Living with ARPKD

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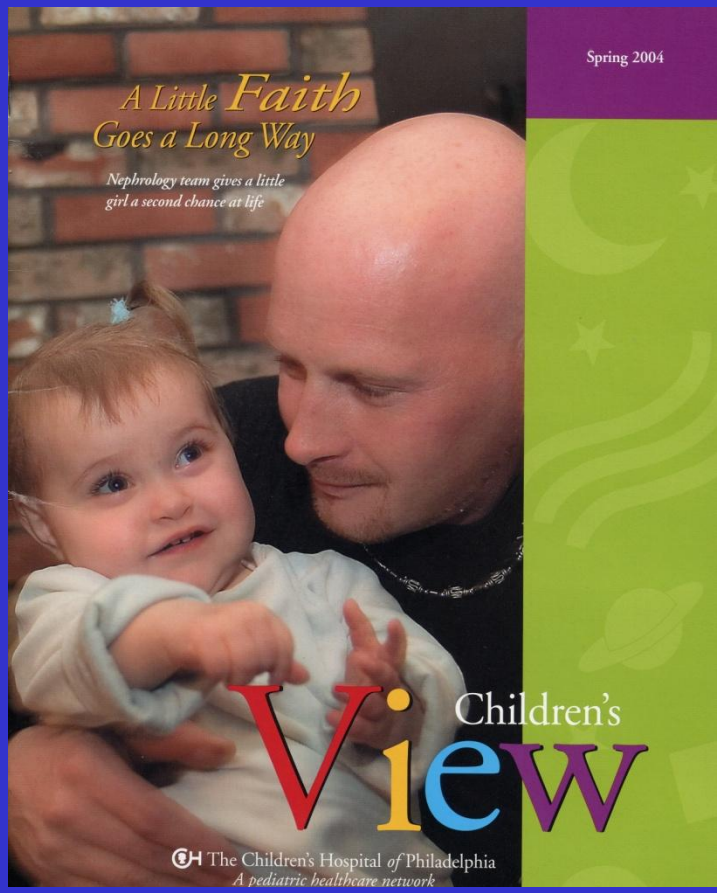
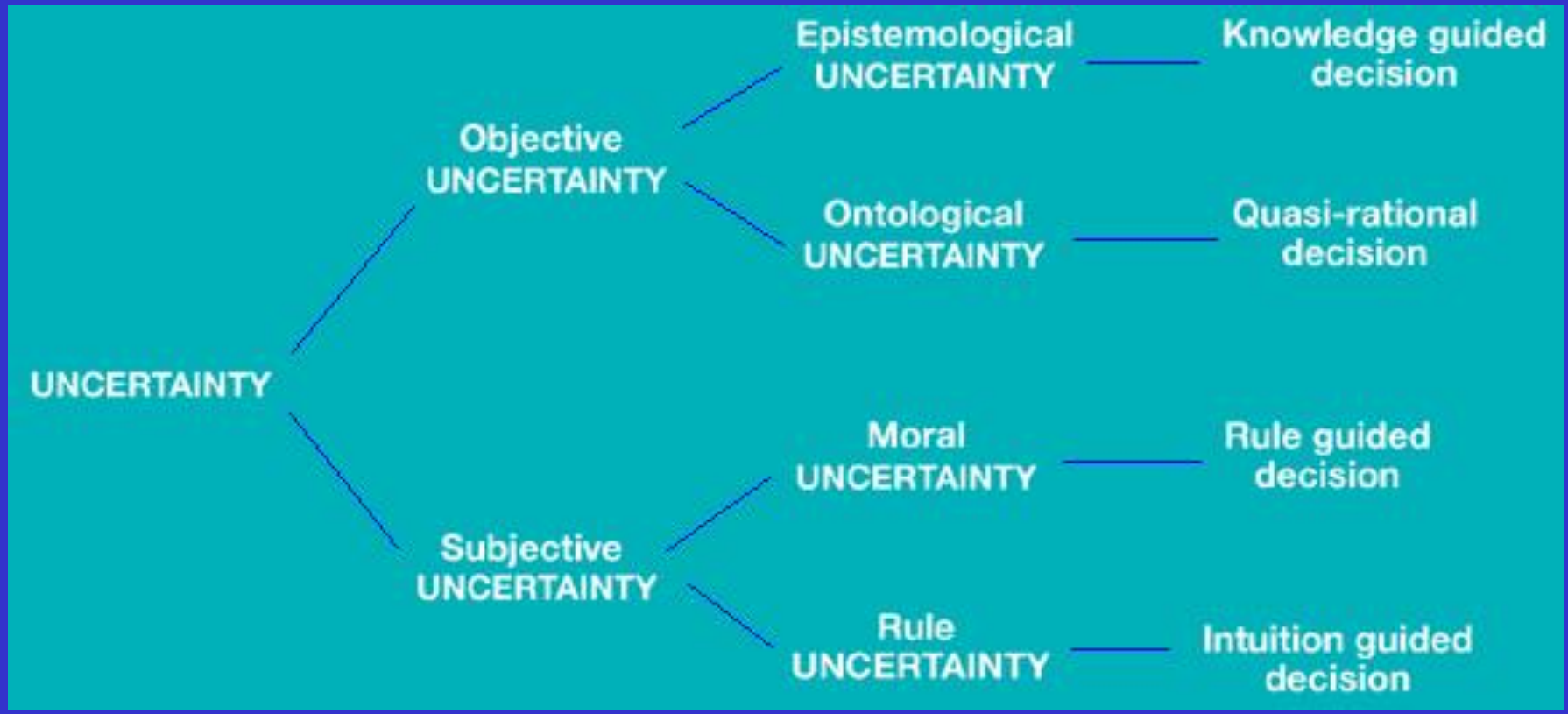


Living with ARPKD

Living with *Uncertainty*



Staff of The Transvaal Memorial Hospital for Children Dec 1969

Rode et al

The rise and fall of children's hospitals in South Africa.

South African Med J. Sep 2006

- **Children usually separated from their families - sometimes for weeks on end.**
- **Order was the keyword – mothers only allowed to breast-feed.**
- **Dying children left in care of men of the cloth.**
- **This unhappy state of affairs prevailed for many years.**
- **These concerns culminated in the Platt Report 1959 - detailed recommendations about non-medical aspects of care of children in hospital.**

- **The most important recommendations were:**

  unrestricted visiting to all children

  mothers should remain with their children

  training of medical and nursing students should emphasize the emotional and social needs of children and their families.

- **Few hospitals accepted these important recommendations.**

- **Established patterns of care did not change.**

- **Reasons for not implementing the recommendations were plentiful:**
- **Children apparently *rapidly adapted to hospitalization***
- **Distress of children in hospital was accepted as inevitable**
- ***Children's memories considered short* – hospitalization seen to have no lasting emotional or psycho-social ill effect on children**
- ***Fear of cross-infection***
- **Mothers often considered 'difficult' and disturbed routine**
- ***Lack of space***
- **Most importantly, *mothers had not asked for changes ….***

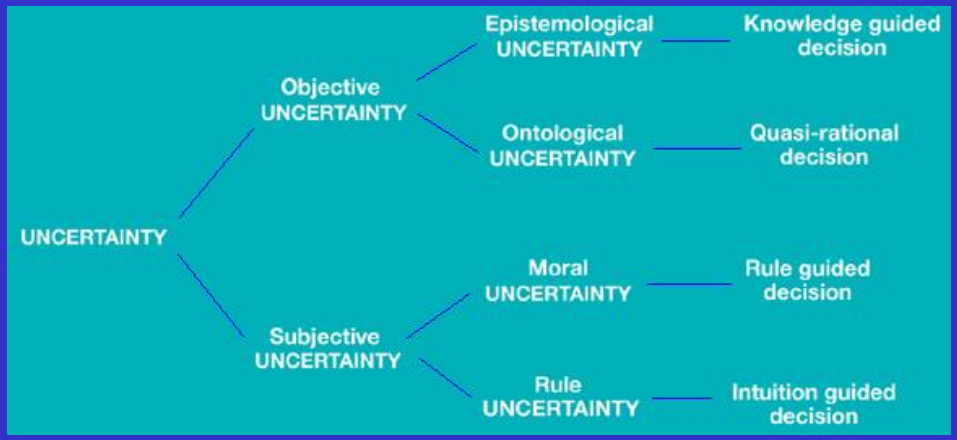
Thank You Colleen Zak for being a pro-active mother -

and

For all YOU have done to help children, families and professionals!

Who has to *live* with ARPKD?

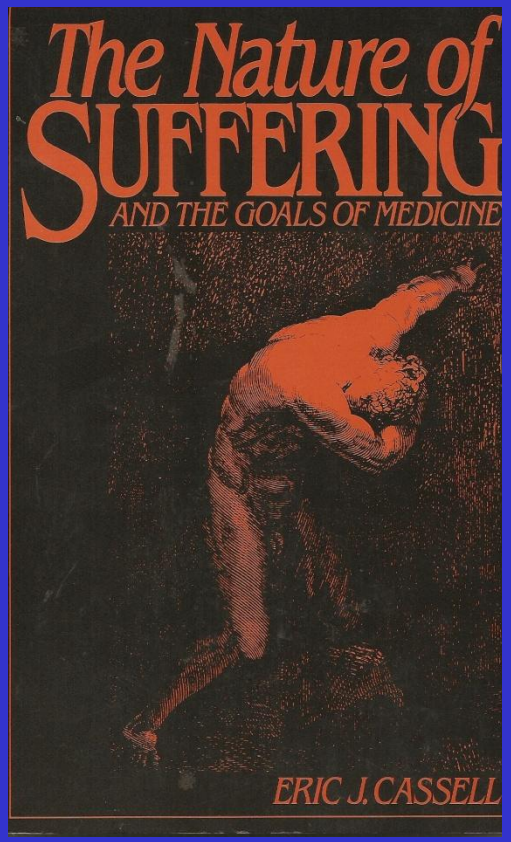
- The Patient
- The Family
- The Physician



Mike Grossman

The Patient

- *there can be no diagnosis, search for the cause of the person's disease, prognostication, or treatment* ***without consideration of the sick person.***



ARPKD is a Chronic *Disease*

- **What is a Chronic Disease?**

- **A DISEASE is a specific entity characterized by disturbances in the structure or function of any part, organ or system of the body**
- **Diseases are defined by Physicians or Scientists**

What is a Chronic *Illness?*

- **Chronic Disease and Chronic Illness are distinct from each other**

- **Illnesses afflict whole persons.**
- **Illnesses are the set of disordered functions, body sensations, and feelings by which persons know themselves to be unwell**
- **An illness is defined by the Patient**

Symptoms

- **Bed wetting**
- **Frequent urination**
- **Large urine volumes**
- **Protuberant abdomen**
- **Growth delay**
- **Anxiety - disease, sport, future**

- **Urine infections**
- **Taking medications**

The Illness of ONE PERSON -

- may be accompanied by disorder in that person's extended system – family, associates and even the community -

What are *Symptoms*?

- **No-one goes to a Physician complaining of high cholesterol levels [a Chronic Disease]**

- **She goes to a Physician complaining of pain or discomfort or anxiety or fear ….**

Strategies for Reducing Suffering

- **Live entirely in the present because suffering requires anticipating a feared future**
- **Develop total indifference to what is happening**
- **Denial permits a person not to suffer in circumstances where they otherwise may live in misery**
- **Flexibility – helping others**

The Patient's Family

Knowledge

http://www.arpkdchf.org/about_arpkd/index.htm

- Why do we need to know?
- What do we need to know?
- How do we find out?
- What do we do with the information?

Why do we need to know?

- **To understand** ***Subjective, emotional***
- **To adjust?** ***Antenatal ultraound***
- **To treat**
- **To take care**
- **To plan** ***Individually, genetic choice***

Knowledge and Experience

False Pessimism *"We were told over the phone that Quinn had an incurable kidney disease …"*

"We were told to be grateful for the time you will have with her …" [Julia Roberts]

http://www.arpkdchf.org/about_arpkd/index.htm

Knowledge and Experience

- **False Optimism** — ***Don't worry. Everything will be OK …***

- **Realistic Approach** — **tell the truth kindly in a balanced way**

  provide support

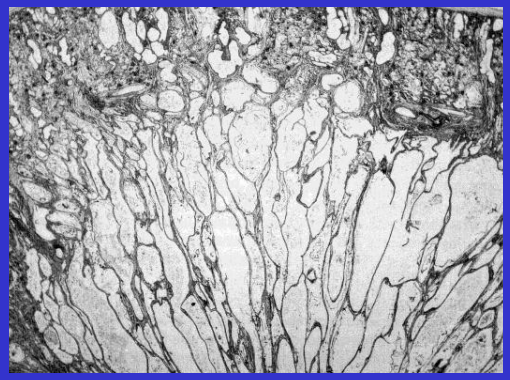
  listen, be available

What Is ARPKD?

http://www.arpkdchf.org/about_arpkd/index.htm

- **Developmental disorder of kidneys and liver caused by mutations in the PKHD1 gene on Chromosome 6.**

- **Abnormality in kidneys that results in markedly dilated tubules.**



What Is ARPKD?

- **Mortality in neonates/newborn can be very high.**
- **If a child makes it through the newborn period, chances of survival increase greatly.**
- **Most survivors develop chronic kidney failure before the age of 30 years.**

- ARPKD/CHF affects approximately 1 in 10,000 live births.

- **The impact of ARPKD/CHF is dramatic and far reaching.**

- **Unfortunately it most often affects children and newborns.**

http://www.arpkdchf.org/about_arpkd/index.htm

- Up to 50% of ARPKD newborns ***die at birth*** or shortly thereafter, usually from undeveloped lungs.
- ***Severe*** high blood pressure is frequent by one year.
- Neonates and infants are the groups ***most severely*** affected.
- After survival of the newborn period up to ***33% experience ESRD by age 15.***
- ***Kidney transplant recipients frequently develop clinical symptoms due to portal hypertension from ongoing CHF.***
- Liver disease is a ***significant feature*** of ARPKD.
- CHF may be ***complicated*** by cholangitis, Caroli Syndrome, portal hypertension, ***sudden GI bleeds***, hypersplenism.
- Liver complications can be ***life-threatening.***
- There is an ***increased risk of cholangiocarcinoma [2 cases]***.

Are there treatments or cures?

- ***Currently, there are no treatments or cures for ARPKD/CHF.***

- ***Medical care is dependent on other diseases, but if the newborn period is survived, there is potential for an excellent quality lifestyle with medical management***

http://www.arpkdchf.org/about_arpkd/index.htm

What are the top complications of ARPKD?

- The mortality in neonates/newborn is very high.
- Early newborn death occurs in 50% from pulmonary hypoplasia (underdeveloped lungs).
- If the newborn period is survived the chances of survival increase to good.
- Most survivors develop chronic kidney failure before
- 30 years.

http://www.arpkdchf.org/about_arpkd/index.htm

The Physician

The Social Worker

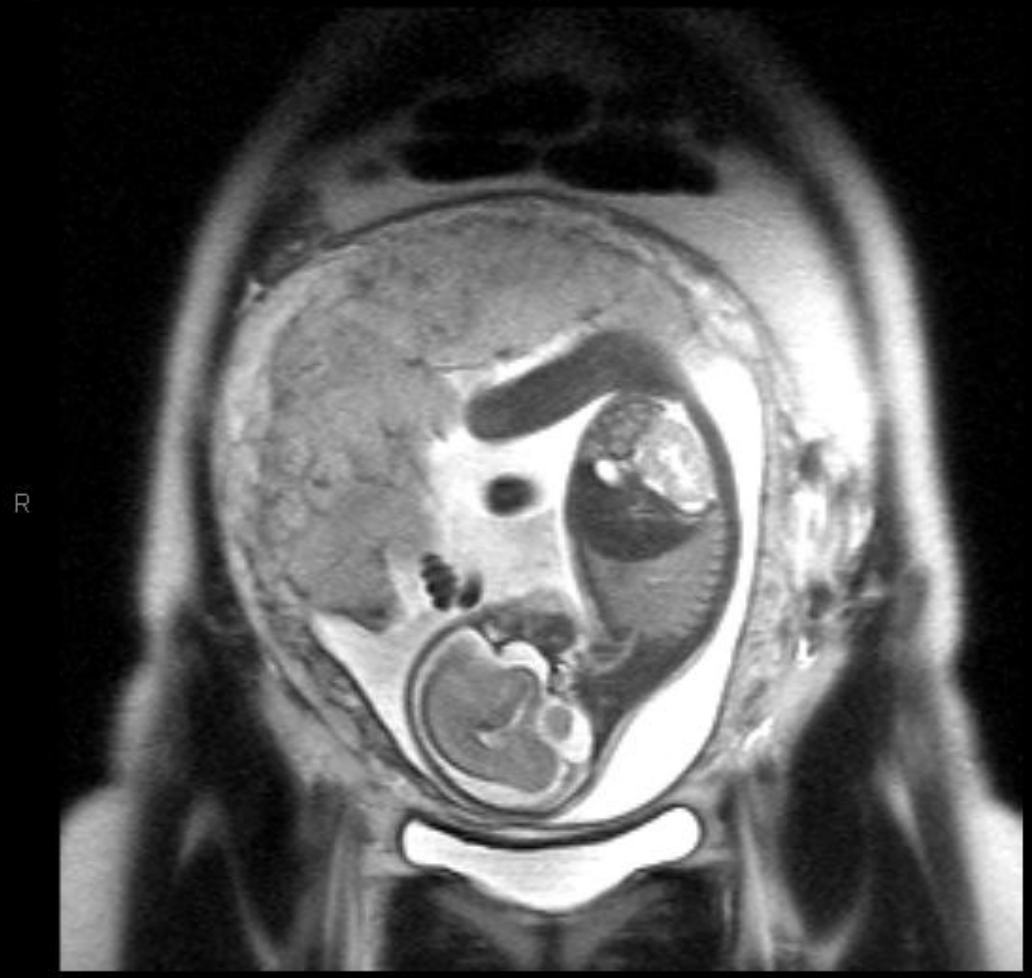
5/09/2001

Criteria for diagnosis of ARPKD

- Typical histopathological features
- Typical renal imaging findings
- Previously affected sibling with histopathological diagnosis
- [Mutation analysis]

ARPKD
Presentations

- *In Utero*
- Newborn period
- Infancy
- Childhood and adolescence
- Adult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Marked intra-familial variability in phenotype

Patient presented at birth (1979) with ARPCKD and respiratory distress - died at 18 hours.

An older sib presented at 16 years of age [1984].

No symptoms. BP 120/80 mm Hg; hepato-splenomegaly; serum creatinine 0.8 mg/dl.

Diagnosis of renal tubular ectasia and CHF made by ultrasonography, radiological studies, and liver biopsy.

Died in her late twenties.

Kaplan et al Am J Med Genet. 1988 29:639-47.

- **The severity of ARPKD is largely age-dependent.**

- **An affected neonate may present with the complications of oligohydramnios sequence with pulmonary hypoplasia, deformations and renal failure.**

- **May be completely normal at birth having being diagnosed in utero by ultrasonography or because of a previously affected sibling.**

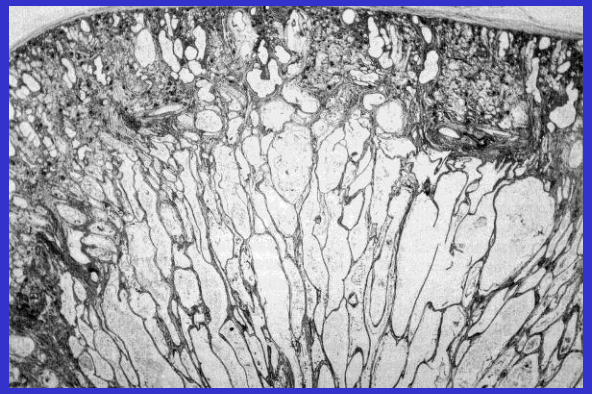
Non-lethal problems in neonates and infants.

- **Hypertension**
- **Hyponatremia** ***low blood sodium***

- **The occurrence of hyponatremia in association with hypertension led to the speculation that they are incapable of maximally diluting their urine.**

- **This is not surprising because the initial anatomical defect is in the collecting duct.**

- **Collecting duct damage results in a concentrating defect with thirst, increased urine and bed wetting.**



- **Progressive deterioration of renal function results in anemia, electrolyte disturbances, acidosis, calcium-phosphorus dyshomeostasis, osteodystrophy.**

- **25% of affected patients do not grow normally whether or not they have a reduced glomerular filtration rate.**

- **Treatment of ESRF requires renal transplantation with or without prior dialysis.**

- **Extrarenal complications are portal hypertension with hypersplenism and bleeding varices.**

- **Occasional cases of cholangiocarcinoma [2 reported]**

Hyponatremia in ARPKD

Kaplan et al Pediatr Nephrol 1989

Case	Plasma Na	Plasma Osm	Urine Osm
1	125	245	119
2	115	250	154
4 2 mth	128		130
5 3 mth	129		175
6 4 mth	118	255	229
7	120	252	223

Hyponatremia in ARPKD

Kaplan et al Pediatr Nephrol 1989

Table 4. Plasma renin activity and plasma aldosterone concentrations

Case	Age	Blood pressure (mmHg)	PRA (ngAl/l/h)	PA (pmol/l)	Plasma creatinine (µmol/l)
2	19 days	110/?	2018	900	49
3	19 days	110/?	285	578	60
	2 months	150/?	1952	–	–
4	2 months	90/60	219	743	46
6	4 months	130/70	943	3663	30
7	22 days	120/?	548	622	49
8	2 months	100/?	154	140	165
	4 months	160/?	88	620	380
9	10 months	120/75	829	–	–
10	11 months	150/80	855	200	36
11	6 years	150/90	679	111	90

Dilutional Hyponatremia in ARPKD

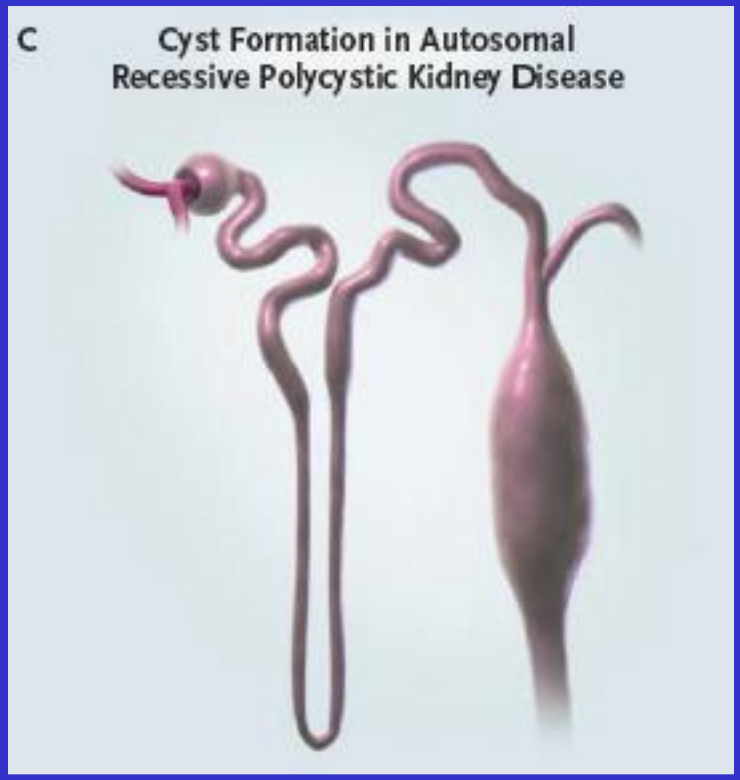
- Hyponatremia before onset of CRF
- No evidence of salt wasting [urine sodium 3 to 25 mmol/l]
- Inability to maximally dilute the urine
- Normal PRA and Aldosterone levels

Presentation in Neonate

- **Respiratory distress**
- **Anuric renal failure**

Presentation in Infancy

- Protuberant abdomen
- Palpable kidneys
- Hypertension
- Urinary tract infection
- Hepatosplenomegaly



N ENGL J MED 350;2 WWW.NEJM.ORG JANUARY 8, 2004

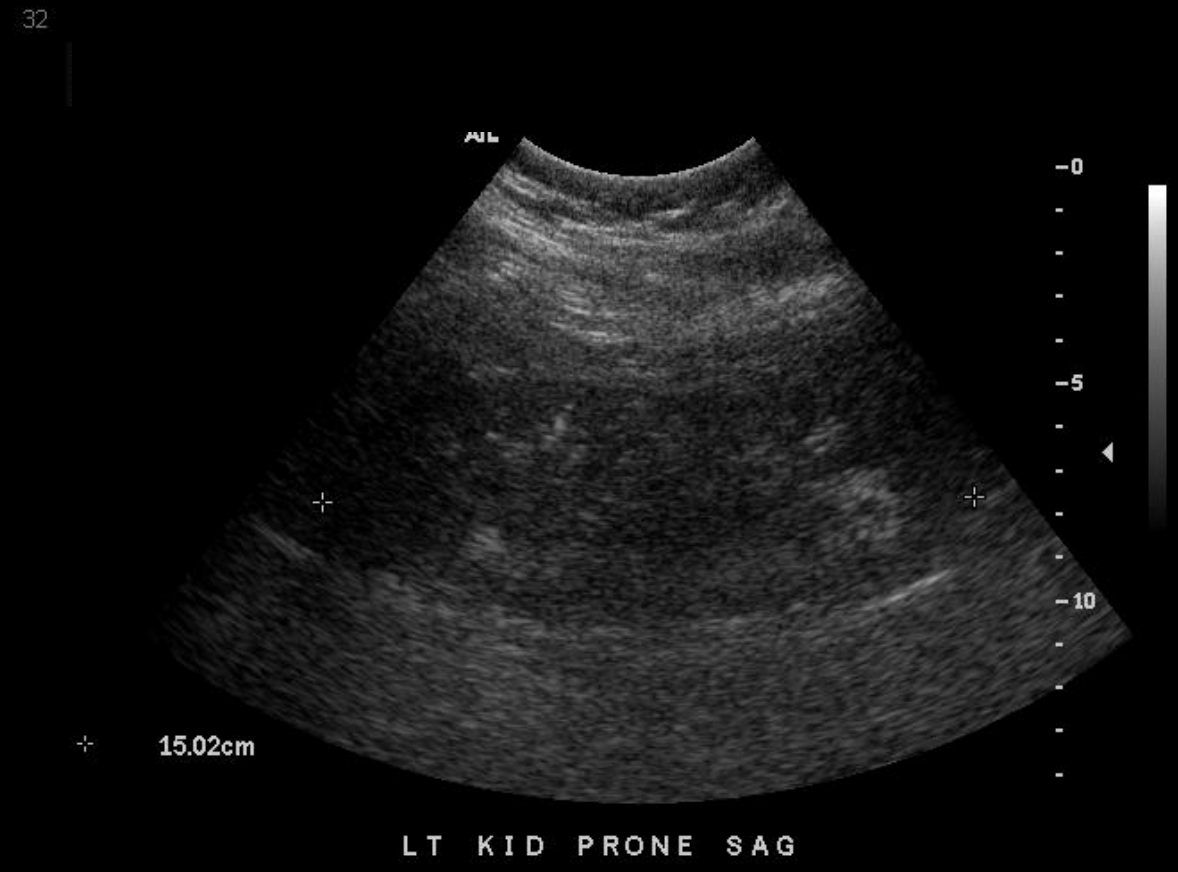
Presentation in Child or Adolescent

- As a result of diagnosis in a sibling
- Hypertension
- Urinary tract infections
- Unexplained fevers
- Hepatosplenomegaly
- Esophageal varices

Presentation in adult

- Chronic renal failure
- Portal hypertension
- Cholangitis
- [Cholangiocarcinoma]

ARPKD Age 21 years



Renal outcomes in ARPKD

1. Anuria from birth and death [respiratory]

2. Severe renal failure from birth, nephrectomy, dialysis and transplant

3. ESRF between 10 and 15 years

4. ESRF in adulthood

Long term outcomes of ARPKD

Kaplan et al 1985

- **Retrospective study**
- **Clinical features of 55 cases of ARPKD**
- **Outcomes of 87% cases known**
- **24 died**
- **45% presented under 1 month**
- **38% between 1 month and 1 year**
- **9 cases over 1 year.**

Life-table survival rates

- **Calculated from birth:**

  86% alive at 3 months, 79% at 1 year, 51% at 10 years, 46% at 15 years.

- **Calculations based on patients who survived to 1 year of age:**

  82% alive at 10 years, 79% at 15 years

Bergmann et al Kidney Int. 2005 67:829-48

- **Clinical course of 164 neonatal survivors - from zero to 35 years:**
- **1 year survival rate: 85%**
- **10 year survival rate: 82%**
- **Chronic renal failure first detected at a mean age of 4 years.**

Bergmann et al Kidney Int. 2005 67:829-48

- **Actuarial renal survival rates [end point defined as start of dialysis/renal transplantation or death from end-stage renal disease:**

  86% at 5 years

  71% at 10 years

  42% at 20 years.

Actuarial renal survival

- **From birth: 46% at 15 years. [Kaplan et al 1989]**
- **From birth: 42% at 20 years [Bergman et al. 2005]**

- **For patients surviving first month of life:**
  67% at 15 years [Roy et al 1993]

- **For patients surviving 1 year of age:**
  79% at 15 years [Kaplan et al 1989]

Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD).

Mayo Clinic 1961 to 2004

- Follow-up of 8.6 +/- 6.4 years.
- 55 cases had ARPKD
- 12 patients died
- 6 in neonatal period
- 86% of patients alive at 40 years
- Medicine (Baltimore). Jan 2006

CHOP - Outcomes

Advances in the treatment of ARPKD

1. Aggressive ventilator support for respiratory distress
2. ACE inhibitors for hypertension
3. Erythropoietin for Anemia
4. Growth hormone for Growth
5. Calcitriol for Bones
6. Nephrectomy for severe respiratory compromise
7. Prevention of cholangitis
8. Dialysis and transplant for ESRF

Pediatric CT research elevates public health concerns: low-dose radiation issues are highly politicized.

- The authors highlight an important policy document issued jointly by the National Cancer Institute and the Society for Pediatric Radiology—specifically:

  a small dose of radiation from CT represents "a public health concern."

- Several contentious issues and proposes policy initiatives that, if implemented, could result in significant reductions of future radiogenic cancers and chronic injuries.

- The authors call for discussions between professional radiology societies and public interest health organizations, thereby involving all stakeholders.

•Int J Health Serv. 2007

Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort.
Radiology. 2007 Oct

The data support a positive association between gadolinium-based contrast agent administration and development of nephrogenic systemic fibrosis in the established renal failure population.

Positive association between cumulative dose of gadolidinium and dosing events.

Recombinant human growth hormone therapy in autosomal recessive polycystic kidney disease.

Growth failure in ARPKD may be attributable to factors other than chronic renal insufficiency alone.

Use of rhGH therapy in ARPKD is safe, effective, and has the potential to improve the physical and psychological well-being of these children.

Lilova, **Kaplan**, **Meyers** Pediatr Nephrol. Jan 2003

Use of growth hormone in children.

Cost-benefit implications need to be considered in the next phases of evaluating the role of rhGH therapy.

rhGH has only received approval for the management of in the US.

As with the other wider growth indications, the lack of formal randomized, controlled trials hampers the full evaluation of efficacy, and a cautious approach should, therefore, be adopted for idiopathic short stature.

rhGH has a good safety record, although there are current concerns about the possible long-term increased risk of colonic and lymphatic malignancy

This will require monitoring through national cancer registries.

Nat Clin Pract Endocrinol Metab. 2006 May

The Concept of Renoprotection

- Treat hypertension
- Use ACE inhibitors
- Avoid excess fluid intake
- Protein intake?
- Salt intake?
- Avoid NSAID
- Do not smoke
- Treat high cholesterol
- Avoid contact sports
- Avoid nephrotoxic antibiotics

The effect of angiotensin-converting-enzyme inhibitors on progression of advanced polycystic kidney disease.

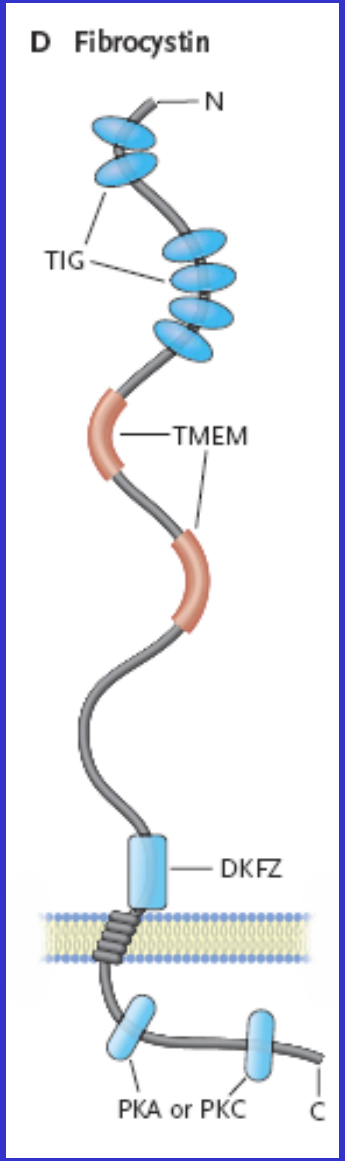
The effect of ACE inhibitors to slow kidney disease progression in PKD is inconclusive.

- Kidney Int. 2005 Jan

Fibrocystin

Fibrocystin/Polyductin Modulates Renal Tubular Formation by Regulating Polycystin-2 Expression and Function

Ingyu et al. *J Am Soc Nephrol* Jan, 2008



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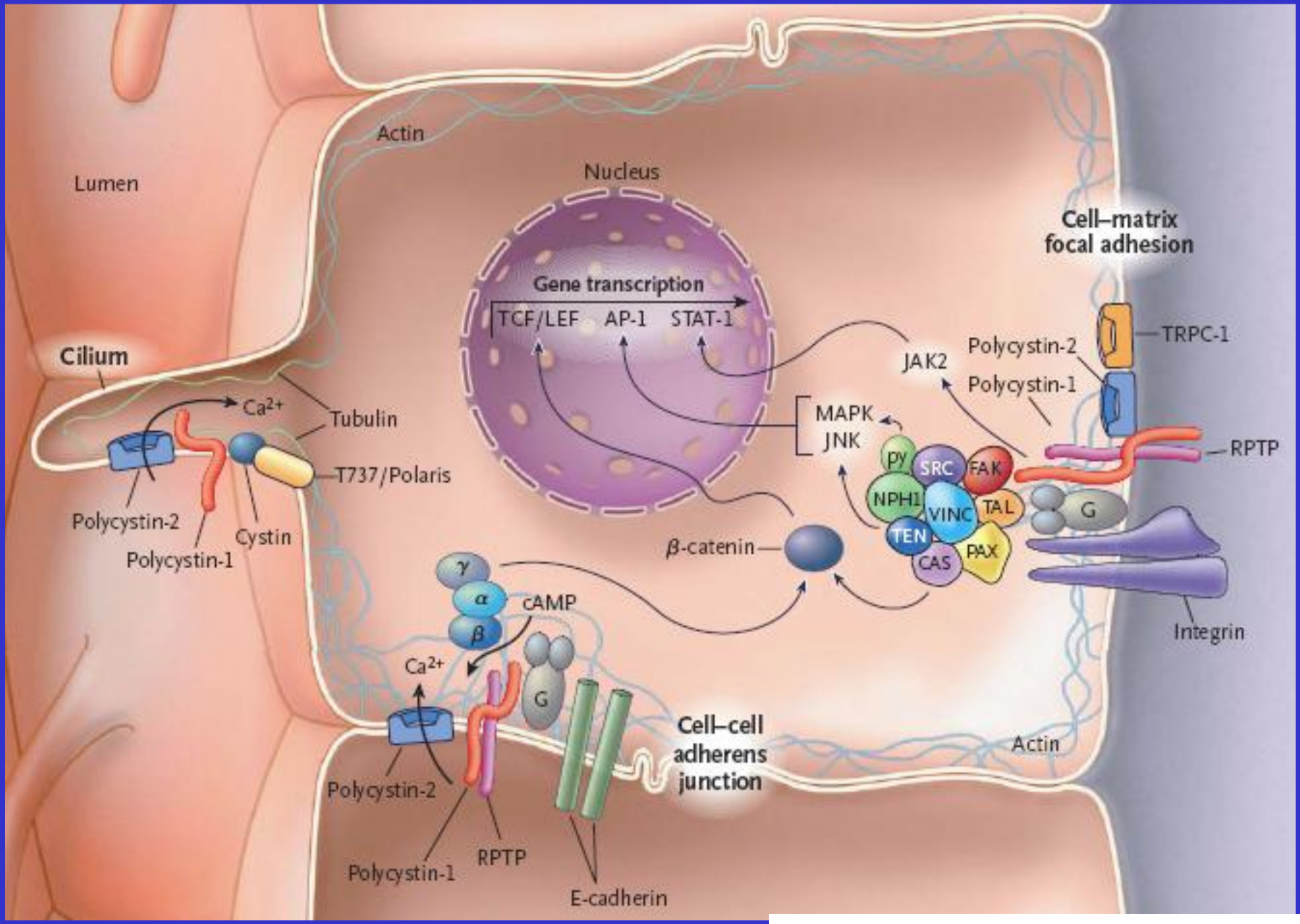
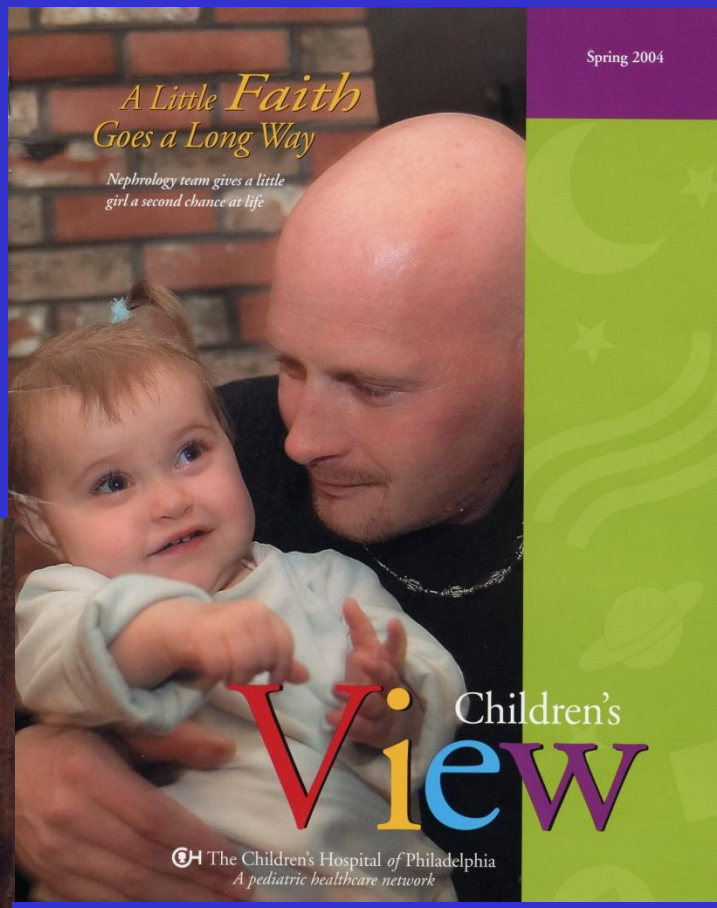

Lumen
Actin
Nucleus
Gene transcription
TCF/LEF
AP-1
STAT-1
Cell–matrix
focal adhesion
Cilium
Ca2+
Tubulin
T737/Polaris
Polycystin-2
Polycystin-1
Cystin
JAK2
Polycystin-2
Polycystin-1
TRPC-1
MAPK
JNK
RPTP
PY
SRC
FAK
NPH1
VINC
TAL
TEN
CAS
PAX
G
β-catenin
γ
α
β
cAMP
Ca2+
G
Integrin
Cell–cell
adherens
junction
Actin
Polycystin-2
Polycystin-1
RPTP
E-cadherin


Spring 2004
A Little Faith
Goes a Long Way
Nephrology team gives a little
girl a second chance at life
Children's
View
The Children's Hospital of Philadelphia
A pediatric healthcare network