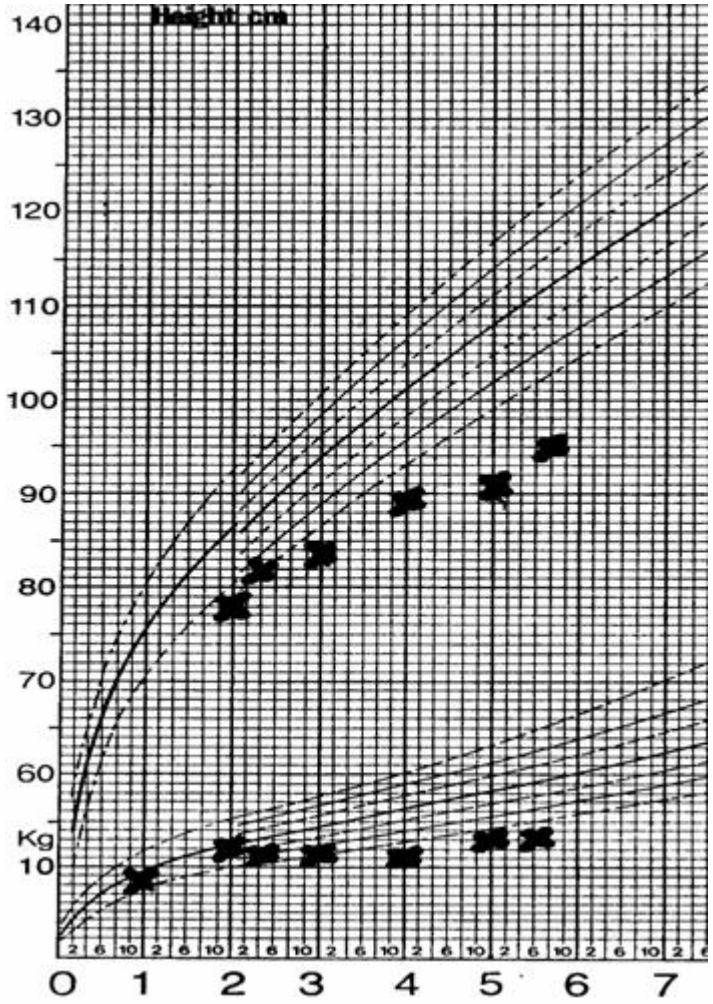
Cystinosis.

Rickets



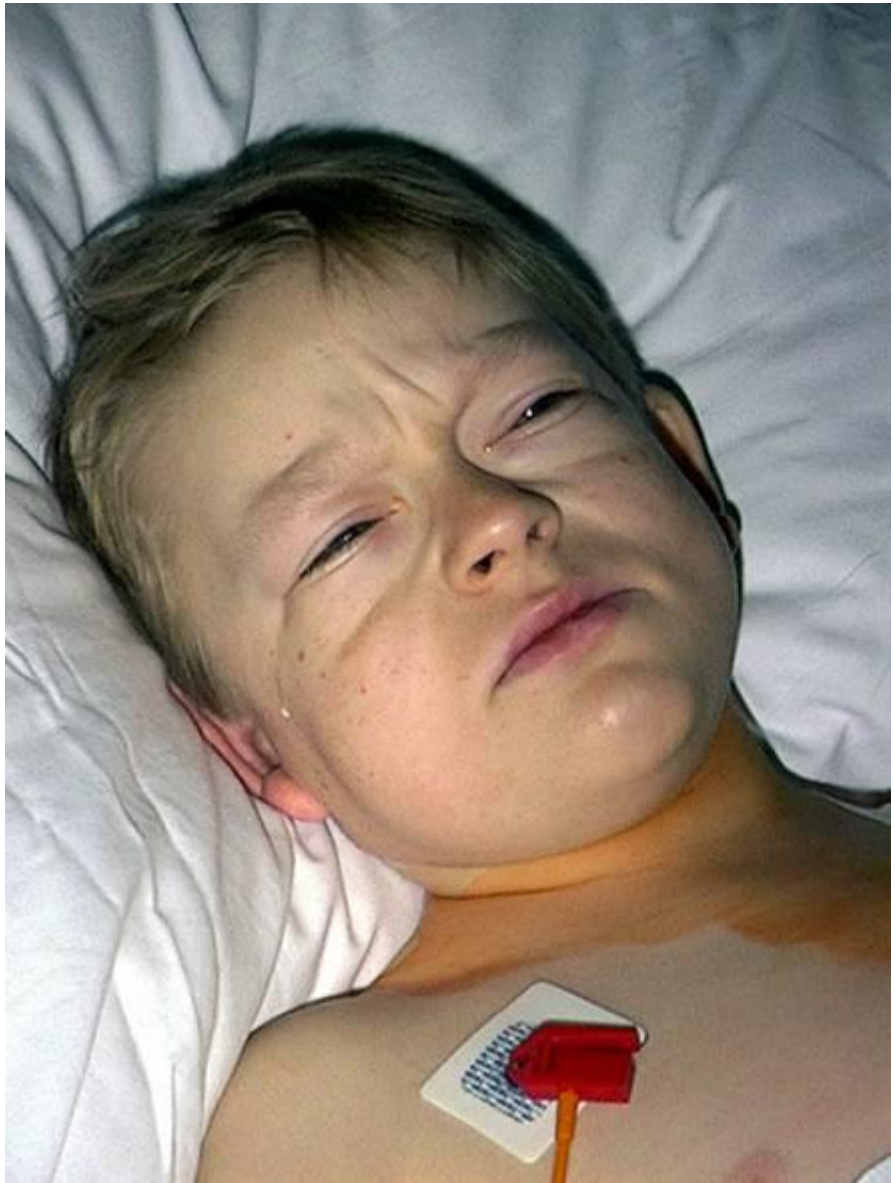
Cystinosis.



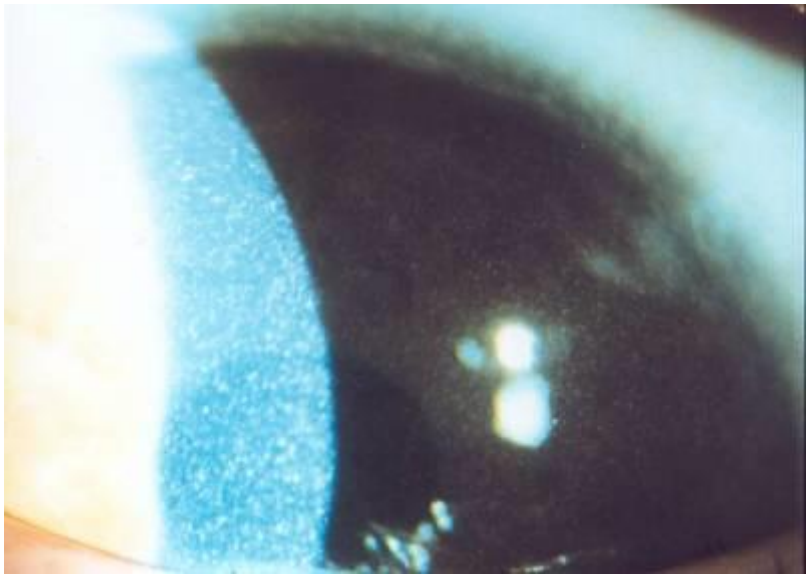


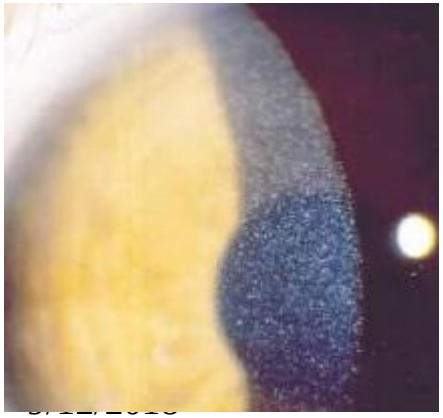
- Growth retardation

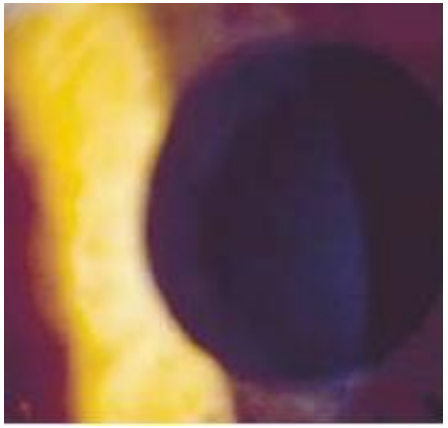
Cystinosis photophobia.



Cystinosis.

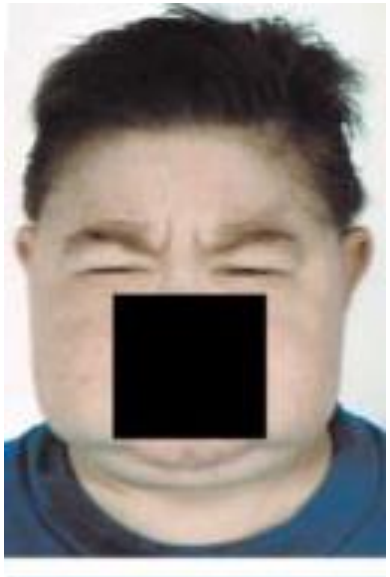


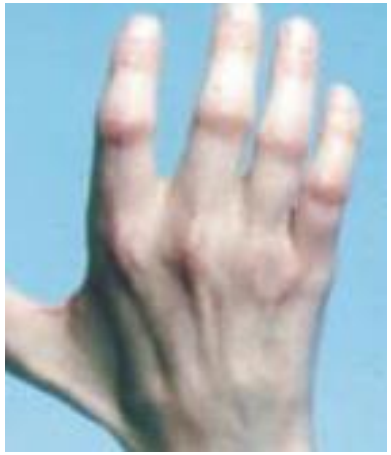




- Cystin christals in the cornea

Cystinosis. Evolution





- 7-8 y: ESRD
- 5-10 y hypothyreosis
- 12-40 y myopathy, difficulty to swallow
- 13-40 y degeneration of the retina, blindness
- 18-40 y diabetes mellitus
- 18-40 y male hypogonadism
- 21-40 y lung dysfunction
- 21-40 y CNS involvement
- -- late outcome ??

Medical treatment(3.5 y 14 kg)

- Fluid intake: 3-3.5 l = cca. 250 ml/kg
- K 350 mmol/day = 25 mmol/kg
- HCO3 300 mmol/day = 21.5 mmol/kg

- Ca Sandoz 2x250 mg
- P Sandoz 4x500 mg
- Alpha-D3 50 mikrogramm/day
- Amilorid 1.25 mg
- HCTZ 12.5 mg

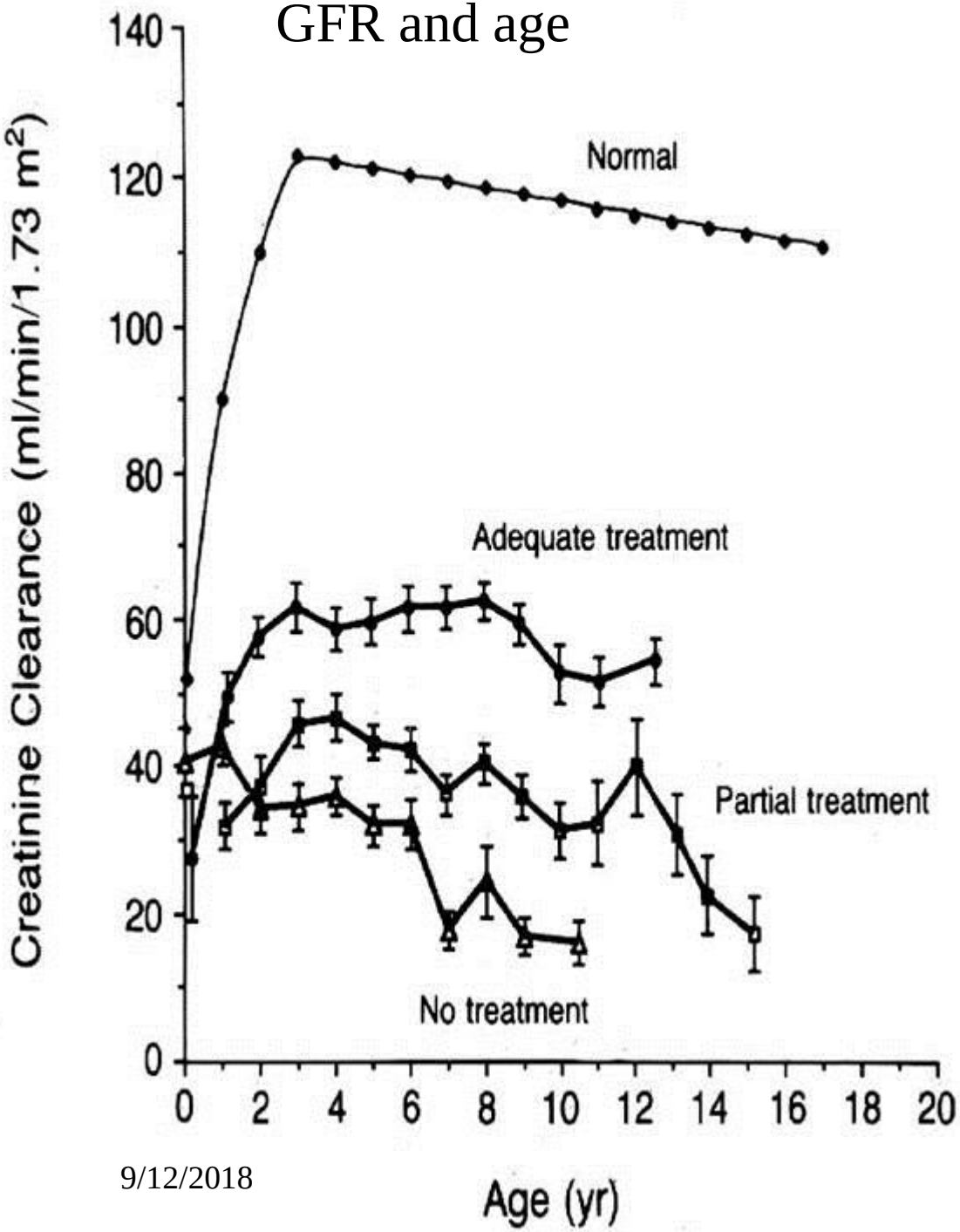
- L-Thyroxin 25 mikrogramm
- Folic acid/iron supplementation

- *Cystagon 5x250 mg*
- *Cysteamin eye drops 5x daily*

Aims of treatment

- To conserve kidney function
- Growth
- To stop extrarenal manifestations
  - Eye
  - Thyroid
  - Glucose metabolism
  - Gonads
  - Muskle
  - CNS

GFR and age



Follow-up:
Intracellular cystin level

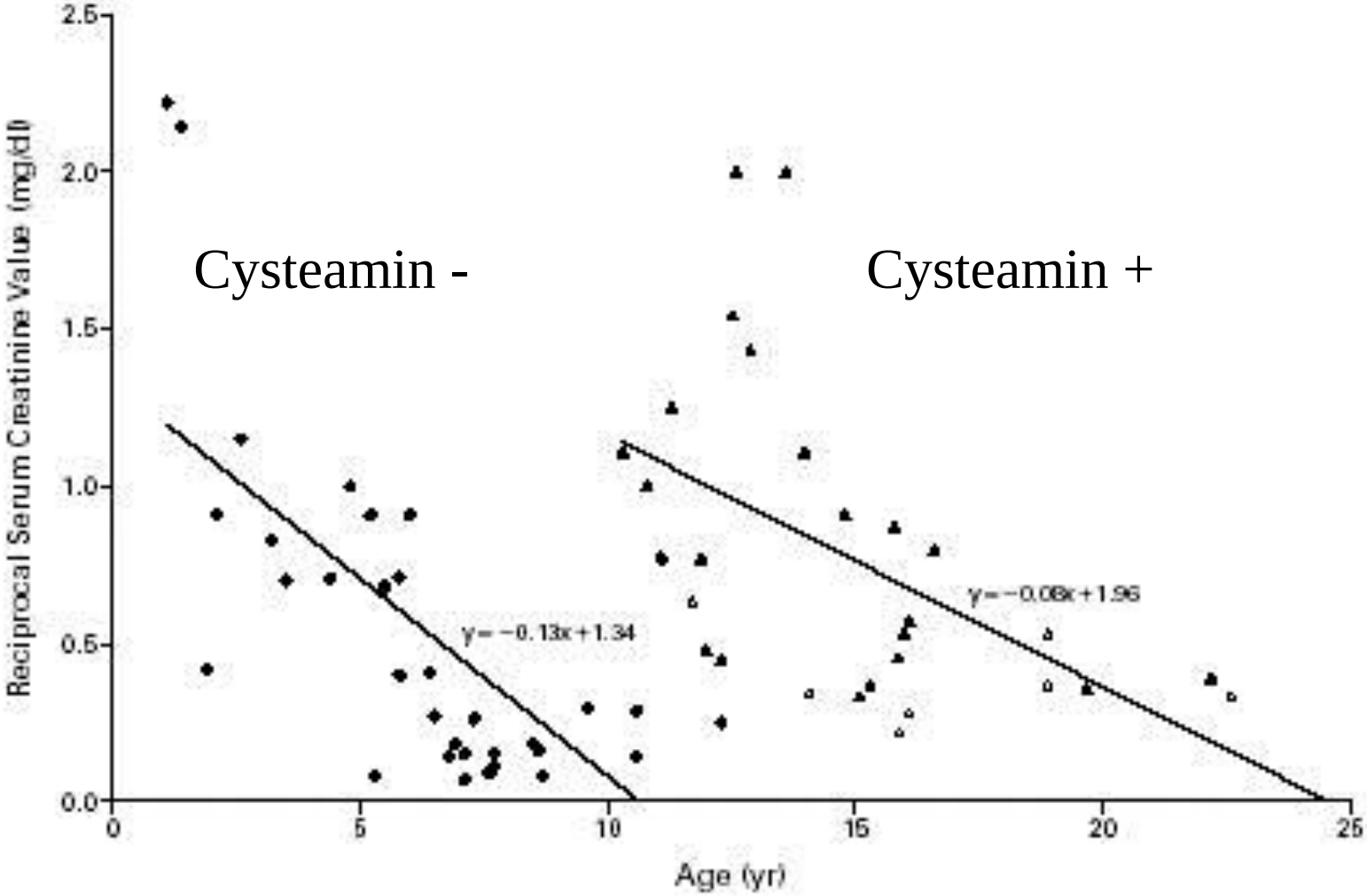
On treatment: n= 17

Partially successful tr: n= 32

Off treatment: n=67

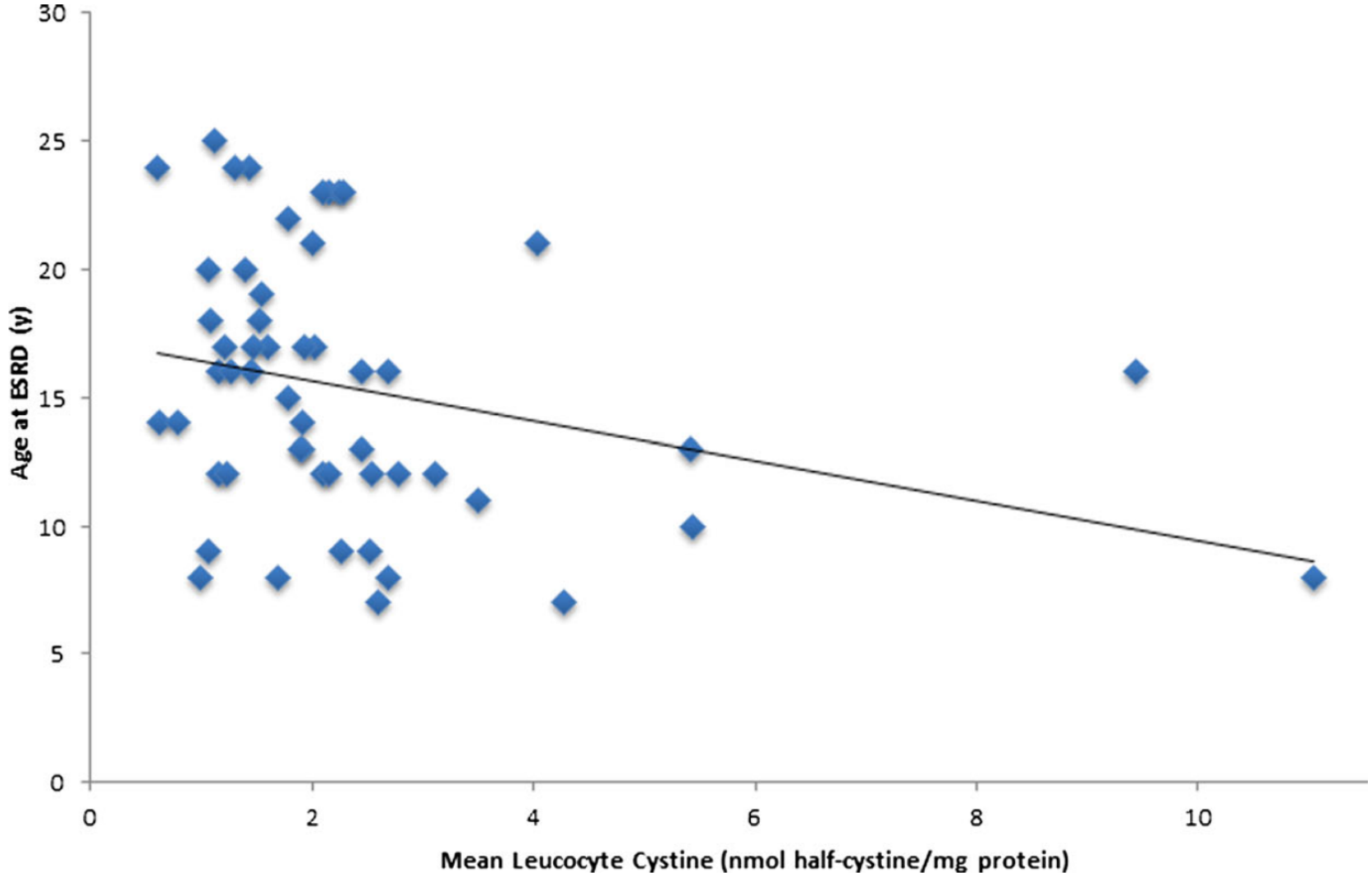
Markello: N Engl J Med, 328: 1993.1157-1162

Kidney function and age



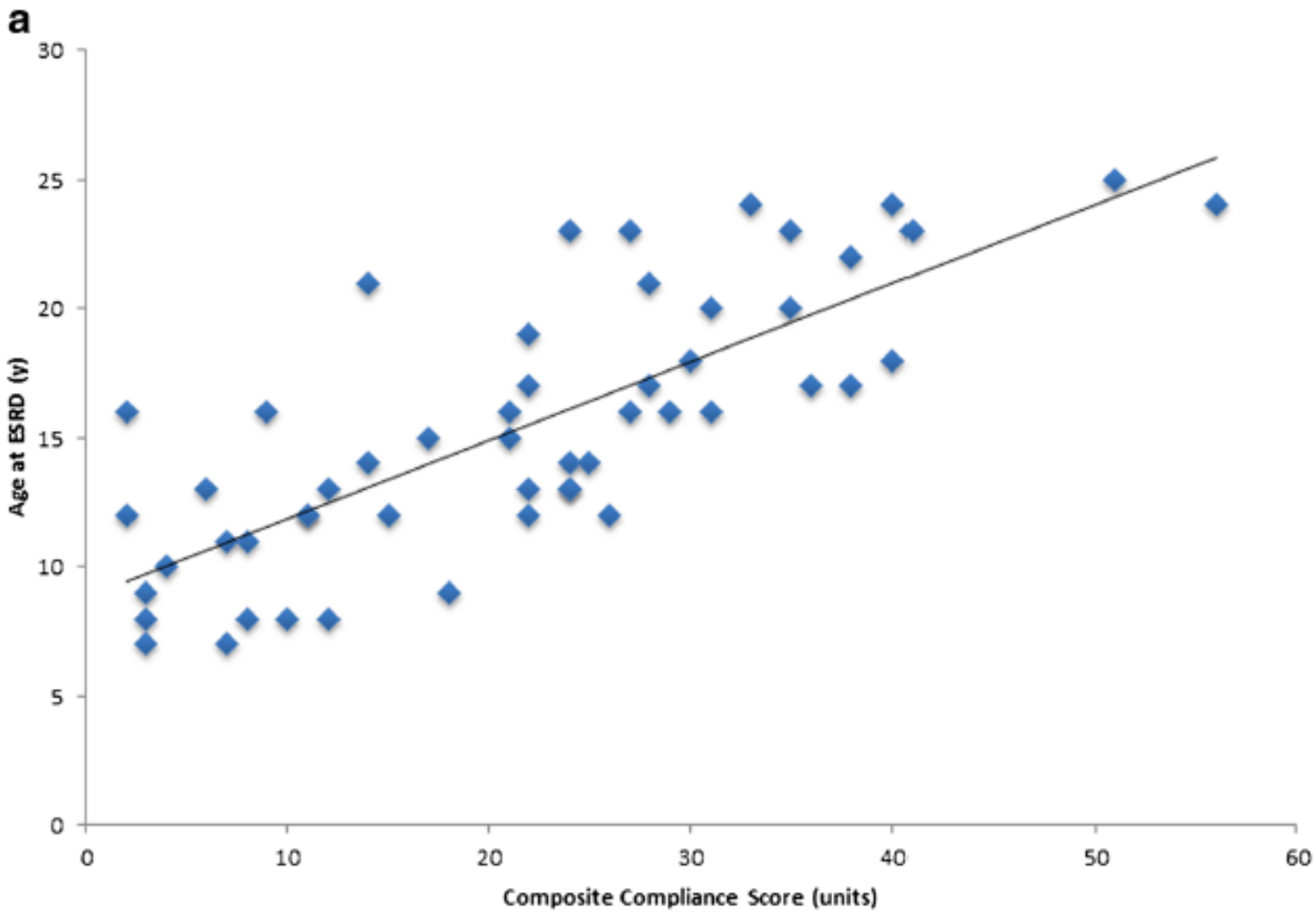
Gahl: N Engl J Med, Volume 347, 2002.111-121

Leucocyte cystin level and CKD



Nesterova et al: Pediatr Nephrol (2015) 30:945–951

„Compliance score" and evolution to ESRD



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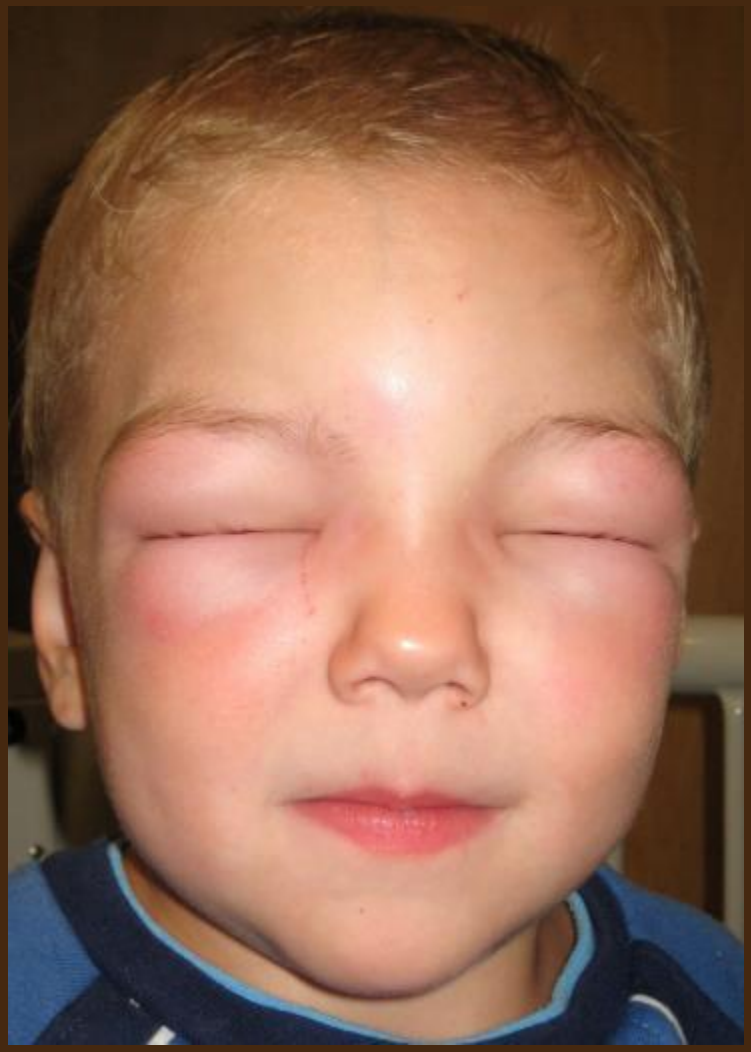
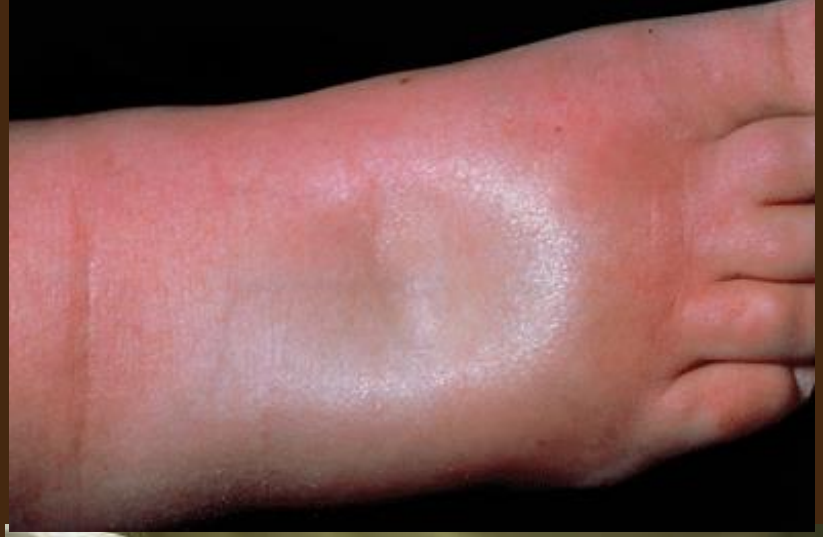
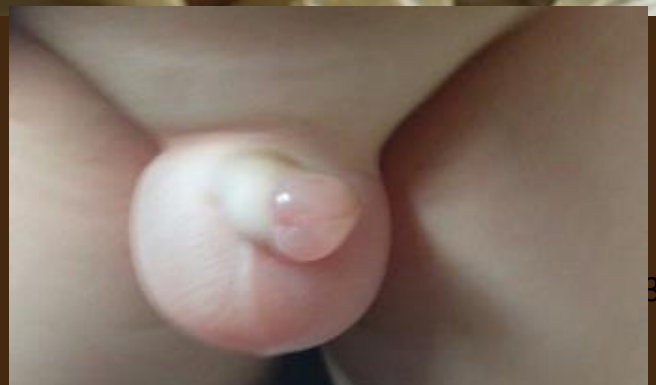
Glomerular diseases

Congenital nephrotic syndrome





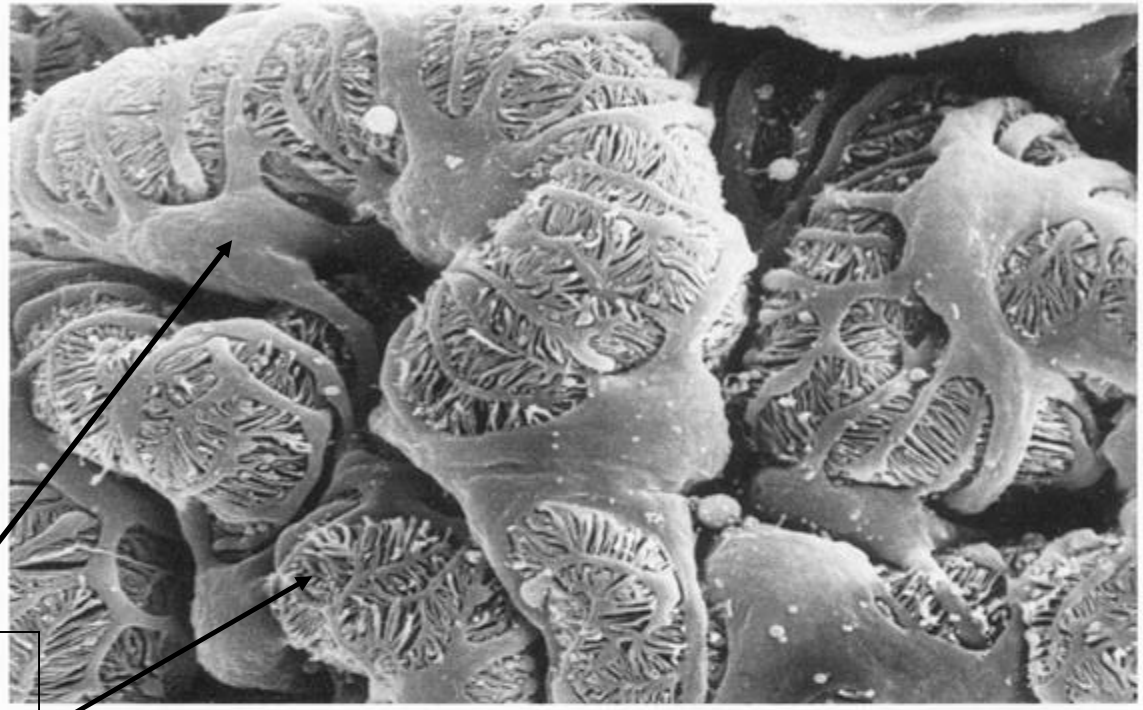


Categories of FSGS

1. Primary (idiopathic) FSGS – immunologic origin
2. FSGS due to mutations of the podocyte-basement mebrane unit (AD, AR)

3. Secondary FSGS (hyperfiltration)

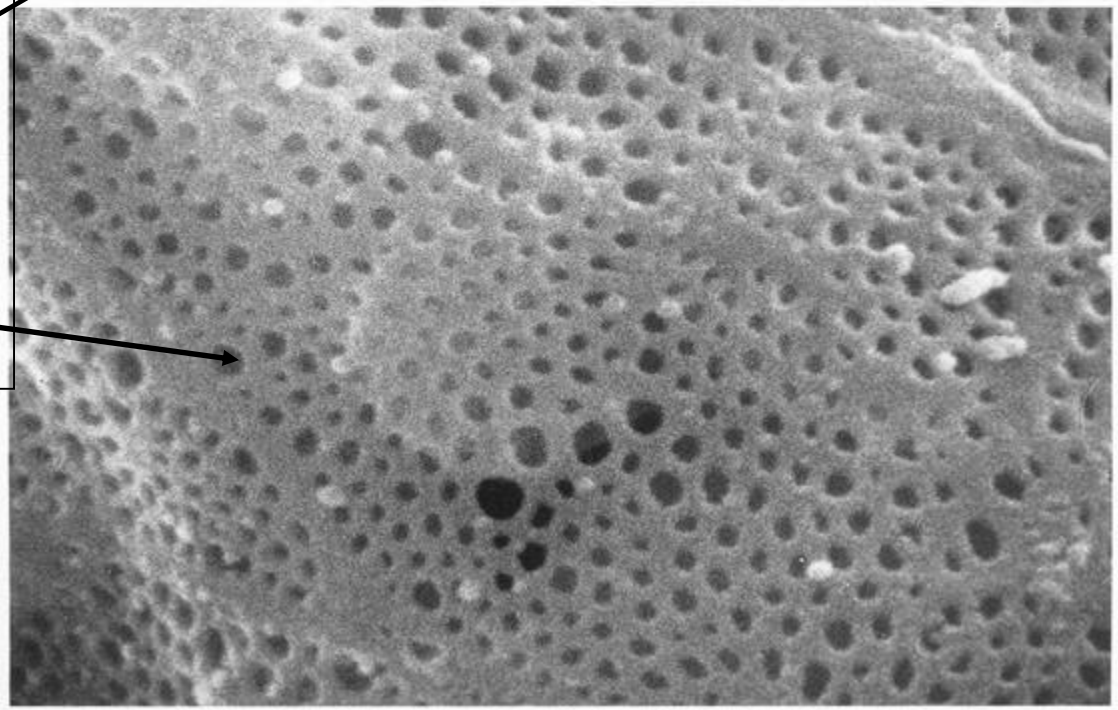
Scannig EM vue of the podocyte



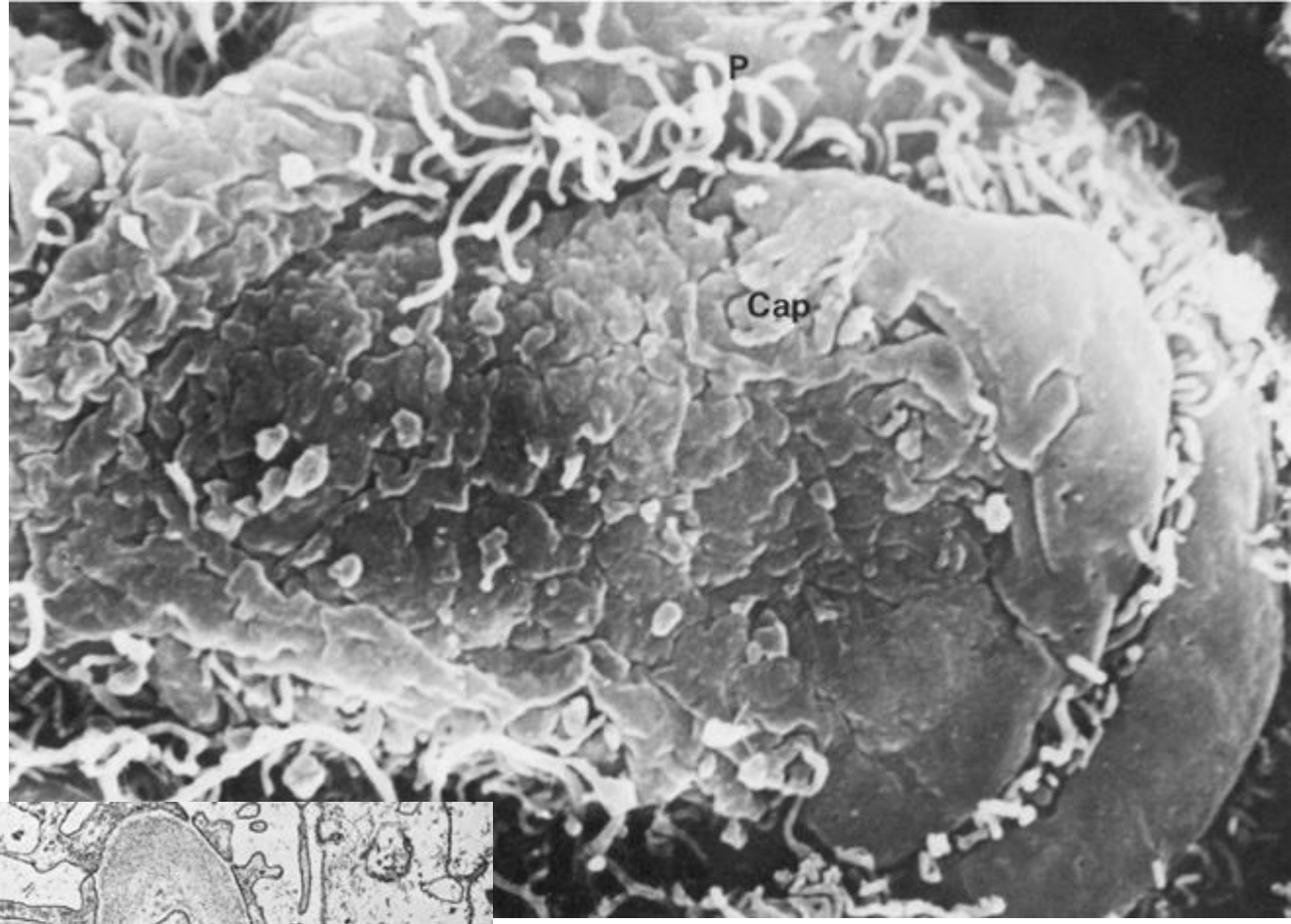
Podocyte body

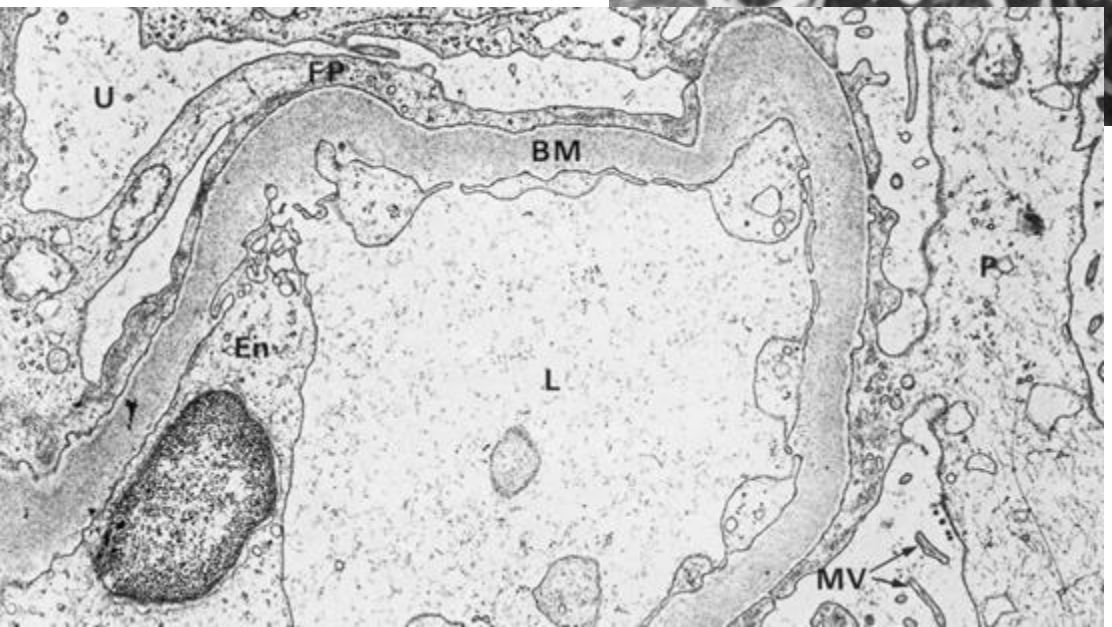
Foot processes

Fenestrated endothelial cell



Scanning electron-microsopic picture of a glomerular capillary

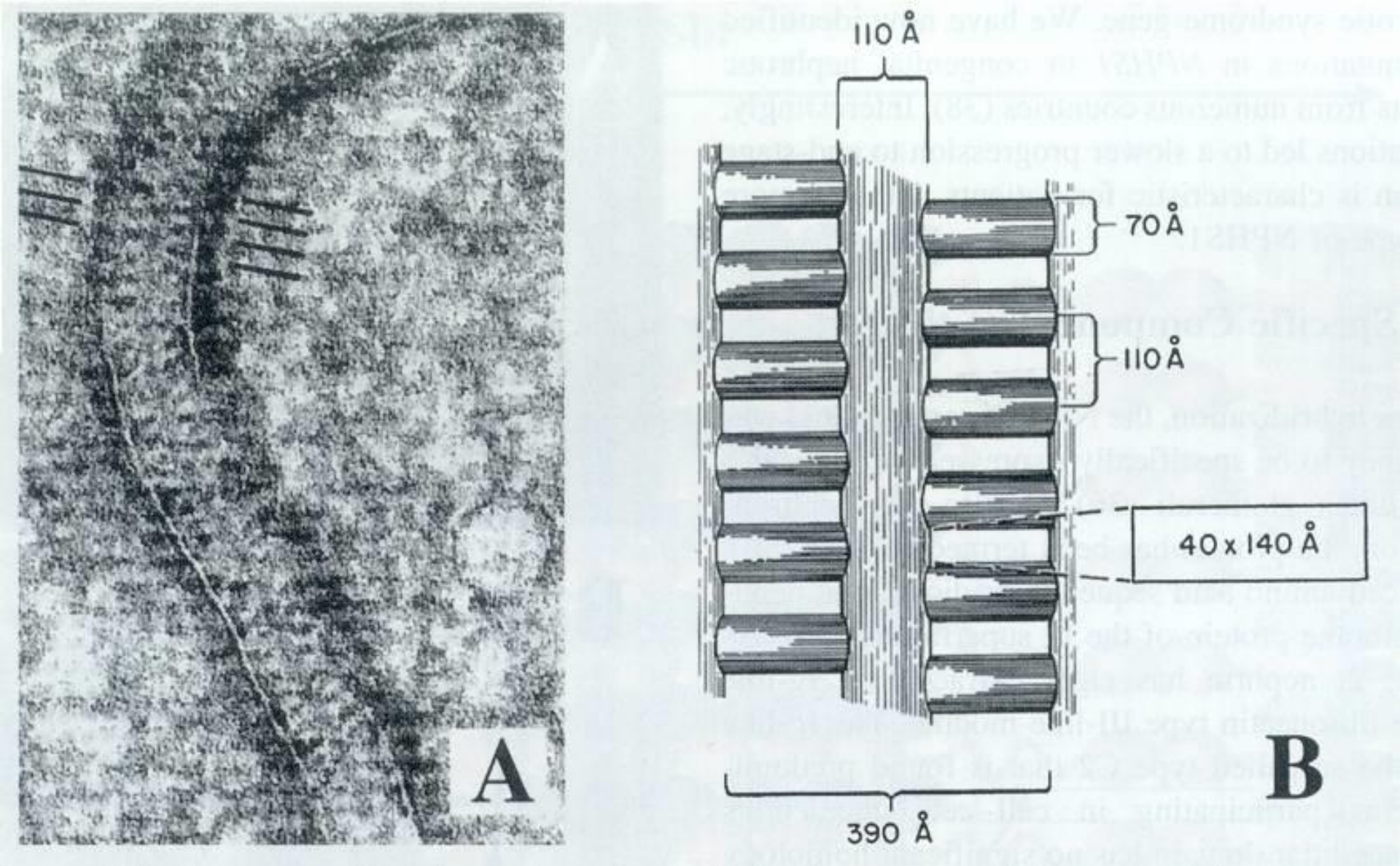


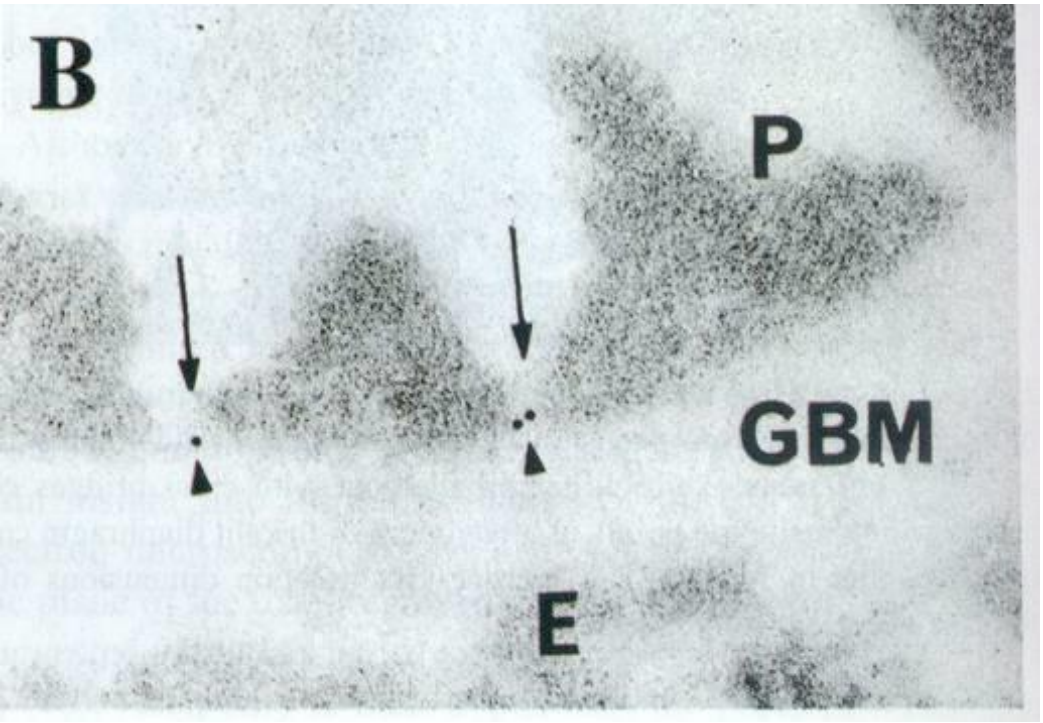


in nephrotic syndrome

Zipper-like morphologic structure of the podocyte slit diaphragm

Rodenwald R, Karnovsky MJ: J. Cell Biol, 1974,

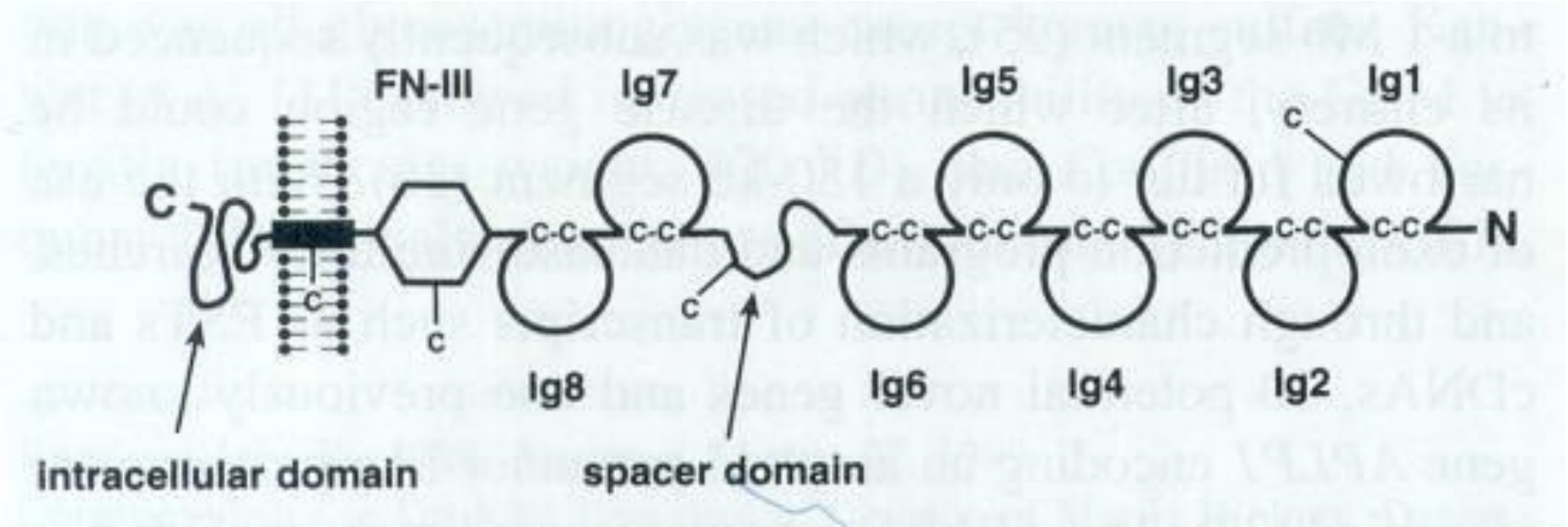




Immunoelectronmicroscopy using IgG against recombinant human nephrin and gold-coupled second antibody

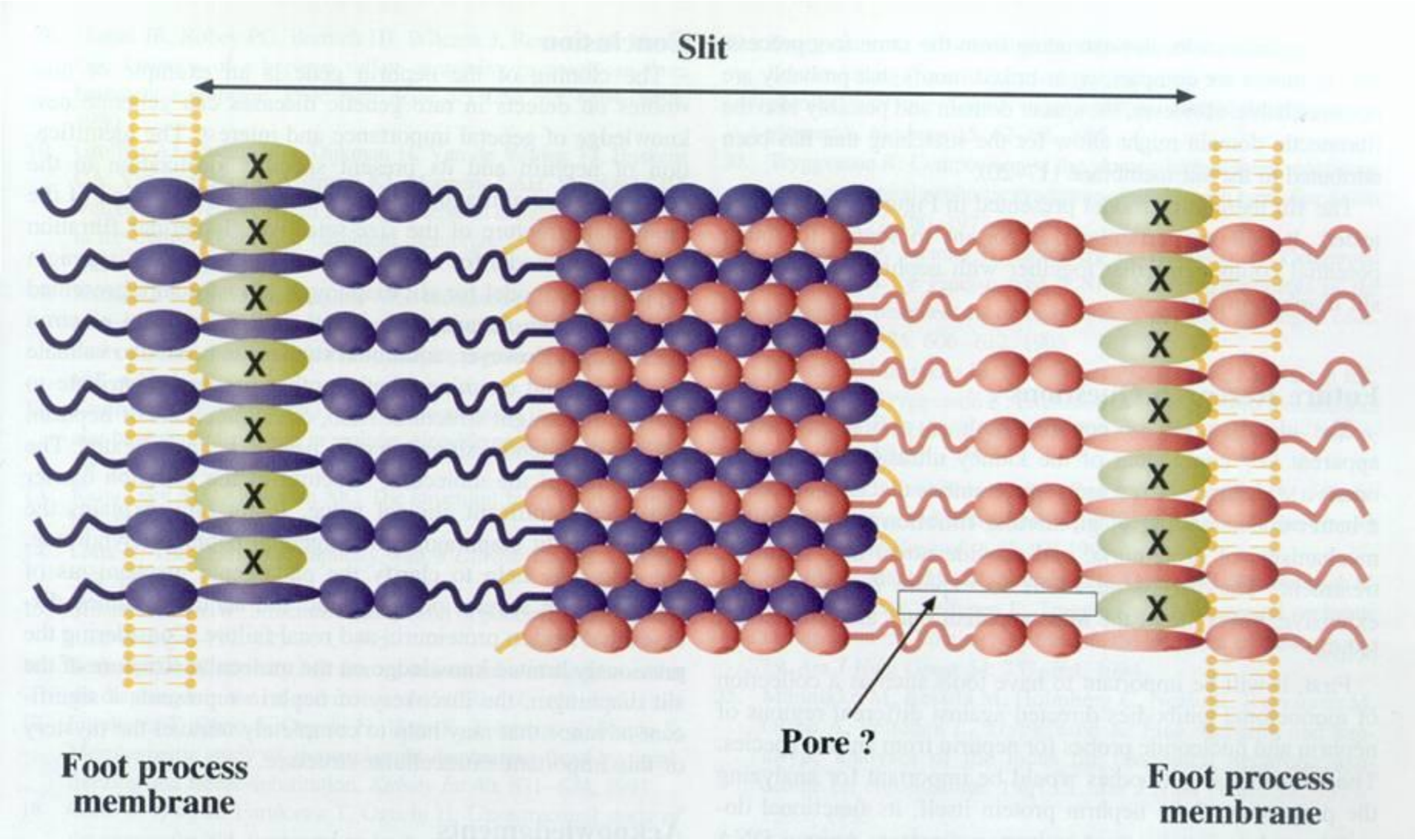
Routsalainen V et al, Proc Natl Acad Sci USA, 1999

Schematic structure of human nephrin



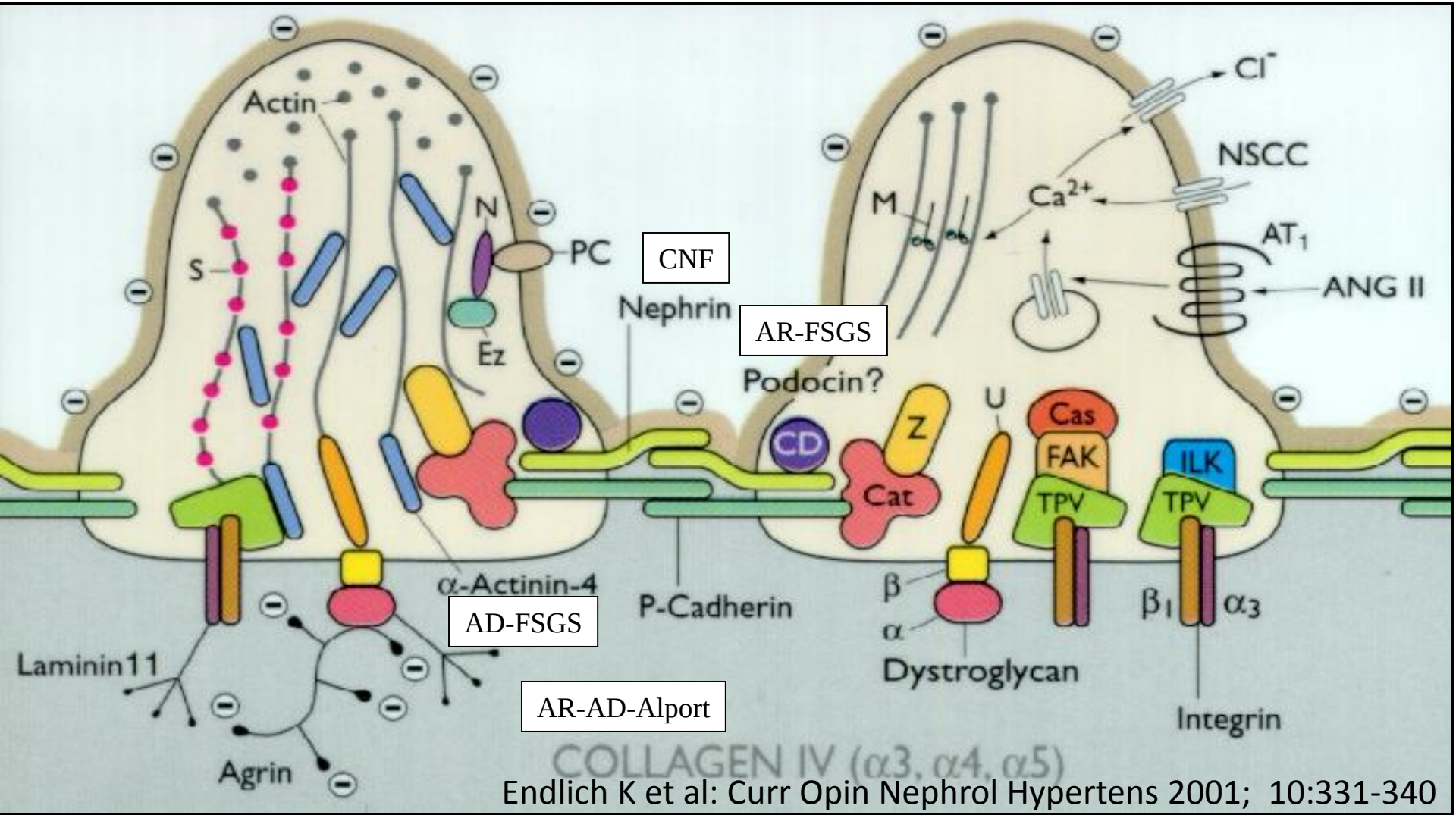
Hypothetic assembly of nephrin into an isoporous filter of the podocyte slit diaphragm

Tryggvason K, JASN, 1999



Molecular composition of the podocyte slit membrane

Cat=Catenin; CD=CD2 associated protein; Ez= ezrin; FAK=focal adhesion kinaze; ILK=integrin linked kinaze; M=myosin; PC=podocalycin; S=synaptopodin; TPV= talin, paxillin, vinculin; U=utrophin; Z=Z-1; FSGS= focal segmental glomerulosclerosis; CNF=finnish type congenital nephrotic syndrome



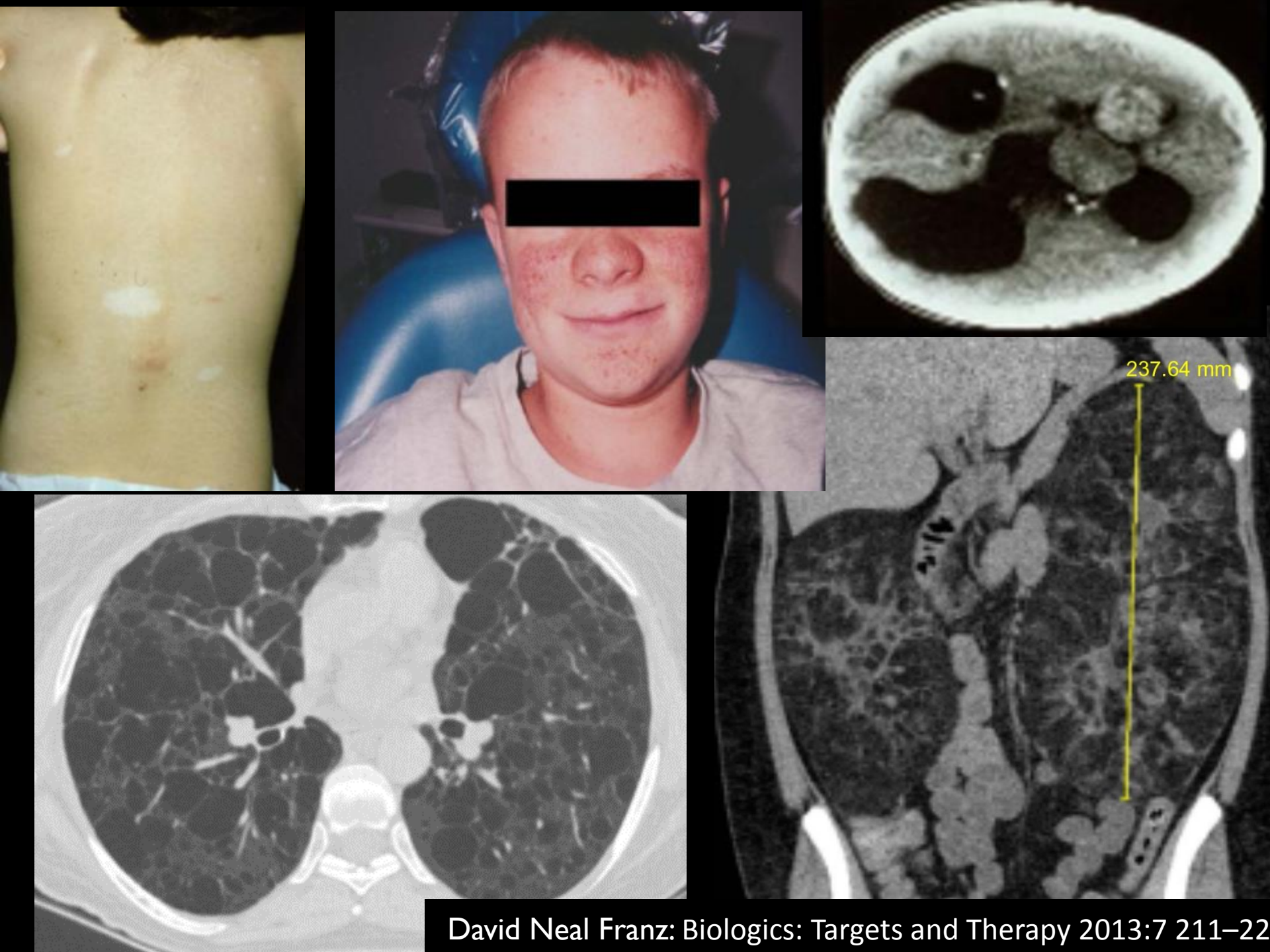
Endlich K et al: Curr Opin Nephrol Hypertens 2001; 10:331-340

Importance of FSGS categories

1. Primary FSGS (Cause? Mechanism?) Immunological process)
   - 60% recurrence after Tx
2. Congenital (hereditary)
   - Only exceptionally relapses after Tx (anti-nephrin AB)

3. Secondary FSGS (hyperfiltration)
   - Needs conservative therapy (RAAS blockade)
   - No recurrence after Tx

Tuberous sclerosis



David Neal Franz: Biologics: Targets and Therapy 2013:7 211–22

Tuberous Sclerosis Complex (TSC)

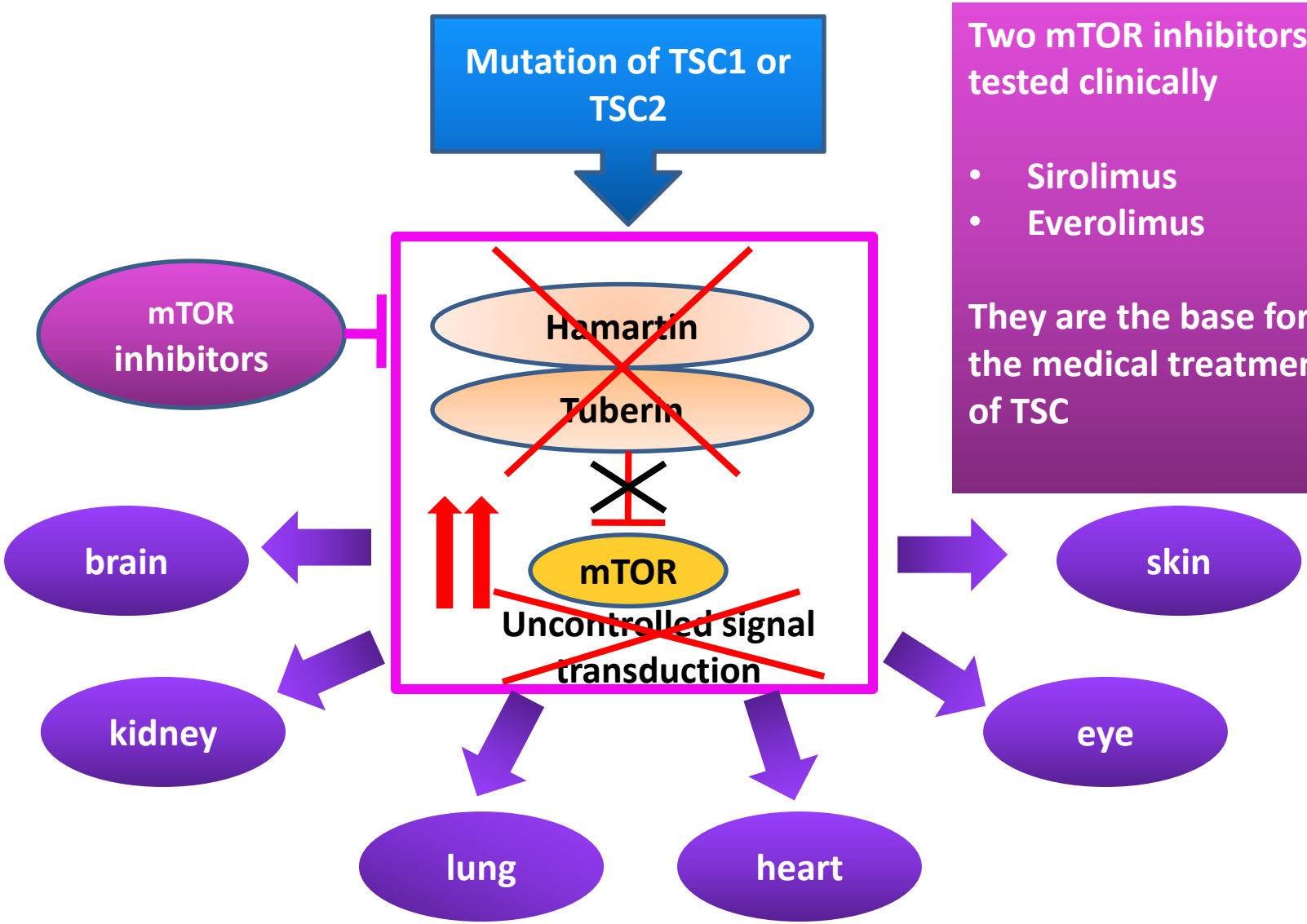
- Rare, autosomal dominant disease.
- Incidence: 1/6000
  - Benign hamartomas in different organs [1-3]

- Caused by inactivating mutations of tumor suppressor genes
  - TSC1 (hamartin) or
  - TSC2 (tuberin) [1]

  - Hamartin and tuberin are forming a complex, that indirectly inhibits the activity of the mTOR pathway[1,4]

1. Franz DN: Biologics, 2013;7:211-221
2. Northrup H et al: Pediatr Neurol, 2013;49:243-254
3. Curatolo P et al: Lancet, 2008;372(9639):657-668
4. Napolioni V, Curatolo P: Curr Genomics, 2008;9:475-487

Mechanism of developing TSC



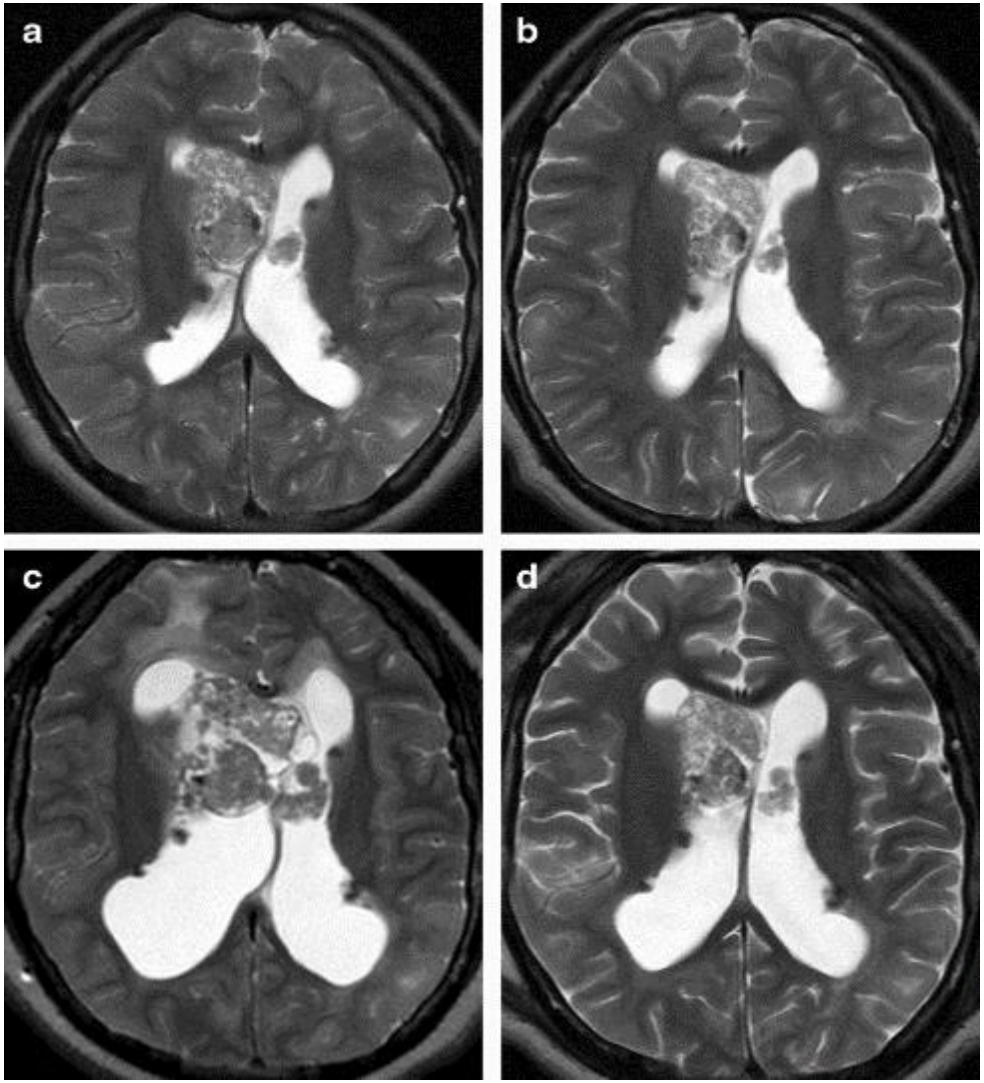
Two mTOR inhibitors tested clinically

- Sirolimus
- Everolimus

They are the base for the medical treatment of TSC

Everolimus treatment and SEGA

Prior to treatment



6 month therapy

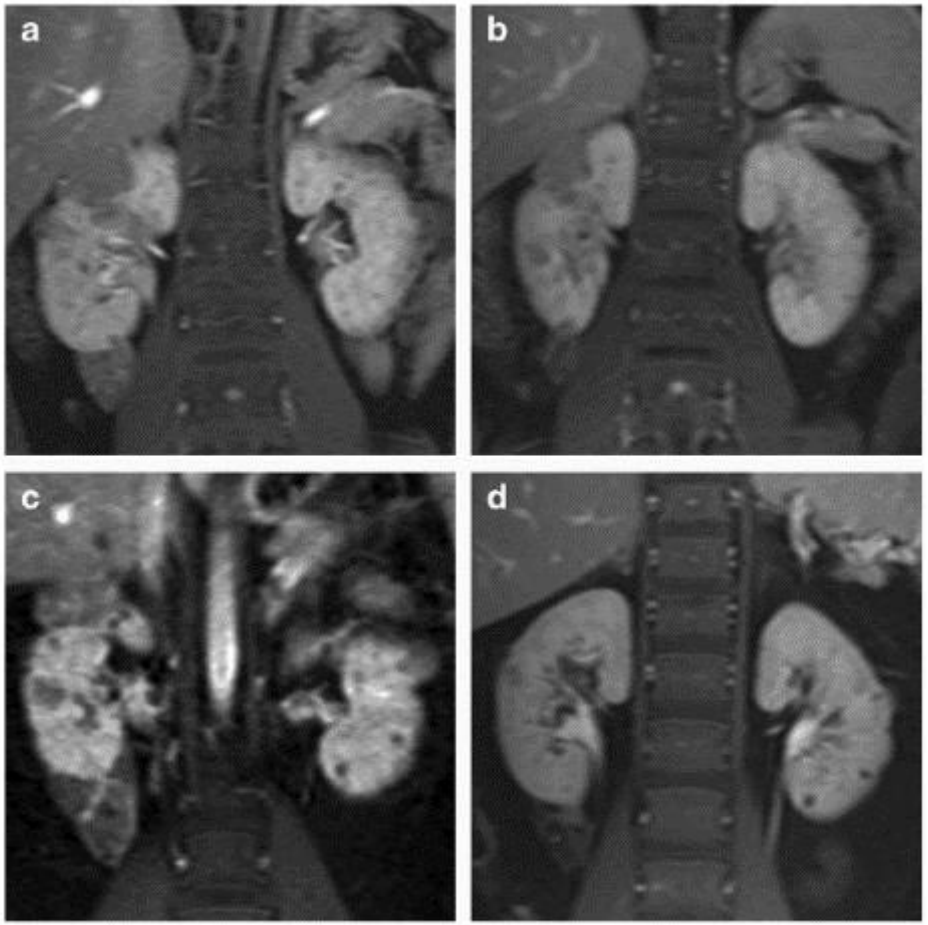
Suspension of therapy
(36 mo)

Reintroduction of treatment
(42 mo)

Miller JM et al : Pediatr Nephrol 2014 DOI 10.1007/s00467-014-2949-6

Everolimus treatment and AML

Prior to treatment



6 month therapy

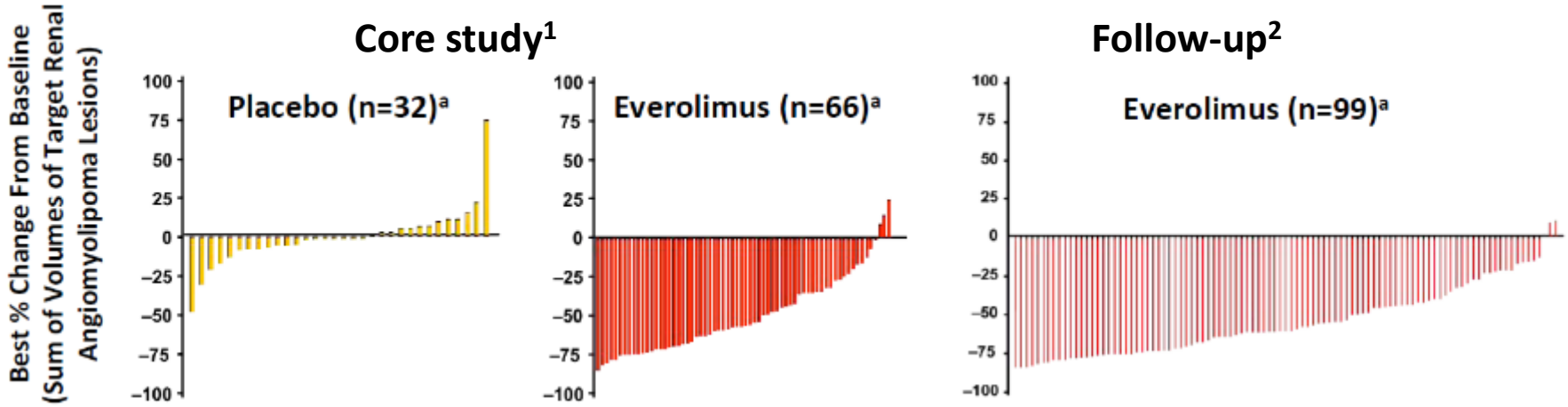
Suspension of therapy (36 mo)

Reintroduction of treatment (42 mo)

Pediatr Nephrol 2014 DOI 10.1007/s00467-014-2949-6

EXIST 2 study: sustaind effect of Everolimus on AML of the kidney

- Mor than 50% mass reduction
- No bleeding during the AML study



1. Bissler J et al: Lancet, 2013;381:817-824
2. Bissler J. Presented at: 29th Annaual European Association of Urology Congress, April 11-14, Stockholm, Sweden

Recommendations for the use of mTOR inhibitors in TSC

mTOR inhibitors are included in the management of several TSC manifestations

- Brain
  - Surgical resection or treatment with mTOR inhibitors may be used for growing, asymptomatic SEGA
- Kidney
  - mTOR inhibitors are the recommended first-line treatment option for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter
- Lung
  - mTOR inhibitors may be used to treat patients with LAM with moderate to severe lung disease or rapid progression

Krueger D, Northrup H. *Pediatr Neurol*. 2013;49(4):255-265.

Level of evidence for recommendations on mTOR inhibitor use in TSC

Manifestation	Category of Evidence
SEGA	Category 1: High-level evidence
Epilepsy	Not evaluated
TAND	"Insufficient to support"
Renal angiomyolipoma	Category 1: High-level evidence
LAM	Category 1: High-level evidence
Skin lesions	Category 3: No consensus achieved

Krueger D, Northrup H: Pediatr Neurol, 2013;49(4):255-265

Transition: from pediatrics towards the unknown

(unknowing - ignorant)

Kidney transplantation in pediatrics

- Tx: treatment of choice for RRT in children
- Growing number of RTX children
- Growing number of adolescents in transition
- Specific needs to deal with
  - Somatic
    - Specific diagnoses and care, growth, cognitive functions
  - Psychologic
  - Social

- Old structures and solutions, financial issues, pressures
- Increasing number of therapeutic failures during transition

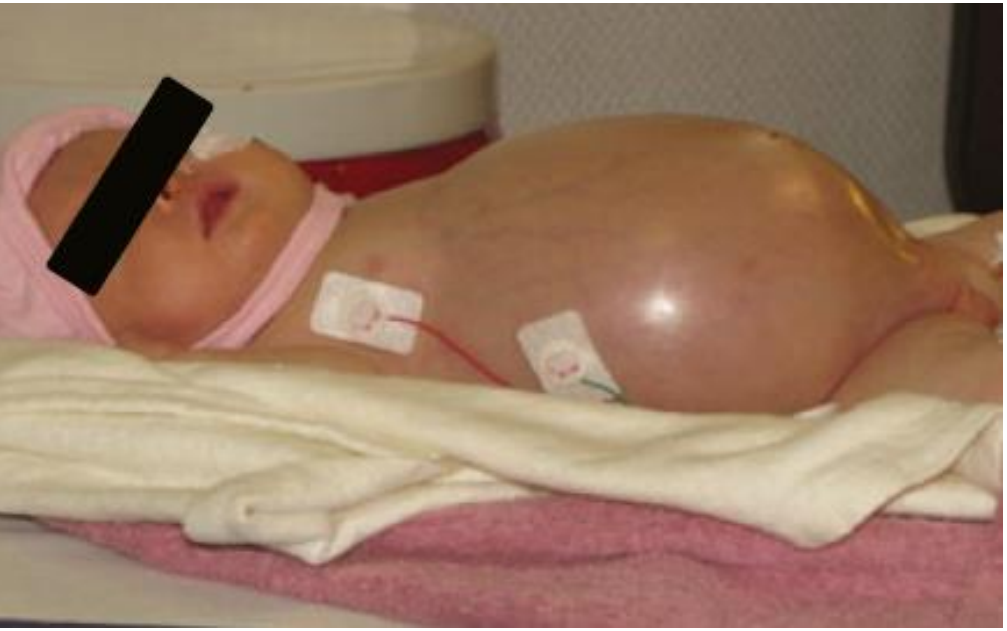
Fotó:Dr Grózli Csaba

Leading causes of ESRD

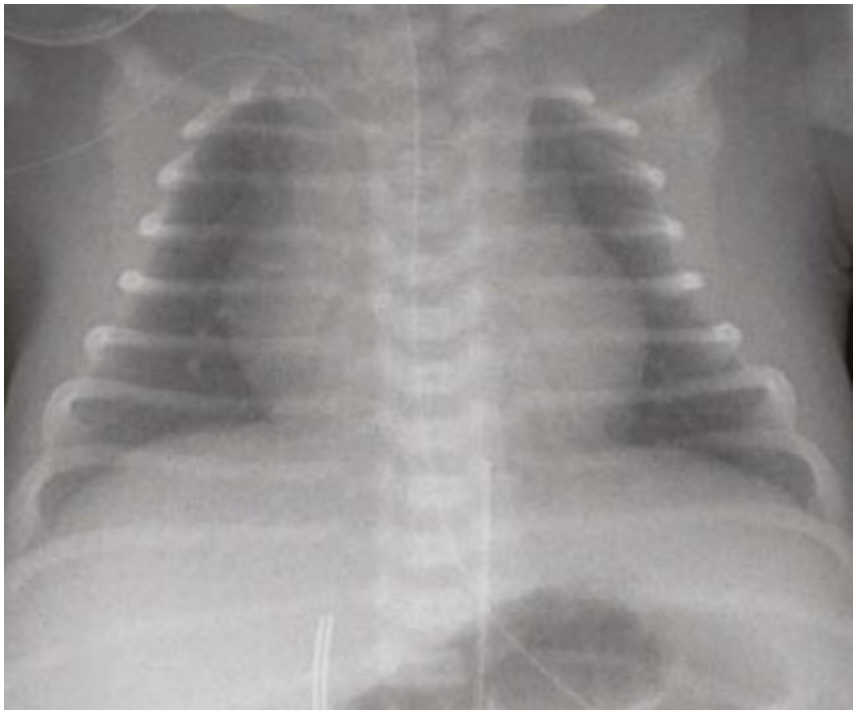
- Adults
  - Hypertension, diabetes
- Children
  - Malformations+/-infections
  - Inherited diseases

Specialized team (pediatric nephrologist, teacher, social worker, dietetician) needed to deal with specific problems

Ten-day-old preterm infant (34th week) with autosomal recessive polycystic kidney disease

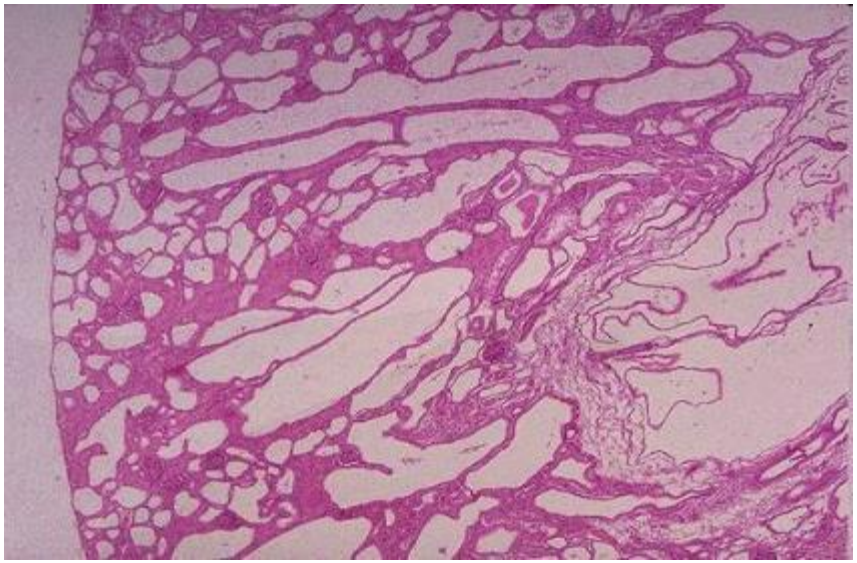


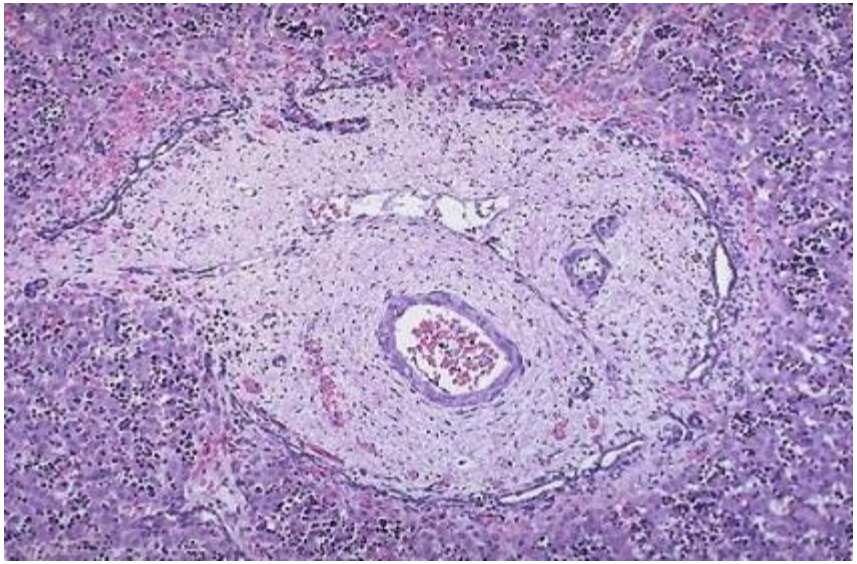
Pulmonary hypoplasia in ARPKD



Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

ARPKD





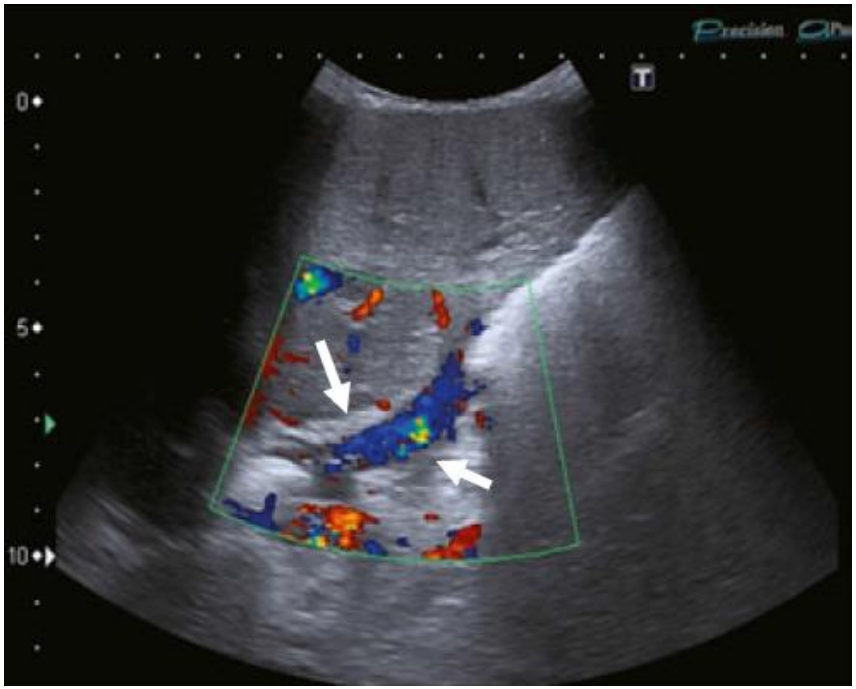
the kidney parenchyma is replaced by cysts

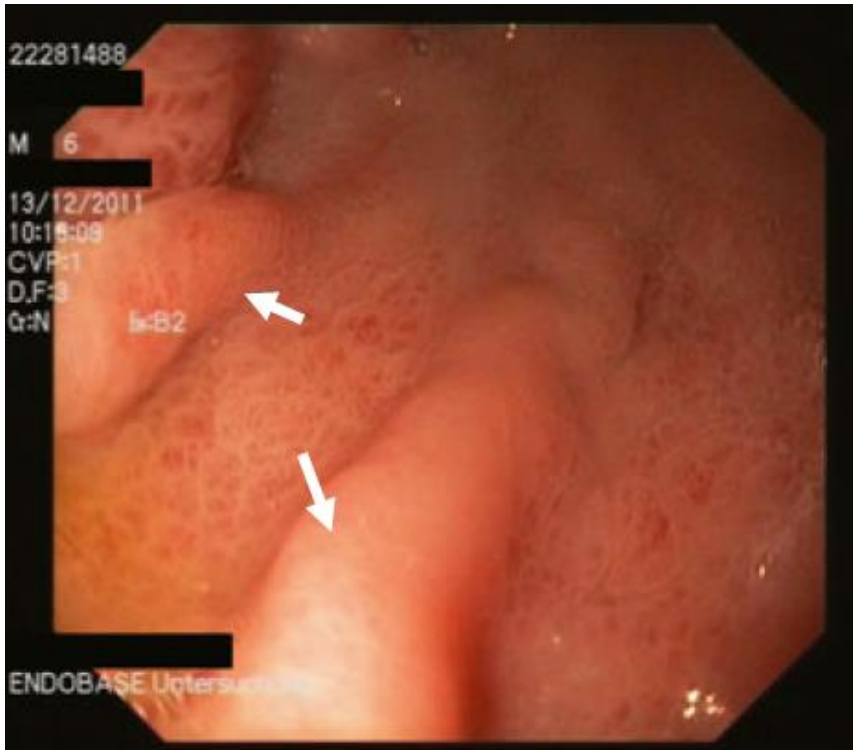
ARPKD: congenital liver fibrosis

The defective fibrocystin (see later) is present in the kidney, the liver and the pancreas as well

Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

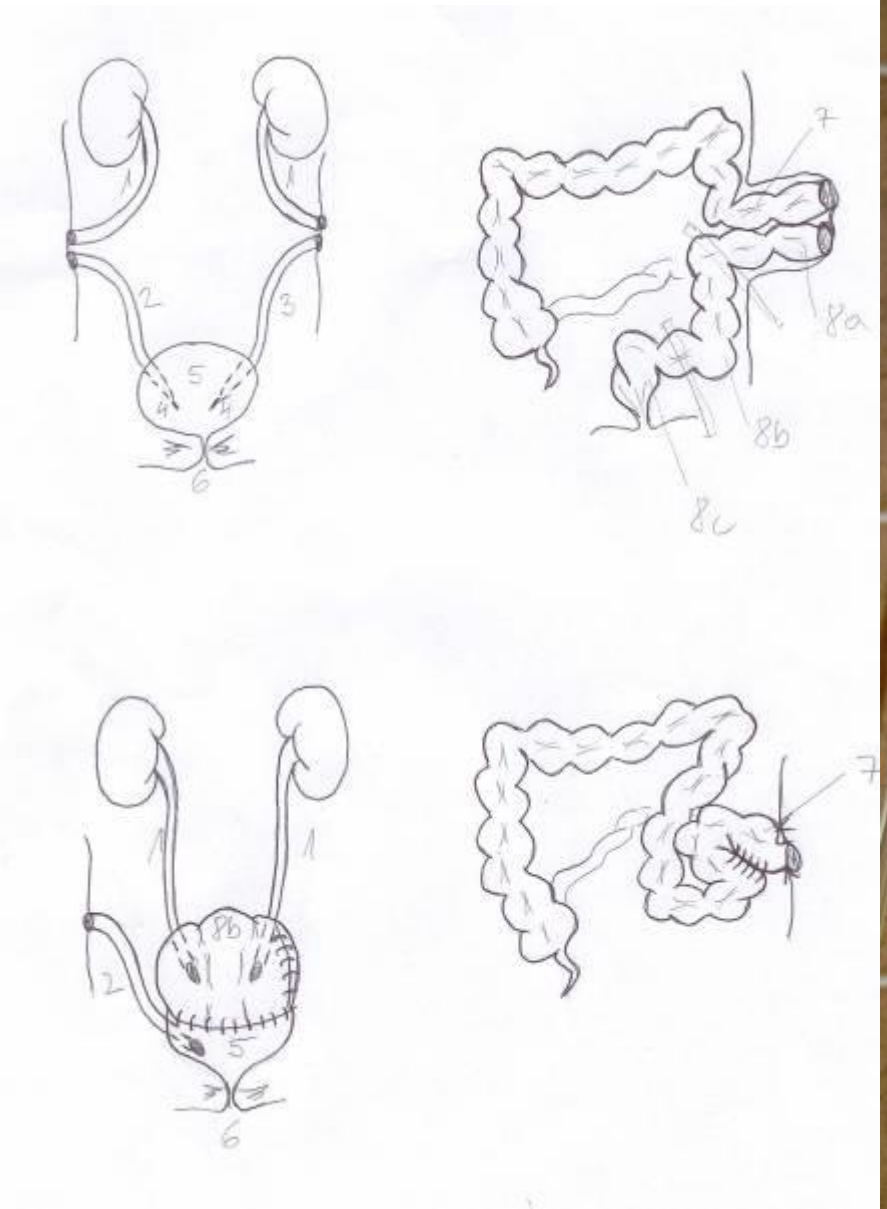
Color Doppler ultrasound and endoscopy of a 8-year-old boy with ARPKD and esophageal and gastric varices

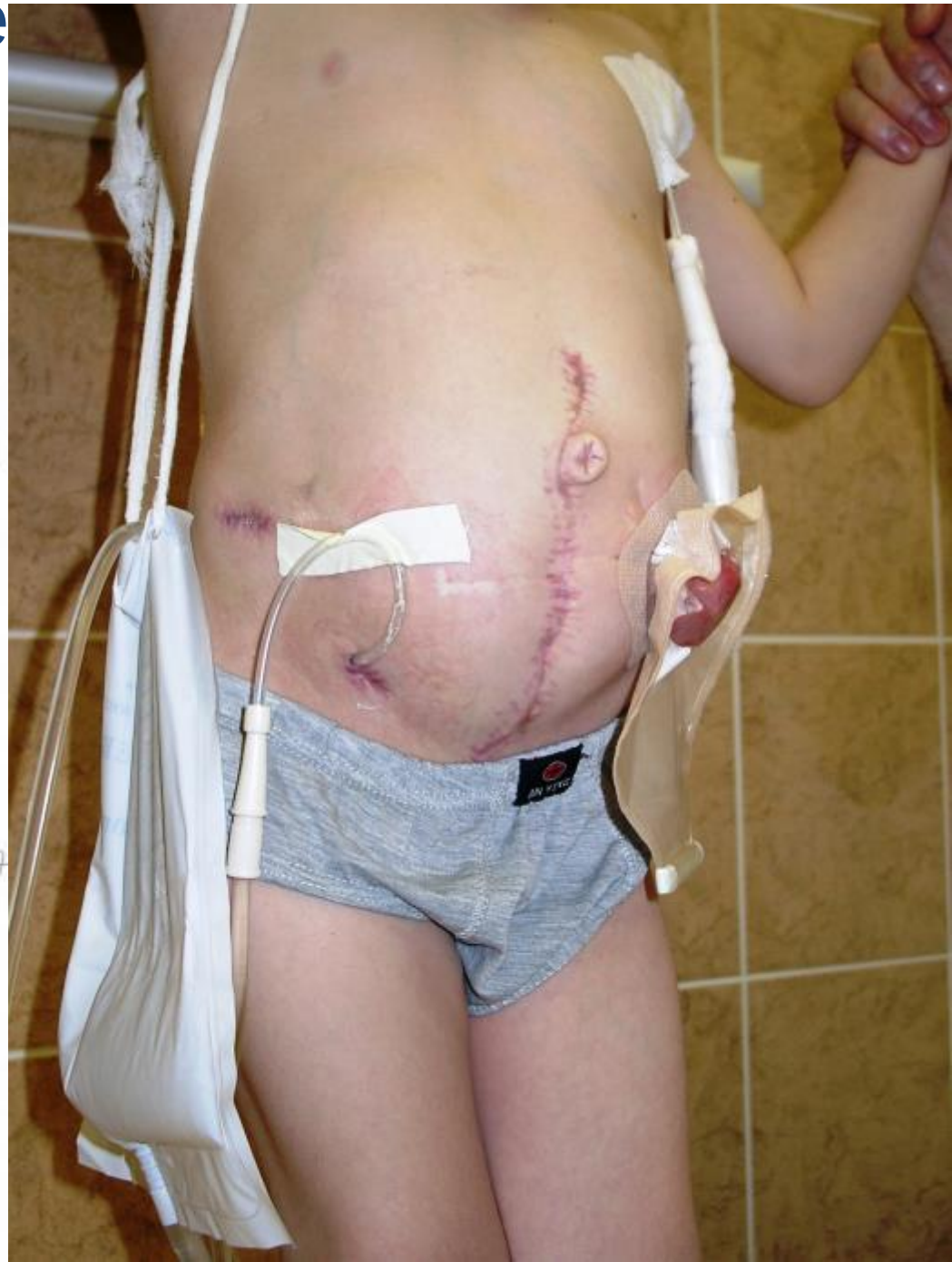




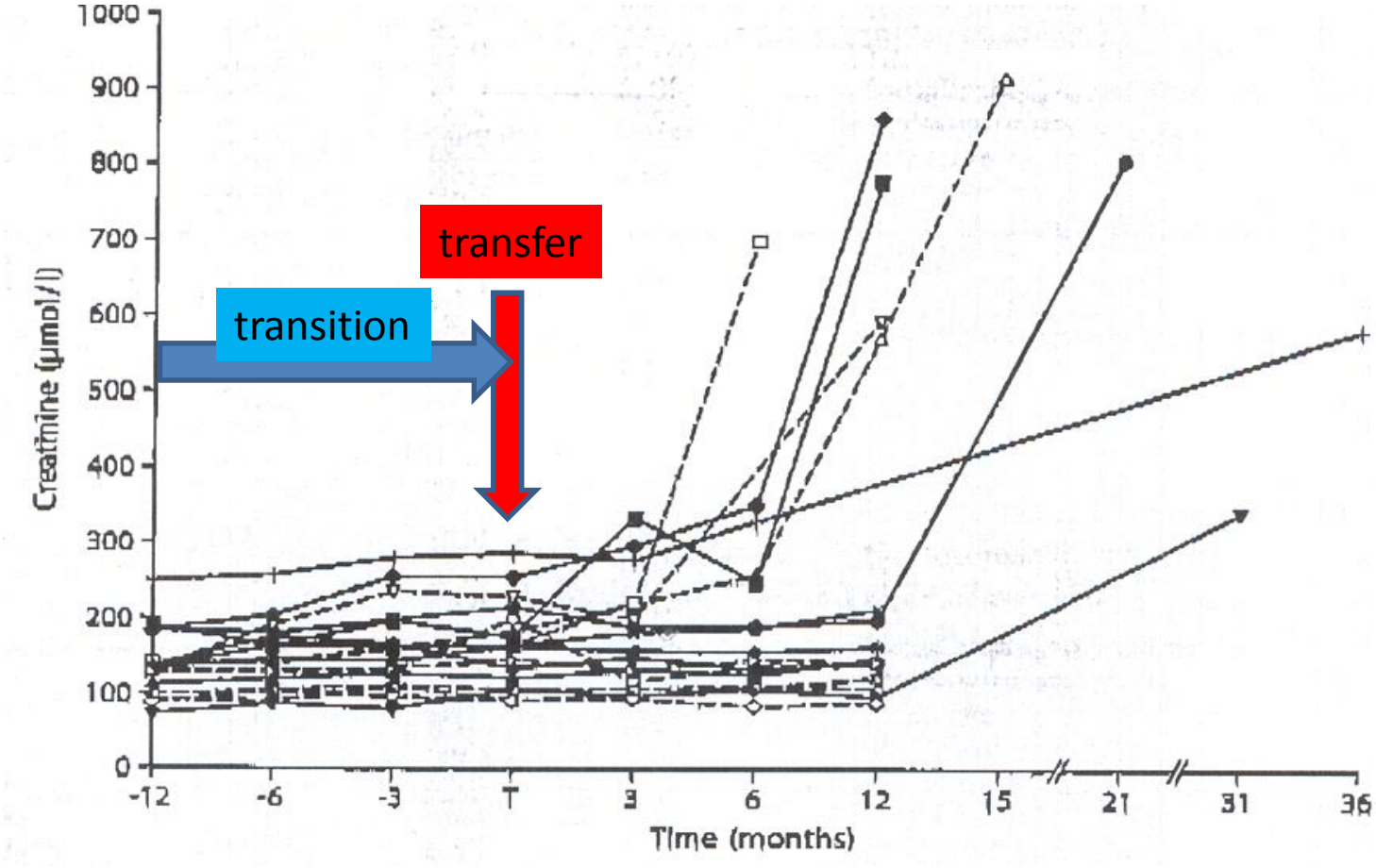
Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

(Re)construction of the bladder and Tx





The problem



35% unexpected graft loss
Watson AR et al (2000) Pediatr Nephrol 14:469-472

From transition to transfer

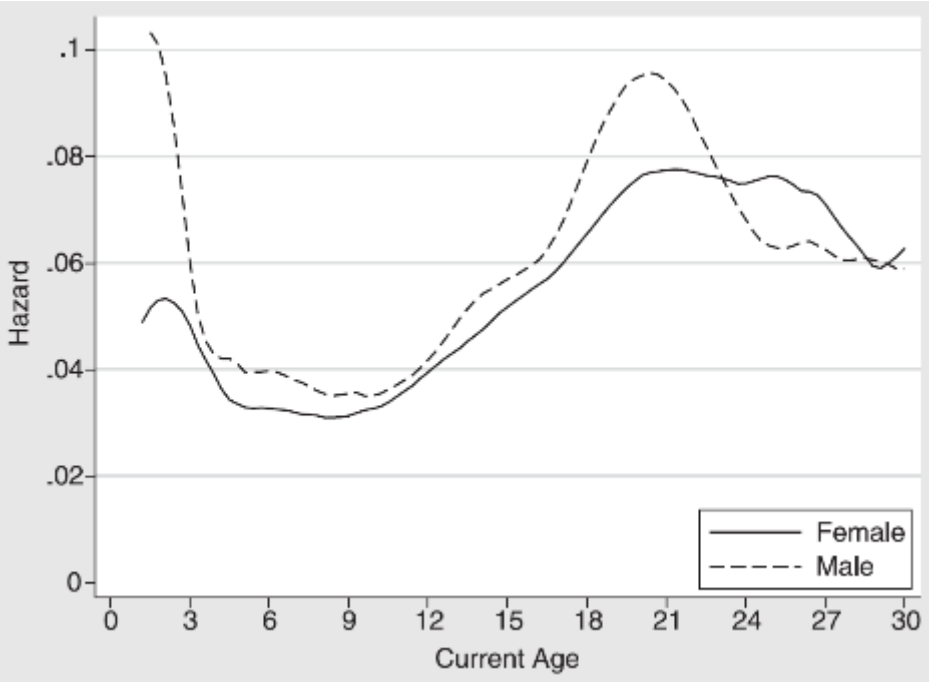
- Definitions
  - Transition
    - purposeful, planned efforts to prepare the pediatric patient to move from
      - caregiver-directed care to
      - disease selfmanagement in the adult unit
  - Transfer
    - takes place at the end of a transition process
    - concerted effort to accept responsibility for his/her disease management
- Transfer should occur only after
  - the adolescent/young adult has been prepared
  - patient care information has been delivered to the receiving adult service

Watson AR: Pediatr Nephrol (2011) 26:1753–1757

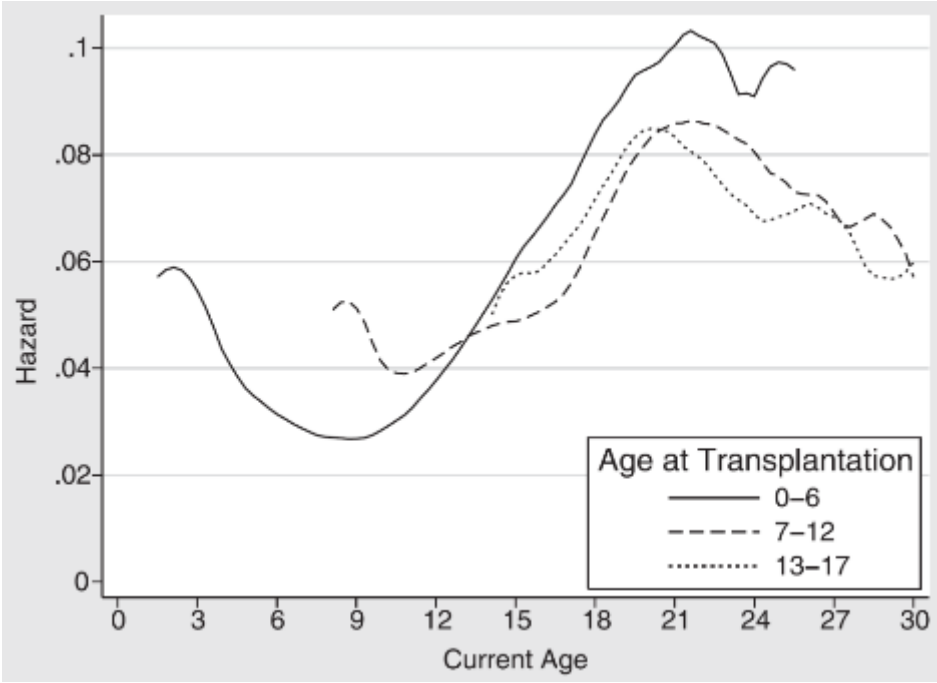
Age at Graft Loss after Pediatric Kidney Transplantation:

Exploring the High-Risk Age Window

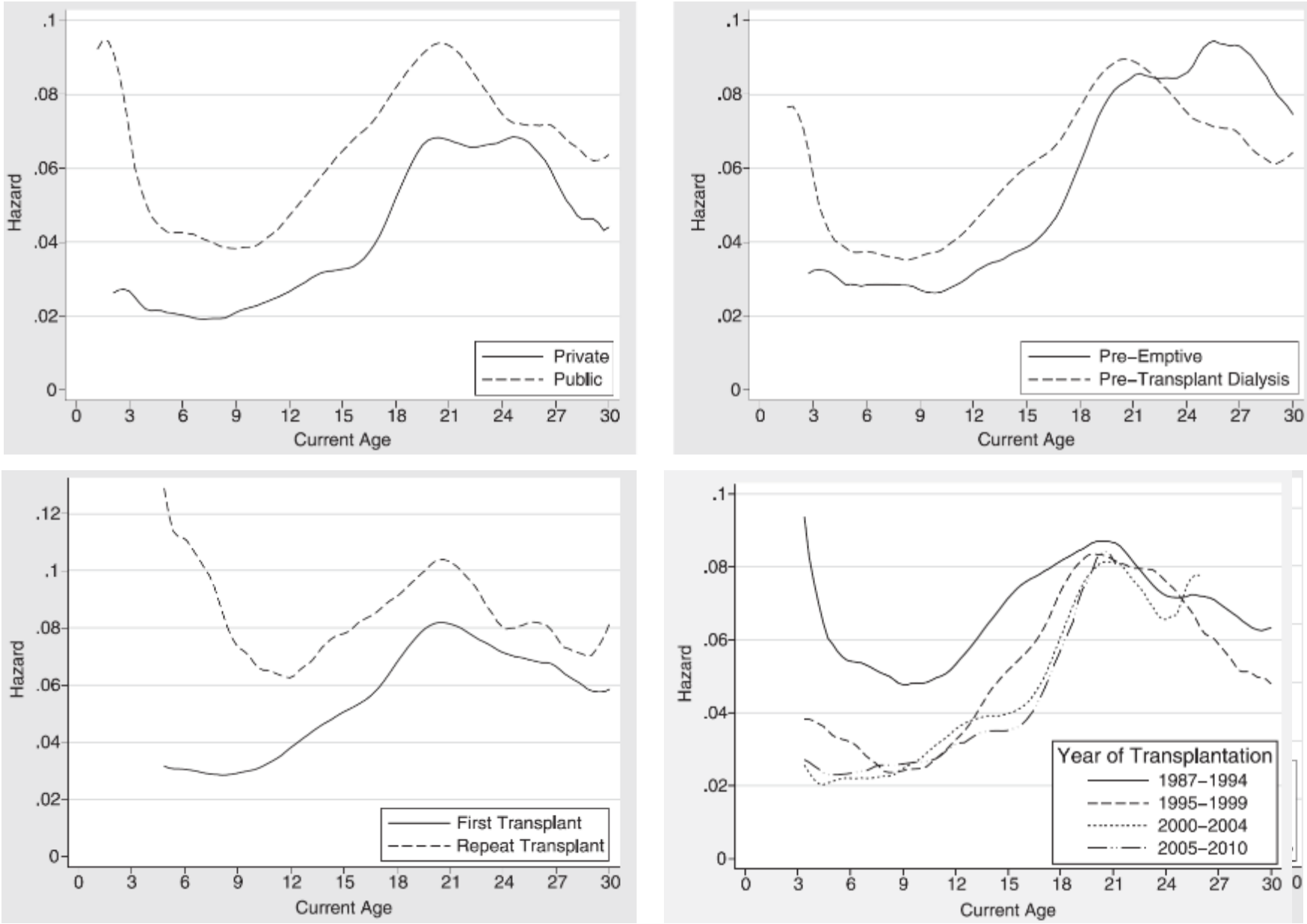
GENDER



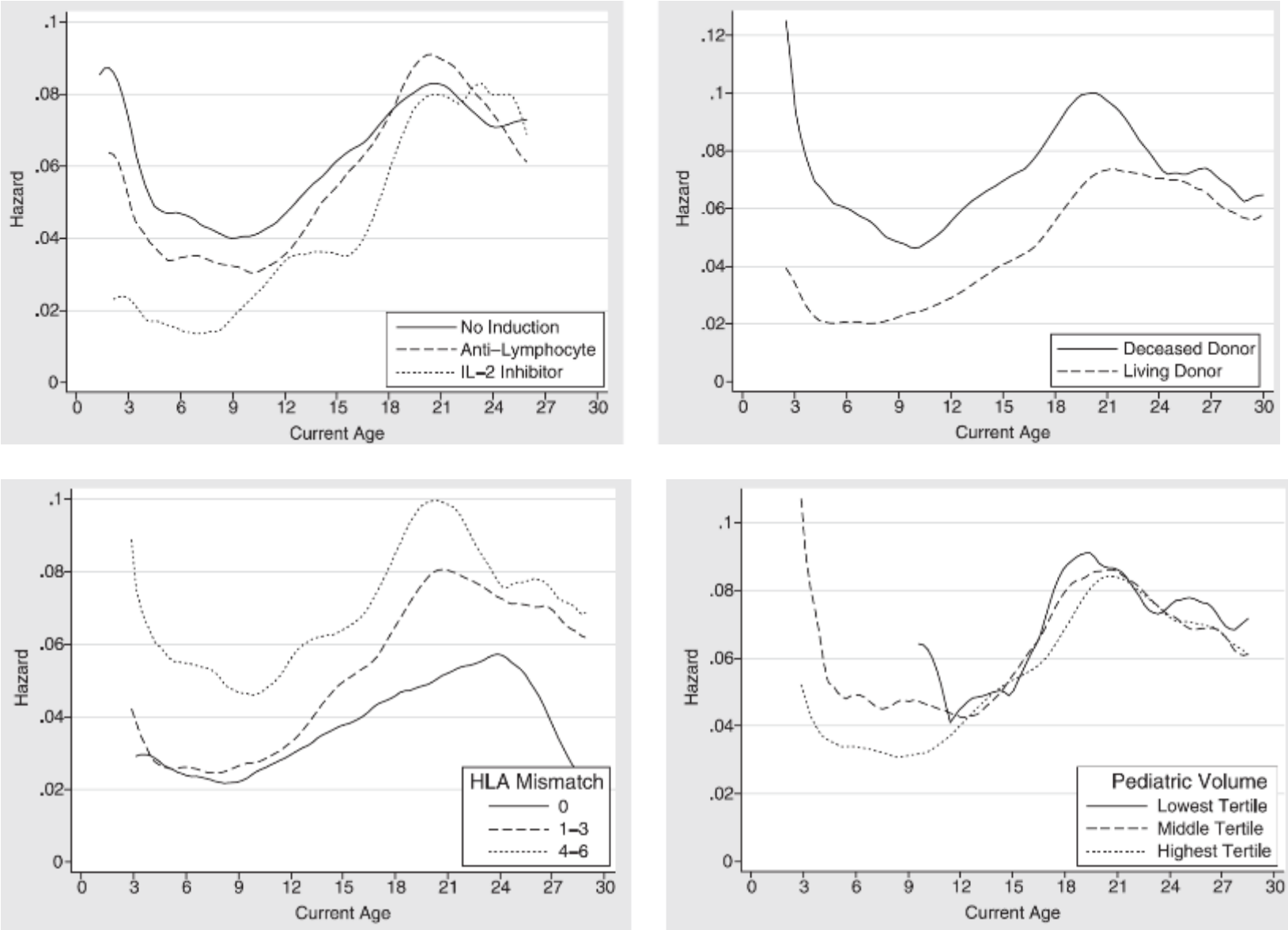
Age at TX



Van Arendonk KJ et al. Clin J Am Soc Nephrol 2013. doi: 10.2215/CJN.10311012



Van Arendonk KJ et al. Clin J Am Soc Nephrol 2013. doi: 10.2215/CJN.10311012



Van Arendonk KJ et al. Clin J Am Soc Nephrol 2013. doi: 10.2215/CJN.10311012

Conditions of succesful transfer

- transition plan individualized for each patient
- be agreed upon jointly by the
  - patient and
  - family/carers
  - pediatric and adult renal care teams
- completion of physical growth
  - educational, social and psychological attainment
- take place during a period without crises, especially if there is unstable social support
- consideration of financial factors, no financial pressures

Watson AR: Pediatr Nephrol (2011) 26:1753–1757

Example of competencies expected of a young adult transferring to an adult renal unit

- I understand my condition and can describe it to others
- I know my medications and what they are for
- I can make decisions for myself about my treatment
- I know what the adult clinic arrangements are and who will be reviewing me in clinic
- I know how to make my appointments
- I can make my own transport arrangements to get to the hospital for appointments
- I know who to call in a medical emergency
- I am able to talk about my worries concerning blood tests and other treatments
- I know the dietary advice that I have to follow and the importance of activity
- I have appropriate knowledge about sexual health matters
- I have discussed alcohol, smoking and drug issues

Watson AR: Pediatr Nephrol (2011) 26:1753–1757

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Transition structures and timing of transfer from paediatric to adult-based care after kidney transplantation in Germany: a qualitative study

Jenny Prüfe,[1] Marie-Luise Dierks,[2] Dirk Bethe,[3] Martina Oldhafer,[4] Silvia Müther,[5] Julia Thumfart,[6] Markus Feldkötter,[7] Anja Büscher,[8] Katja Sauerstein,[9] Matthias Hansen,[10] Martin Pohl,[11] Jens Drube,[1] Florian Thiel,[12] Susanne Rieger,[13] Ulrike John,[14] Christina Taylan,[15] Katalin Dittrich,[16] Sabine Hollenbach,[17] Günter Klaus,[18] Henry Fehrenbach,[19] Birgitta Kranz,[20] Carmen Montoya,[21] Bärbel Lange-Sperandio,[22] Bettina Ruckenbrod,[23] Heiko Billing,[24] Hagen Staude,[25] Reinhard Brunkhorst,[26] Krisztina Rusai,[27] Lars Pape,[1] Martin Kreuzer[1]

IPNA statement and its implementation in Germany

1. Transition to transfer	Aimed for by	Fully applied by
Delivery of necessary patient care information to the receiving adult service	21/21	21/21
2. Transfer from paediatric to adult nephrology should…		
be individualised for each patient after s/he has completed a transition plan depending on completion of physical growth and educational, social and psychological attainment	21/21	1/21
be agreed on jointly by the patient and his/her family/carers in conjunction with the paediatric and adult renal care teams	21/21	5/21
take place during a period without crises, especially if there is unstable social support	21/21	21/21
take place after completing school education	21/21	17/21
take into account treatment plans by other subspecialties, with particular reference to urological supervision	No data	No data
take place with due consideration of financial factors and not be done abruptly without adequate preparation as a result of financial pressures	21/21	21/21
introduction to the concept of transition in early adolescence (12–14 years)	21/21	0/21
information about transition in a gradual manner appropriate to his/her developmental stage and intellectual ability	21/21	21/21 Unstructured process

IPNA statement and its implementation in Germany

3. Transition or transfer clinic	Aimed for by	fully applied by
with both adult and paediatric nephrologist in attendance	21/21	0/21
with specialist nurses for adult patients who liaise with specialist nurses from the paediatric unit can ensure continuity of care	no data	0/21
providing a comprehensive written and verbal summary of all the multidisciplinary aspects of the young person's care including medical, nursing, dietary, social and educational information	21/21	0/21 (summary available but not as part of transition clinic)
offering a transition pathway to assert their autonomy and help provide the relevant information about themselves	21/21	0/21 Not standardised

IPNA, International Pediatric Nephrology Association.


Fotó:Dr Grózli Csaba