ADULT POLYCYSTIC KIDNEY DISEASE

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SCHOOL OF MEDICINE

APCKD

- GENETICS
- SCREENING AND DIAGNOSIS
- MECHANISM OF CYST GROWTH
- RENAL MANIFESTATIONS
- EXTRARENAL MANIFESTATIONS
- COURSE AND TREATMENT
- FUTURE

APCKD

- **GENETICS**
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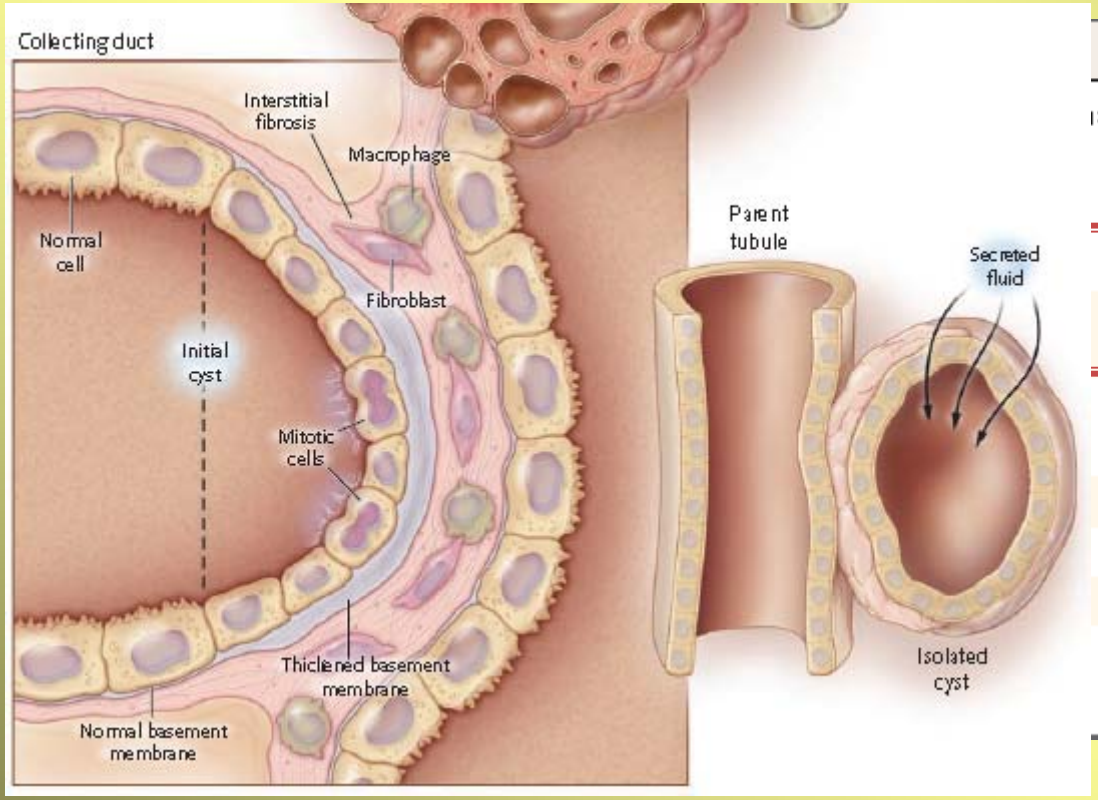
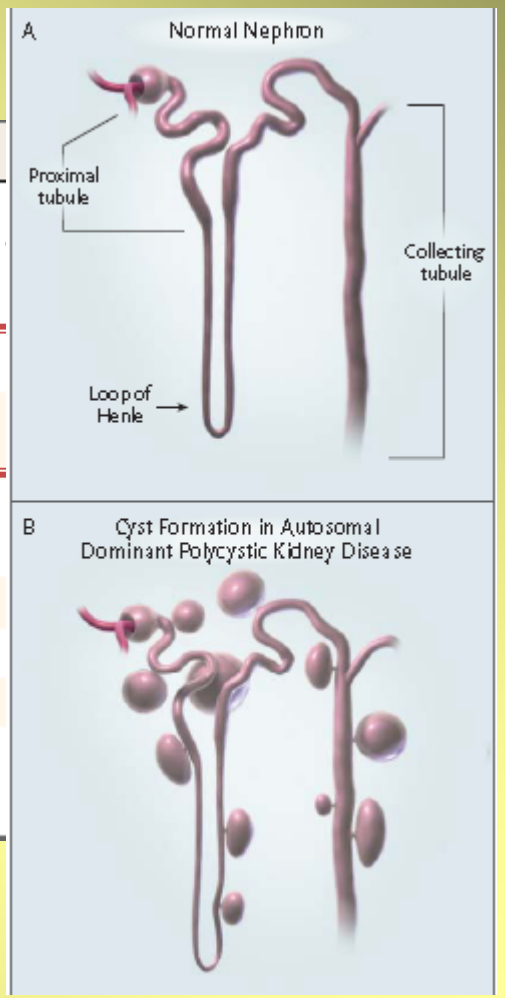
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (APCKD)

- INHERITANCE AS AUTOSOMAL DOMINANT TRAIT
  - AT LEAST 2 LOCI IDENTIFIED
    - 85% WITH CHROMSOME 16 (PKD1 LOCUS); MOST OTHERS WITH CHROMOSOME 4 (PKD2 LOCUS)
  - GENE PRODUCTS IDENTIFIED:
    - **POLYCYSTIN 1 - PKD1: 46 EXONS CODING FOR 4000 AA PROTEIN**
    - **POLYCYSTIN 2 - PKD2: 15 EXONS CODING FOR 1000 AA PROTEIN**
- 1 IN 400-1000 LIVE BIRTHS
- PHENOTYPIC EXPRESSION: KIDNEYS WITH EXTENSIVE CYST FORMATION AND OFTEN EXTRARENAL MANIFESTATIONS
  - 50% DETECTION RATE DURING LIFETIME
  - ESRD PREVELENCE 7-10%

Polycystic Kidney Disease





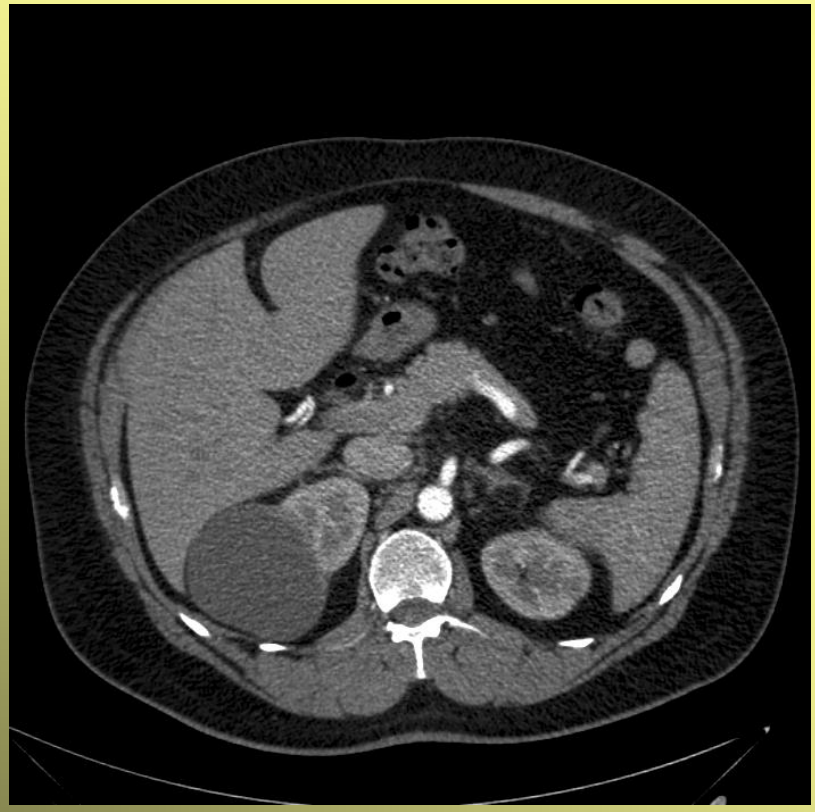
N ENGL J MED 359;14 www.NEJM.ORG OCTOBER 2, 2008

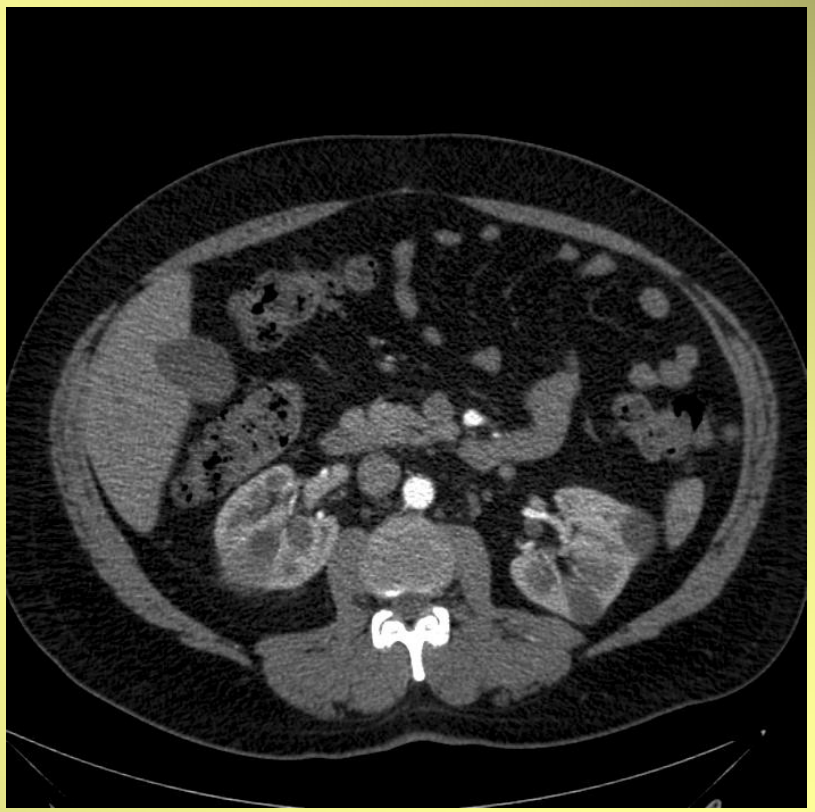
N ENGL J MED 350;2 WWW.NEJM.ORG JANUARY 8, 2004

SECOND HIT HYPOTHESIS

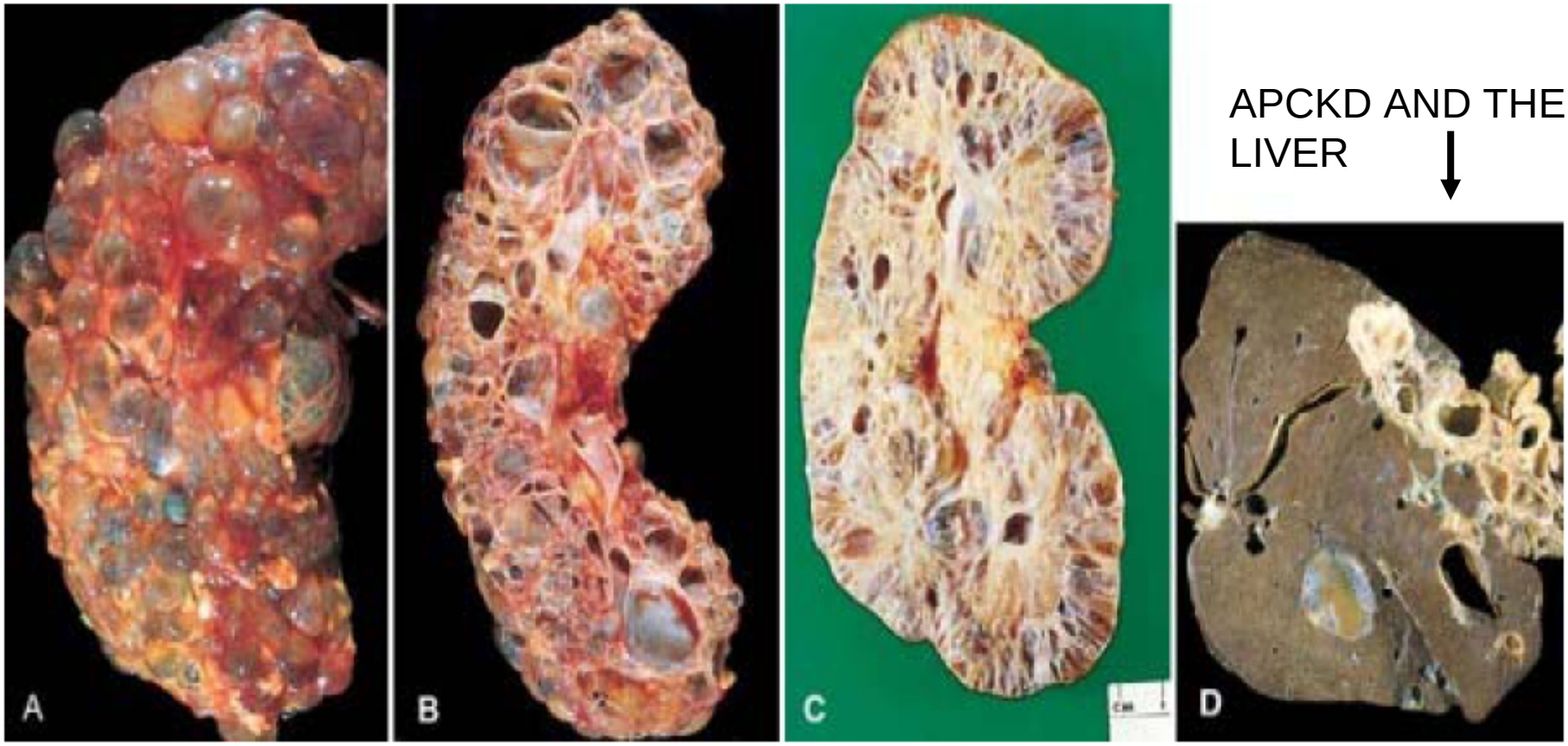
- ONLY SEVERAL HUNDRED TO A THOUSAND NEPHRONS HAVE TO DEVELOP CYSTS TO RESULT IN RENAL FAILURE
- CYSTIC DILATATION IS FOCAL
- CYSTS MAY FORM ONLY WHEN THERE IS LOSS OF THE NORMAL HAPLOTYPE ***IN ADDITION TO*** THE INHERITED ABNORMAL GENE

APCKD: COMPUTERIZED TOMOGRAPHY





CYCTIC KIDNEY DISEASE



APCKD AND THE LIVER

CHARACTERISTICS OF POLYCYTIN-1

- LOCATED IN RENAL TUBULAR EPITHEIAL CILIA AND PLASMA MEMBRANE
  - ALSO LOCATED IN HEPATIC AND PANCREATIC DUCTS
- LOCALIZED TO THE LATERAL CELL MEMBRANE – ALLOWING CELL-CELL AND CELL MATRIX INTERACTION AFFECTING GROWTH AND SURVIVAL OF CELLS
- IN MOUSE MODEL, EARLY PKD-1 INACTIVATION (WITHIN 13 POSTNATAL DAYS) RESULTS IN SEVERE CYST FORMATION
- PART OF THE STRUCTURE OF CILIA: SENSING FLOW IN TUBULAR LUMEN AND IN THE CENTROSOME

CHARACTERISTICS OF POLYCYSTIN-2

- MAY SERVE A ROLE IN CALCIUM SIGNALING
- FOUND IN PLASMA MEMBRANE, PRIMARY CILIUM AND ENDOPLASMIC RETICULUM (MAIN SITE)
- INTERACTS WITH POLYCYSTIN-1

INTERACTIONS BETWEEN THE POLYCYSTINS

- BOTH LOCALIZE TO CILIA
- BOTH ARE FOUND IN THE CELL MEMBRANE AND IN INTRACELLULAR LOCATIONS
- BOTH INTERACT WITH THE JAK-STAT SIGNALING PATHWAY (CYTOKINE MEDIATED)
- BOTH REGULATE G PROTEIN SIGNALING
- BOTH PROTEINS INTERACT AT THE CELL MEMBRANE
- BOTH PROTEINS CREATE A NON-SELECTIVE CALCIUM PERMEABLE CATION CHANNEL
- MECHANICAL STIMULI LEADS TO POLYCSTIN-2 MEDIATED TRANSLOCATION OF A POLYCYSTIN-1 FRAGMENT TO THE NUCLEI LEADING TO AK-1 TRANSCRIPTION

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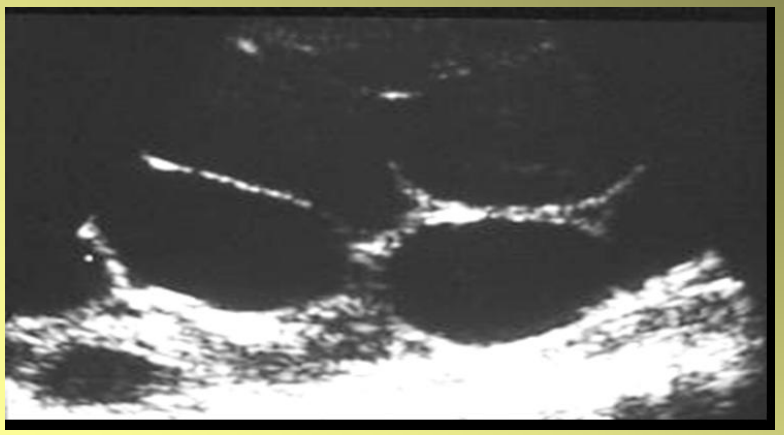
SCREENING

- RENAL ULTRASOUND IS USUAL INITIAL MODALITY; CT AND MRI MAY BE MORE SENSITIVE
- PATIENT AT RISK/UNKNOWN GENOTYPE
  - 15-39 YEARS: $\geq$ 3 UNILATERAL OR BILATERAL CYSTS; SENS 82-96%/SPEC 100%
  - 40-59 YEARS: 2 CYSTS IN EACH KIDNEY; SENS 100%/SPEC 98%
  - 60 + YEARD: 4 CYSTS IN EACH KIDNEY; SENS 100%/SPEC 100%
  - NO CYSTS AT AGE 30 RULES OUT APCKD-1
  - DETECTION OF HEPATIC OR PANCREATIC CYSTS
- PATIENT WITH NEGATIVE FAMILY HISTORY
  - 10 OR MORE CYSTS IN EACH KIDNEY
- GENETIC TESTING
  - LINKAGE ANALYSIS- REQUIRES 4 REELATIVES
  - HPLC- 65% DETECTION OF MUTATIONS
  - DIRECT SEQUENCING

ULTRASOUND PITFALLS



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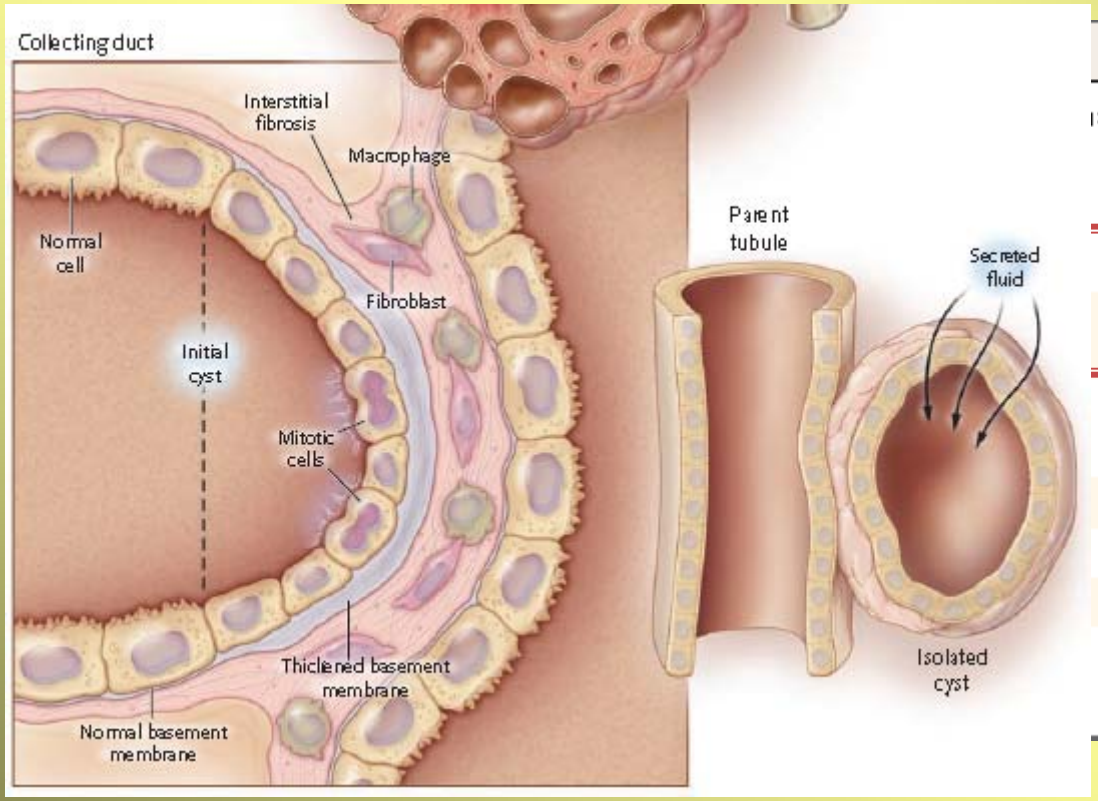
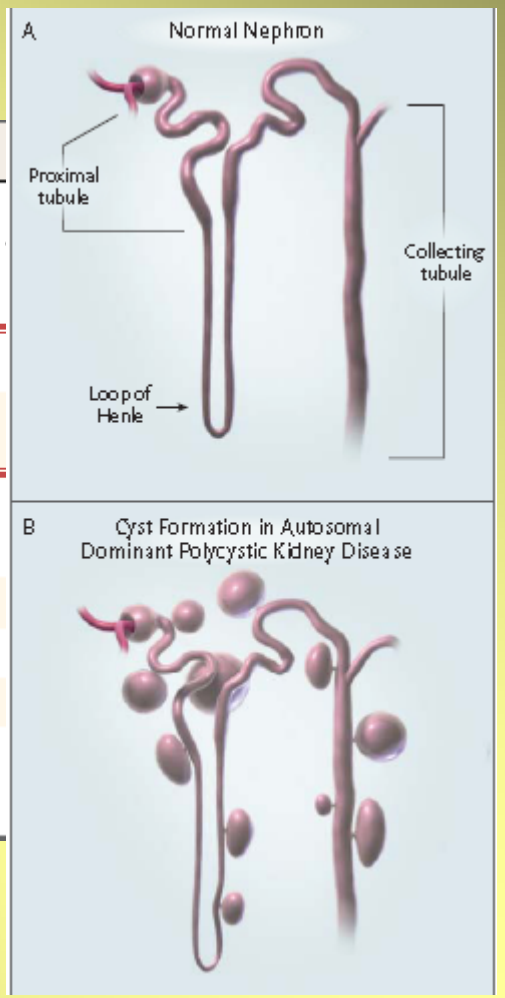
REQUIREMENTS FOR CYST FORMATION AND GROWTH

- EPITHELIAL PROLIFERATION
- FLUID SECRETION
- MATRIX REMODELING
- FIBROSIS

CYST DEVELOPMENT





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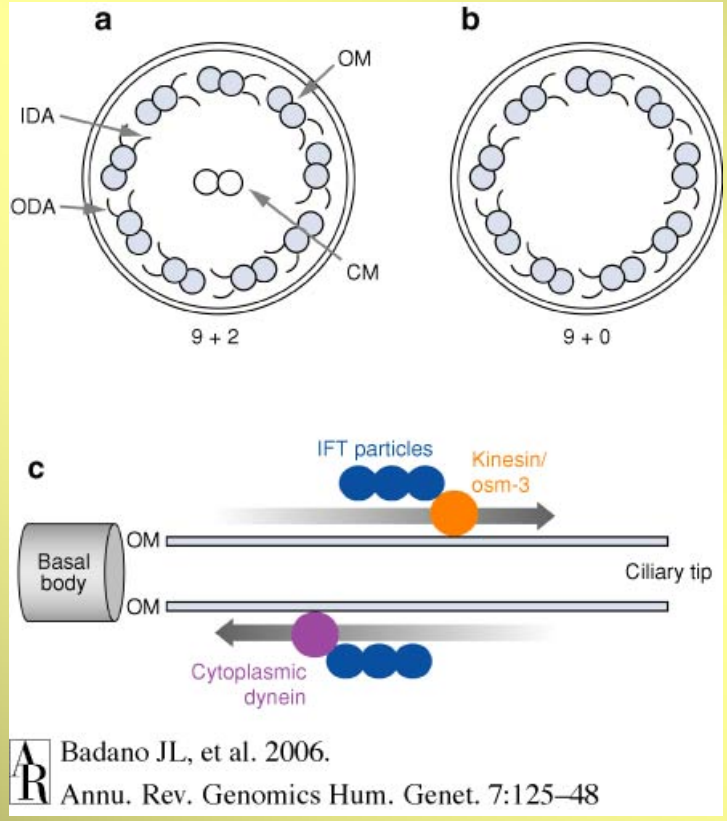
POSSIBLE DERANGEMENTS LEADING TO CYST FORMATION

- ABNORMALITIES IN CALCIUM CHANNELS
- CYCLIC AMP
  - FLUID SECRETION INTO CYSTS
  - EPITHELIAL PROLIFERATION
- POLYCYTINS LOCATED IN THE CELL MEMBRANE AND/OR IN THE CYTOPLASM INTERACT WITH ONCOGENES AND MITOGENS
- INABLITY OF ABNORMAL CILIA TO DETECT LUMIAL FLOW
  - DECREASE IN CALCIUM TRANSPORT
  - ABNORMAL CACLIUM FLUX LEADS TO EPITHELIAL PROLIFERATION DUE TO CYCLIC AMP SIGNALING
- ABNORMAL CILIA ON CENTROSOMES

STRUCTURE OF CILUM



Badano JL, et al. 2006.
Annu. Rev. Genomics Hum. Genet. 7:125–48

Annual Reviews

CILIOPATHIC SYPMTOMS

Clinical symptoms and ciliac roles

A wide variety of symptoms are potential clinical features of ciliopathy.

Chemosensation abnormalities

defective thermosensation or mechanosensation.

Cellular motility dysfunction

Issues with displacement of extracellular fluid

Paracrine signal transduction abnormalities

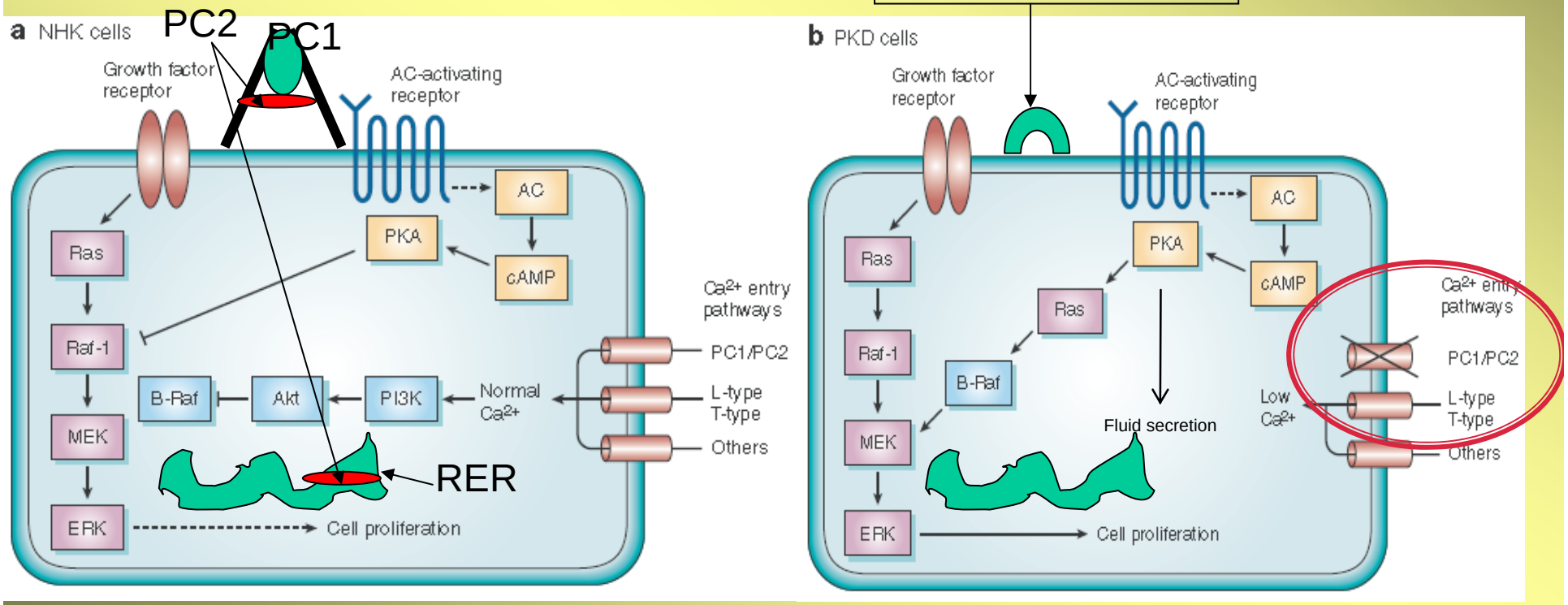
CILIOPATHIES

- BARDET-BIEDL SYNDROME
- JOUBERT SYNDROME
- MECKEL-GRUBER SYNDROME
- NEPHRONOPHTHISIS
- POLYCYSTIC LIVER DISEASE
- DANDY-WALKER SYNDROME
- KARTAGENER SYNDROME
- OROFACIODIGITAL SYNDROME
- RETINITIS PIGMENTOSA
- AGENESIS OF THE CORPUS CALLOSUM

MAP KINASE CASCADE IN NORMAL AND PCKD CELLS

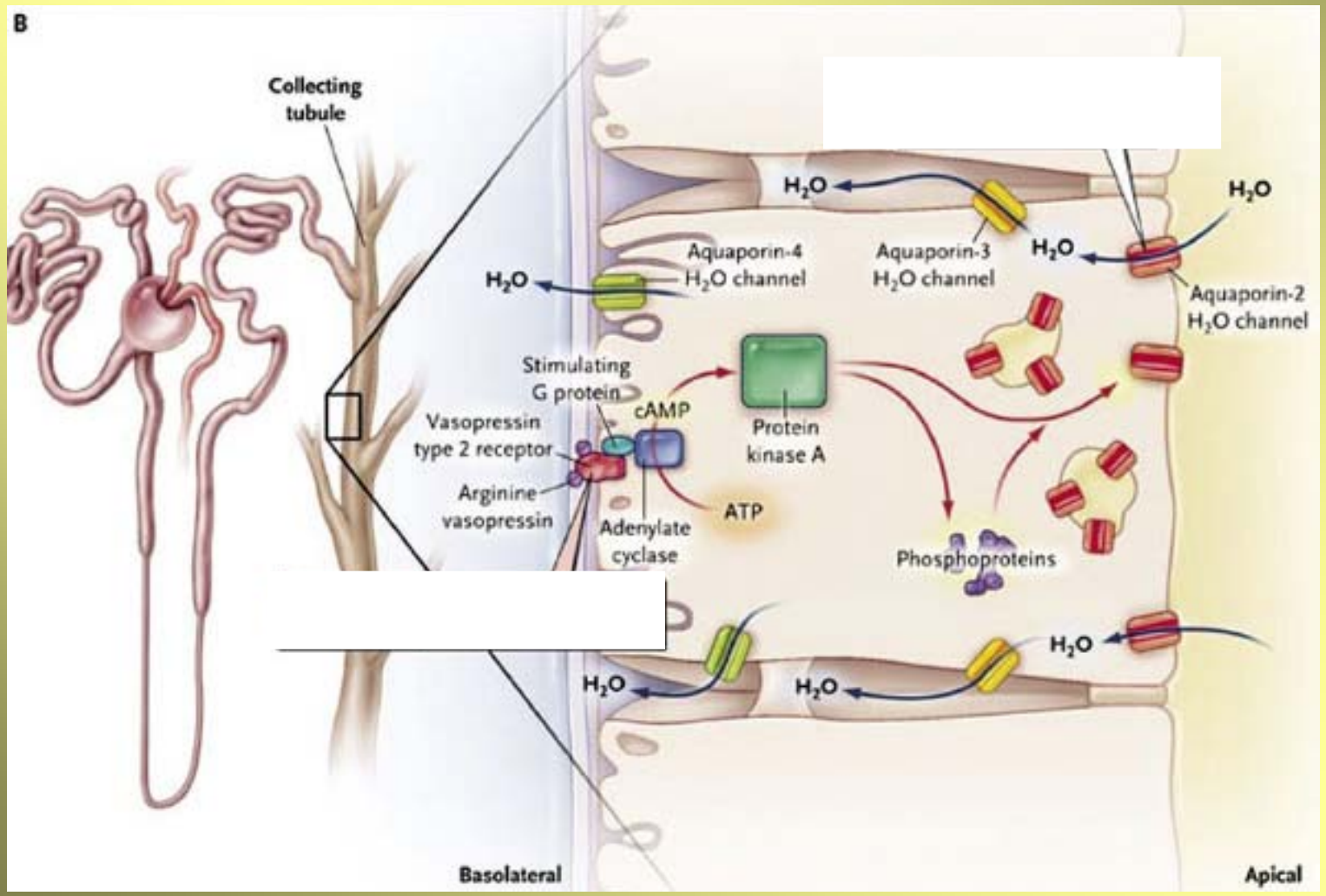
INTACT CILIUM

DEFECTIVE CILIUM



Kidney International (2008) 73, 251–253

VASOPRESSIN SIGNALING AND CYCLIC AMP



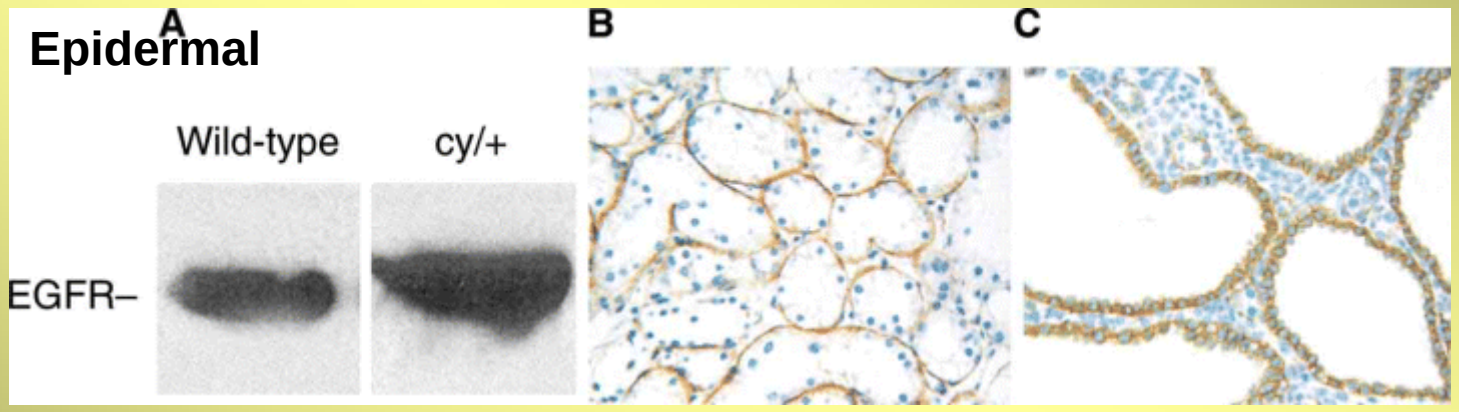
Knoers NVAM. *N Engl J Med*. 2005;352:1847-1850

CYST GROWTH

- INITIALLY EXPANDED BY GFR
- FIBROSIS OCCURS LEADING TO LOSS OF CONNECTION TO FUNCTIONING NEPHRONS
- CYST FLUID CONTAINS GROWTH FACTORS AND STIMULATES SECRETION
  - Na-K ATPase FOUND IN APICAL MEMBRANE OF APCKD CELLS
  - CFTR: CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR A C-AMP-DEPENDENT CHLORIDE CHANNEL,IS IN THE APICAL MEMBRANE OF APCKD CELLS
  - CYST FLUID CAUSES RENAL EPITEILIUM IN CULTURE TO FORM CYSTS
- CYTIC FLUID ACCUMULATION ESTIMATED AT 26-475 mL/year
- SODIUM CONTENT OF CYSTS IS VARIABLE

EGF, EGFR AND TGF AXIS IN Han:SPRD Rat Model

VE Torres et al. Kidney Int. 64:1575-79,2003



Torres et al Kidney Int 64:1573-9; 2003

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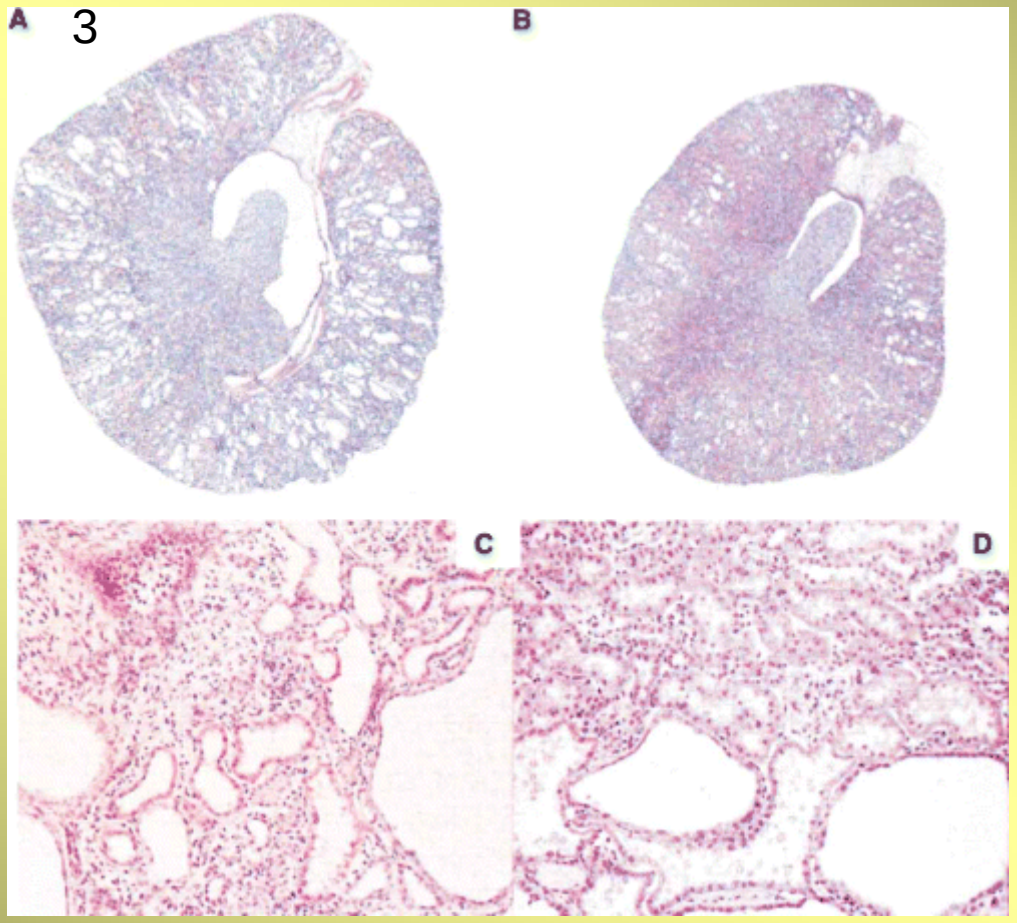

Torres et al Kidney Int 64:1573-9; 2003

EGF, EGFR AND TGF AXIS IN Han:SPRD Rat Model

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	+/+			Cy/+		
EKI-785 *mg/kg body weight*	**Control (*N* = 11)**	**90 (*N* = 7)**	***P* value**	**Control (*N* = 9)**	**90 (*N* = 11)**	***P* value**
Body weight *g*	332.6 22.1	321.7 27.6	0.427	346.6 39.5	320.5 36.25	0.163
Kidney weight *% body weight*	0.82 0.04	0.85 0.03	0.090	2.52 0.30	2.19 0.30	0.032
Liver weight *% body weight*	4.23 0.17	4.42 0.29	0.115	4.03 0.12	4.80 0.41	<0.001
Serum blood urea nitrogen *mg/dL*	20.3 2.5	22.7 4.1	0.177	35.6 4.5	31.6 3.0	0.036
Kidney cyst index %				56.5 3.7	43.4 4.2	<0.001
Kidney fibrosis score %				11.47 0.92	5.73 1.10	<0.001

APCKD, EGFR, and TGFβ

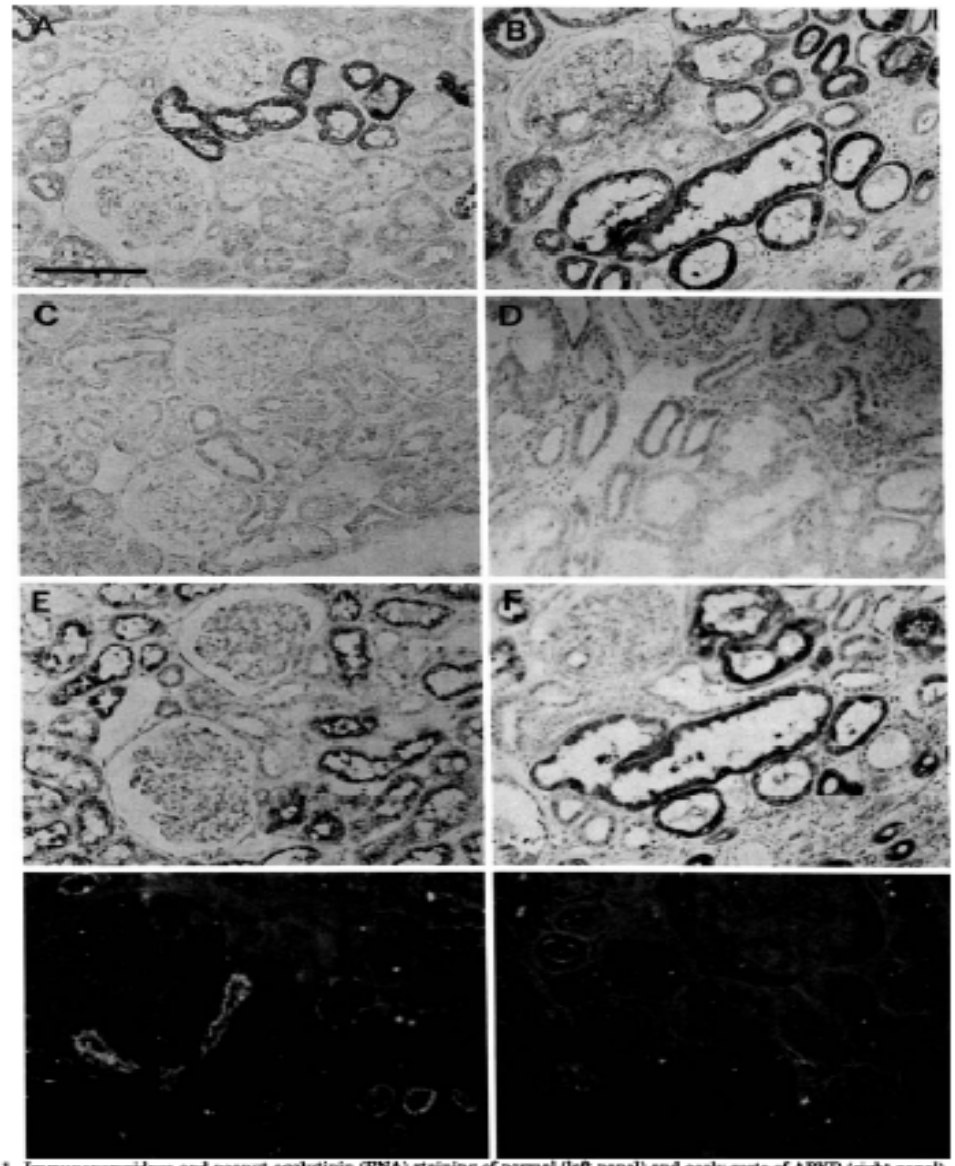


FIG. 1. Immunoperoxidase and peanut agglutinin (PNA) staining of normal (left panel) and early cysts of APKD (right panel). *A*, strong TGFα expression in PCT; *B*, TGFα in early cysts; *C*, EGF receptor in kidney tubules; *D*, increased EGF receptor in cystic epithelia; *E*, gp330 in PCT; *F*, gp330 in cystic epithelia, which, unlike normal PCT, were also strongly positive for TGFα as shown in *B*; *G*, PNA staining in DCT; *H*, PNA staining in DCT (arrow), but not in cysts. PCT: proximal convoluted tubules, DCT: distal convoluted tubules, Bar = 0.05 mm.

APCKD, EGFR AND TFGβ

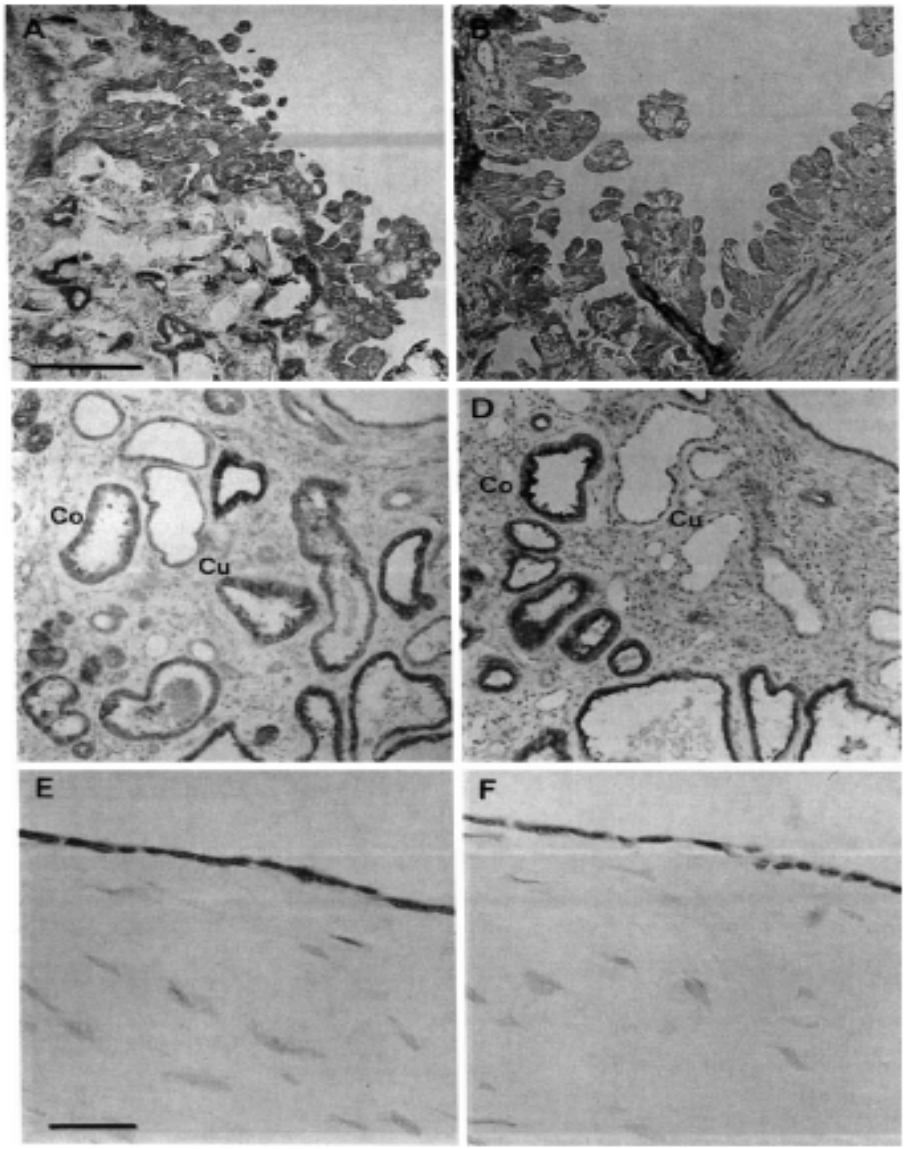
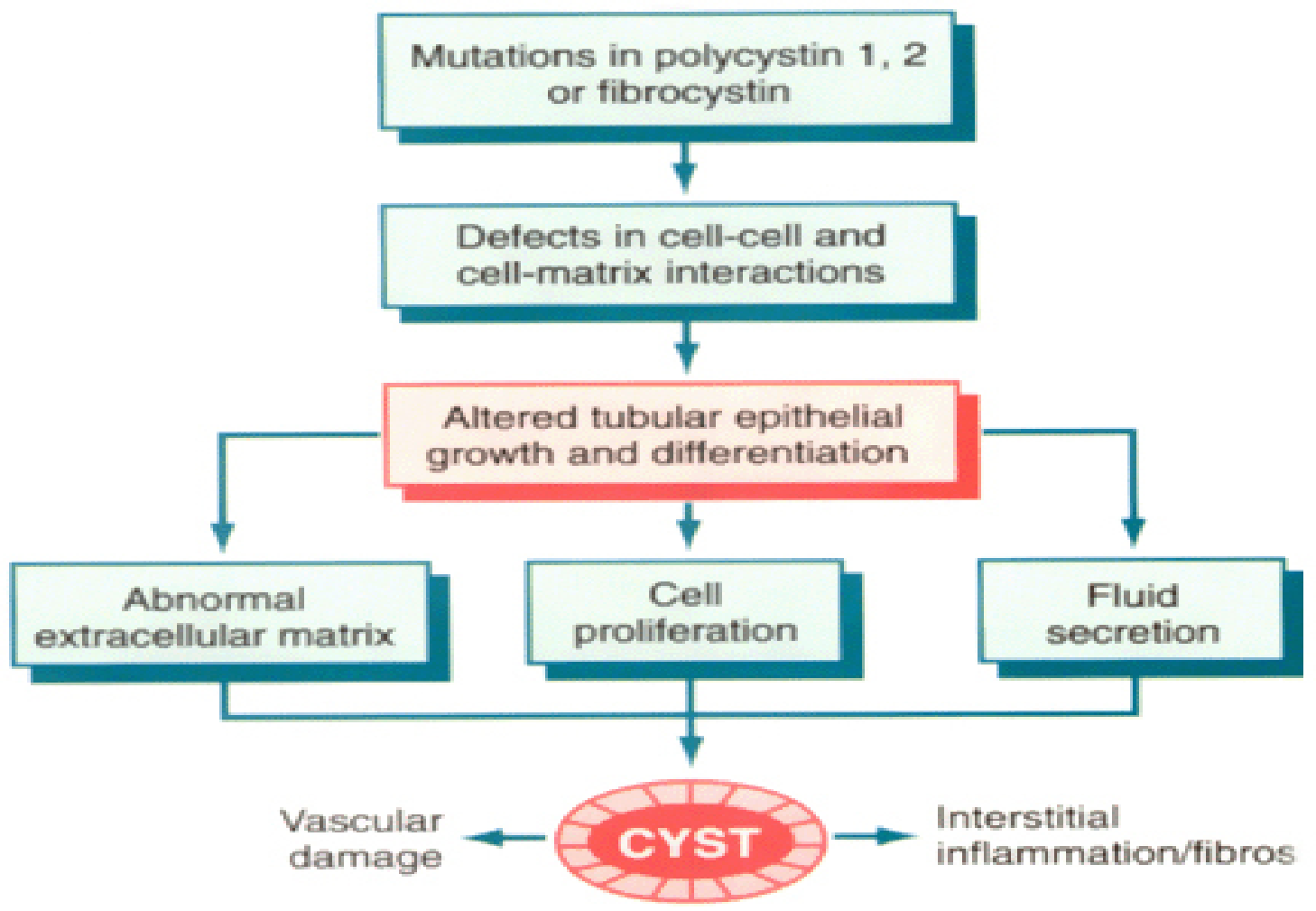


FIG. 2. Immunostaining of different types of cystic epithelia in the end-stage polycystic kidney. *A* and *B*, TGFα and EGF receptor staining, respectively, in multicellular type epithelium; *C* and *D*, TGFα and gp100 staining, respectively, in cuboid (Cu) and columnar (Co) epithelia; *E*, TGFα staining in flattened epithelium; *F*, negative control of *E*. *A–D*, Bar = 0.00 mm; *E–F*, Bar = 0.01 mm.

POSSIBLE MECHANISMS OF CYST FORMATION IN POLYCYSTIC KIDNEY DISEASE



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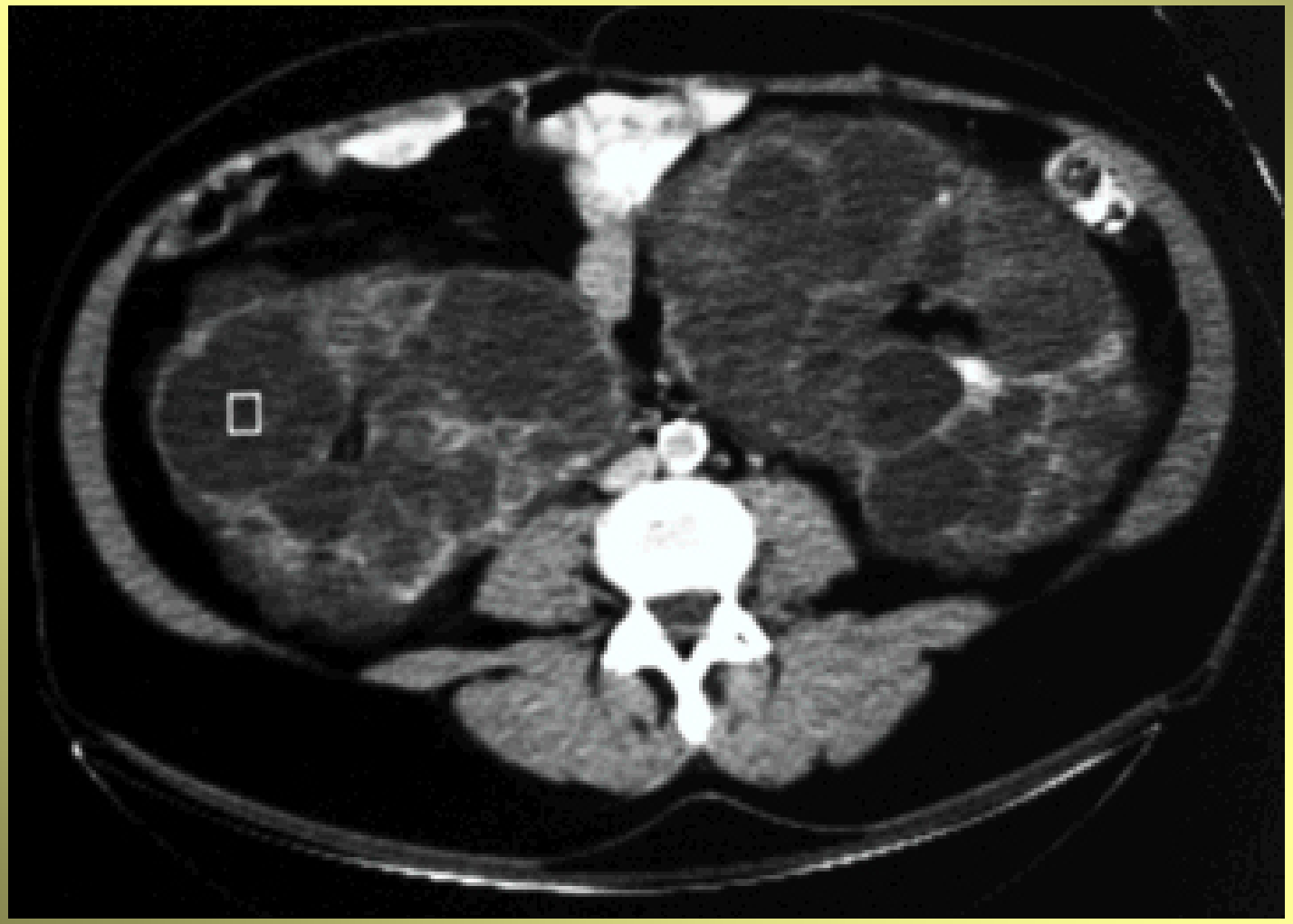
RENAL EFFECTS OF APCKD

- CYST GROWTH AND RENAL FAILURE
- HYPERTENSION
- HEMATURIA
  - CYST RUPTURE
- PROTEINURIA
  - 300MG – 1 GRAM /24 HOURS
- RENAL CALCULI
  - MOST OFTEN URIC ACID
- LOSS OF CONCENTRATNG ABILITY
- INFECTION
- PAIN SYNDROMES
- POLYCYTHEMIA

APCKD: COMPUTERIZED TOMOGRAPHY



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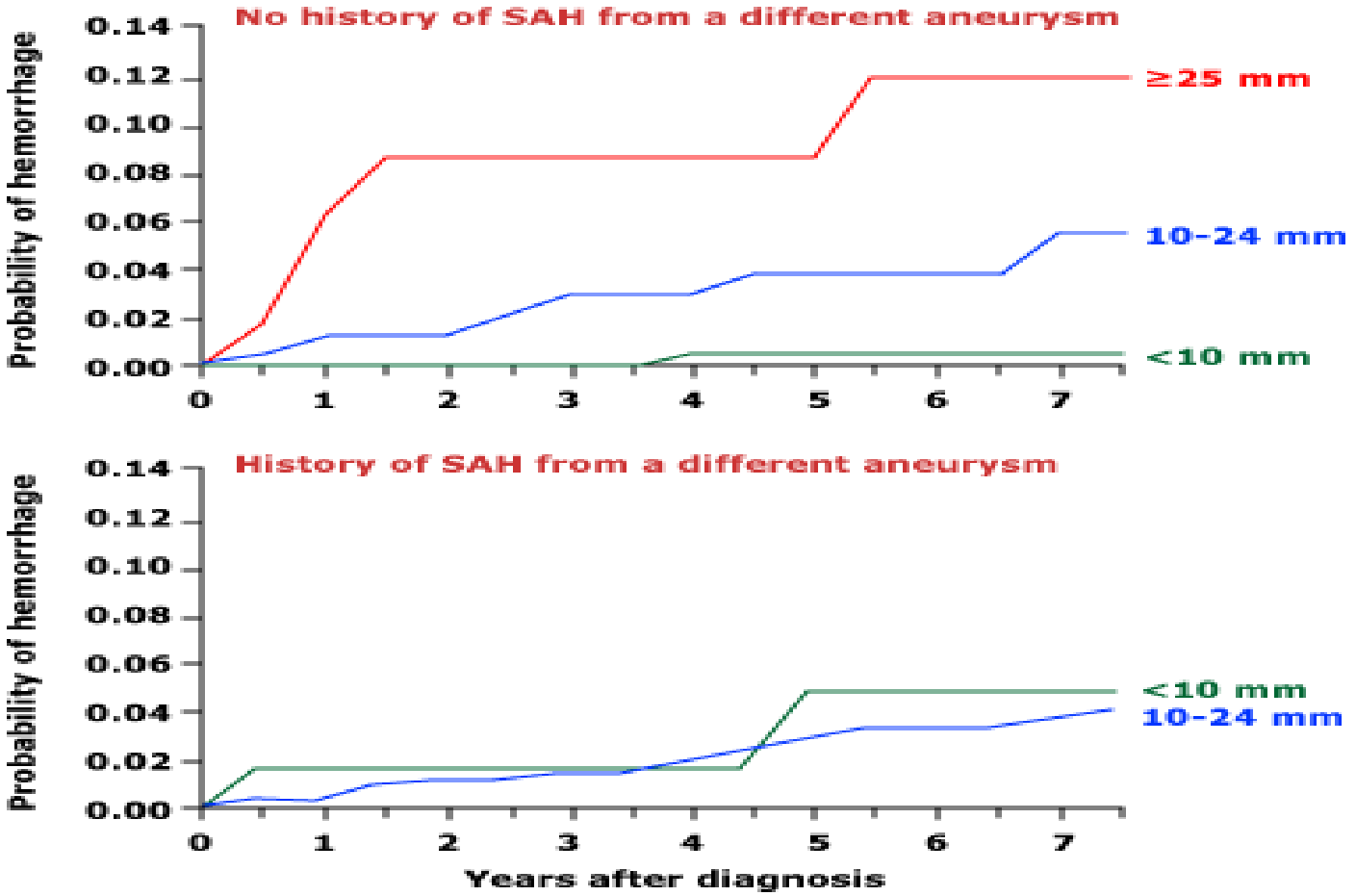
EXTRARENAL EFECTS OF APCKD

- CEREBRAL ANEURYSMS
- HEPATIC CYSTS
- CARDIAC VALVE DISEASE
- COLONIC DIVERTICULI
- HERNIAS

ANEURYSMS

- INTRACEREBRAL HEMORRHAGE/SAH
  - 4%-10% INCIDENCE
  - 22% IF A RELATIVE SUFFERED A BLEED
  - 50% DEATH OR DISABILITY
- SCREENING
  - PATIENTS WITH BLEED, POSITIVE FAMILY HISTORY, WARNING SYMPTOMS, HIGH-RISK OCCUPATION, HYPERTENSION, NEED FOR ANTICOAGULATION
- RE-SCREENING
  - HIGH-RISK PATIENTS
    - IF INITIAL STUDY IS NEGATIVE THE IS A 2.6% INCIDENCE OF AN ANEURYSM AFTER 10 YEARS OF FOLLOW-UP
    - RE-SCREEN EVERY FIVE YEARS IF INITIAL STUDY IS NEGATIVE; EVERY 2-3 YEARS IF ANEURYSM IS SMALL ~ 7-10M
  - LOW-RISK PATIENTS (- FAMILY HISTORY) ?

LIKELIHOOD OF RUPTURE OF INTRACRANIAL ANEURYSM



OTHER ORGANS

- HEPATIC CYSTS
  - UP TO 80% OF PATIENTS WILL HAVE CYSTS
  - EQUAL MALE/FEMALE INCIDENCE BUT MORE SEVERE IN FEMALES
  - RARELY TRANSPLANTATION IS REQUIRED; RAPAMYCIN REDUCES HEPATIC CYSTS
- CARDIAC
  - MITRAL VALVE PROLAPSE AND AI
  - INCIDENCE 20%
- COLONIC DISEASE
  - DIVERTICULI

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FACTORS AFFECTING PROGRESSION

- YOUNGER AGE
- MALE GENDER
  - PKD 1
- PKD 1 vs PKD2
  - ESRD AT 54 YEARS vs 74 YEARS
- EPISODES OF GROSS HEMATURIA
- PROTEINURIA
- HYPERTENSION
- RAPID RENAL GROWTH
- 25% ESRD AT AGE 50; 40% ESRD AT AGE 60; 70% ESRD AT AGE 70

FAMILIAL FACTORS

- CONTROVERSY REGARDING INTRAFAMILIAL HOMOGENEITY
- CONFOUNDERS
  - DIAGNOSTIC TECHNIQUES
  - NATURE OF THE GENETIC ABNORMALITY
  - GENETIC ANTICIPATION IN OFFSPRING
  - OTHER GENETIC MODIFIERS
  - ENVIRONMENT

GENETIC ANTICIPATION

Anticipation of age at renal death in autosomal dominant polycystic kidney disease (ADPKD)? 1605

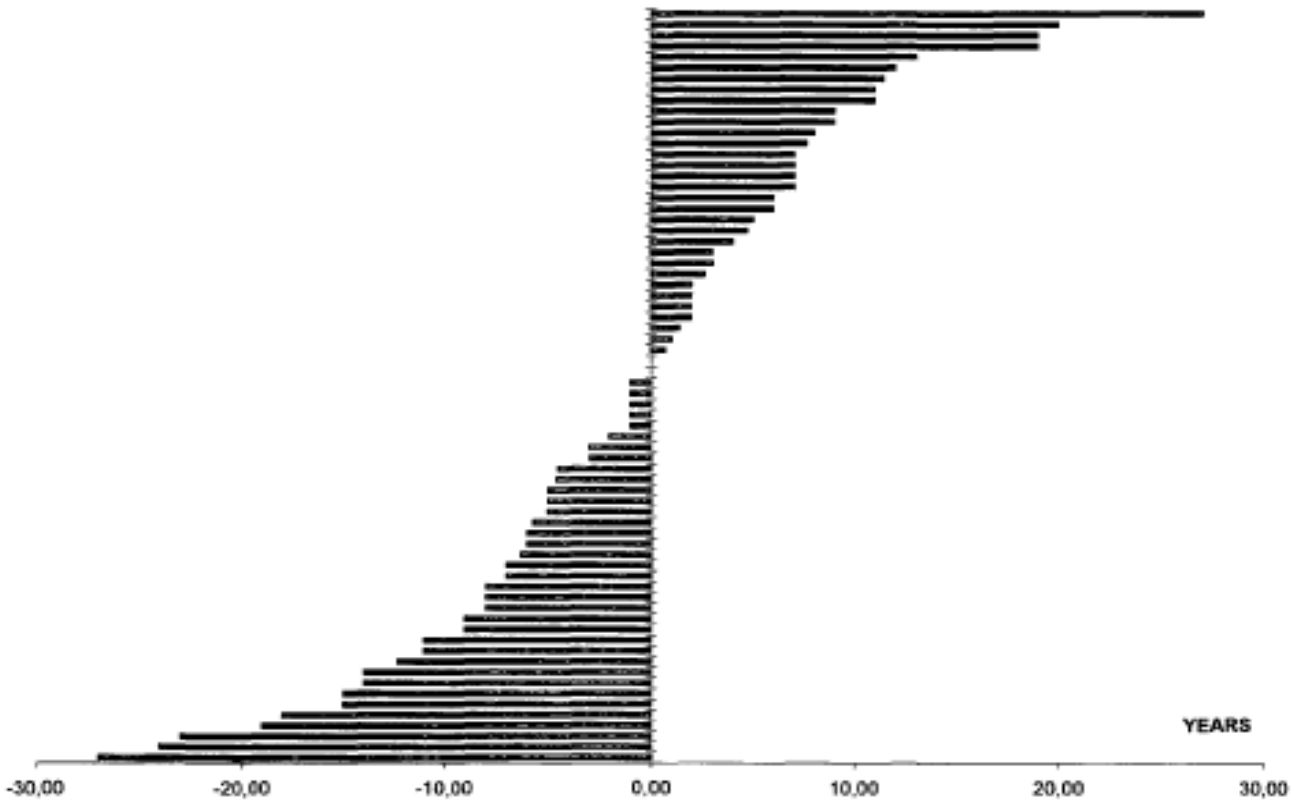


Fig. 1. Difference of age at renal death, (ranked according to the magnitude of the difference [in years] of offspring minus parent) of 70 families with one parent/offspring pair each.

TREATMENT STRATEGIES

- PREVENTION OF CYST GROWTH
  - INIBITION OF TRANSPORT
    - VASOPRESSIN ANTAGONISTS
    - REDUCED CAFFEINE INTAKE
    - SOMATOSTATIN
  - INHIBITION OF CELL PROLIFERATION
    - VASOPRESSIN, STEROIDS, RAPAMYCIN
  - INHIBITION OF FIBROSIS
    - RAAS BLOCKADE, PROTEIN RESTRICTION
  - CYST REDUCTION
  - CONTROL OF HYPERTENSION

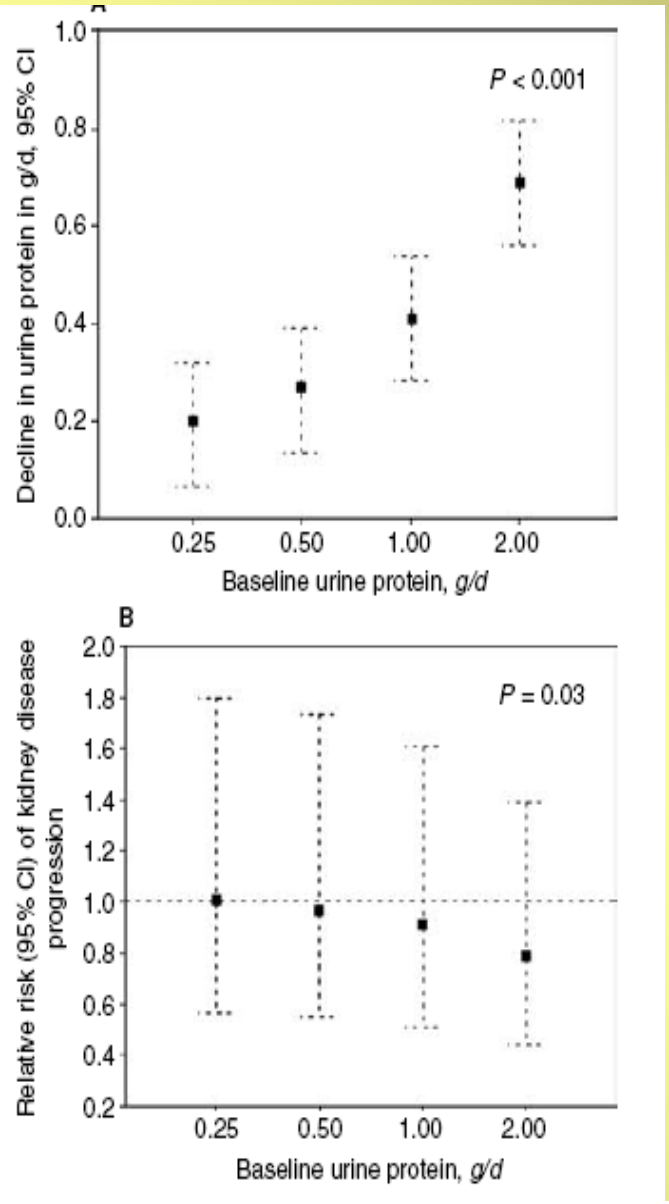
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND PROGRESSION

Table 3. Unadjusted and adjusted treatment effect

Analysis	Decline in urine protein *g/day*[a]	Doubling of baseline serum creatinine or onset of kidney failure relative relative risk (95% CI)[b]
Unadjusted	0.52 (0.36, 0.68)	0.73 (0.41 to 1.29)
Adjusted for baseline characteristics	0.34 (0.21, 0.47)	0.81 (0.44 to 1.47)
Adjusted for baseline characteristics and change in systolic blood pressure during follow-up	0.34 (0.21, 0.47)	0.81 (0.44 to 1.47)
Adjusted for baseline characteristics and change in urine protein excretion during follow-up	N/A	0.88 (0.49 to 1.61)
Adjusted for baseline characteristics changes in systolic blood pressure and urine protein during follow-up	N/A	0.91 (0.49 to 1.68)

[a]Declines in blood pressure and urine protein excretion were calculated by subtracting the respective values at each follow-up visit from the baseline value.
[b]Kidney failure is defined as the onset of long-term dialysis therapy.

ACE-I, PROTEINURIA & PROGRESSION



APCKD AND ESRD

- CHALENGES IN APCKD
  - LARGE KIDNEYS
    - LOWER PERITONEAL SURFACE
    - DIFFICULTY IN PLACING TRANSPLANT
  - CYST INFECTION/UTI
    - RISK IN TRANSPLANT PATIENTS
    - PERITONITIS IF INFECTED CYSTS RUPTURES
  - DIVERTICULAR DISEASE
    - RISK IN TRANSPLANT PATIENTS
    - RISK IN PD PATIENTS
  - POLYCYTHEMIA, HEMATURIA, CHRONIC PAIN

ESRD MANAGEMENT

- OVERALL ESRD SURVIVAL IS ABOVE AVERAGE IN APCKD
  - APCKD RR DEATH 0.6 vs OTHER HD PATIENTS
- PD
  - DESPITE CHALLENGES APCKD PD SURVIVAL MAY BE SUPERIOR TO APCKD HD SURVIVAL (HR 1.4) COMPARED TO PATIENTS WITHOUT APCKD
- TRANSPLANT
  - INDICATIONS FOR NEPHRECTOMY
    - FREQUENT UTI, SIZE, PAIN, CHRONIC HEMATURIA
  - COLECTOMY MAY BE REQUIRED

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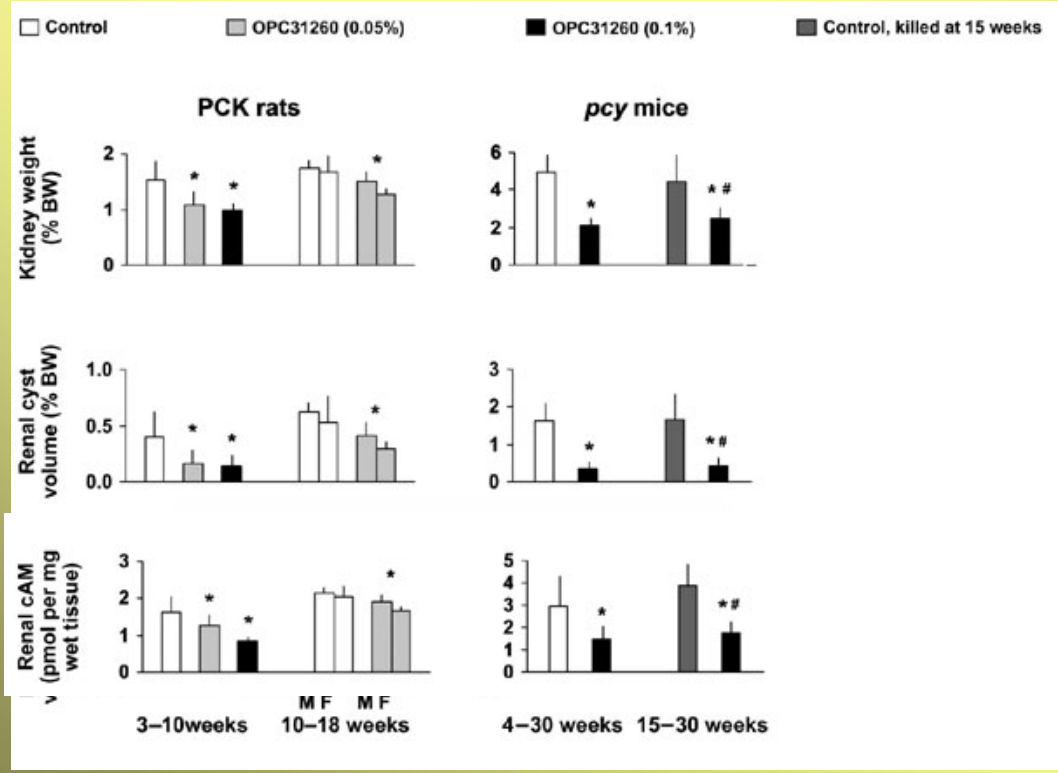
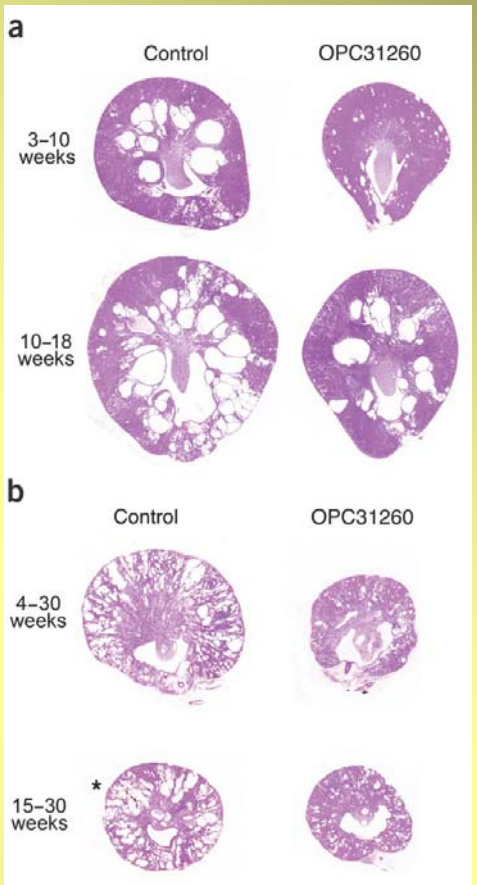
- FUTURE DEVELOPMENTS

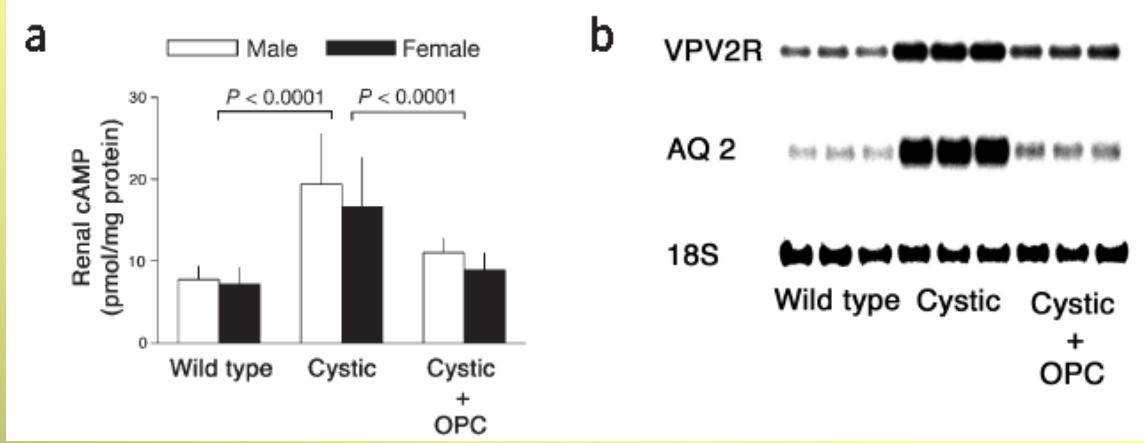
V_2 RECEPTOR ANTAGONISM

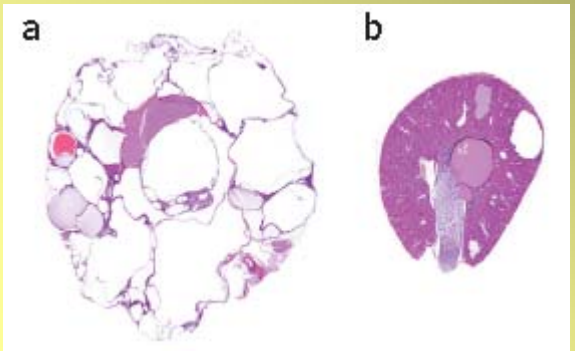


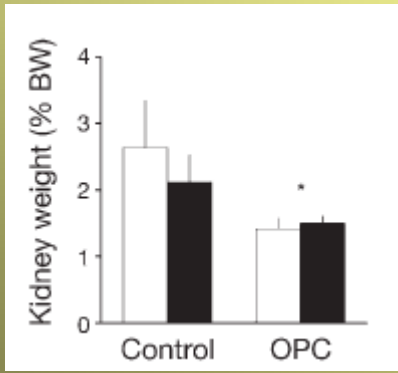


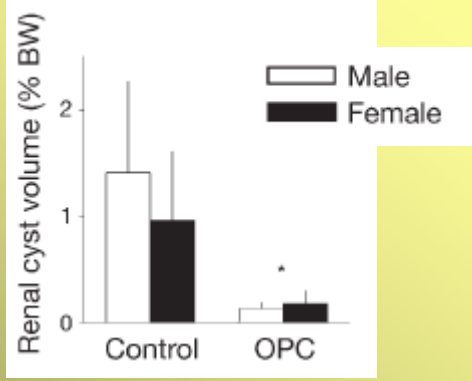
Nature Medicine **9**, 1323 - 1326 (2003)

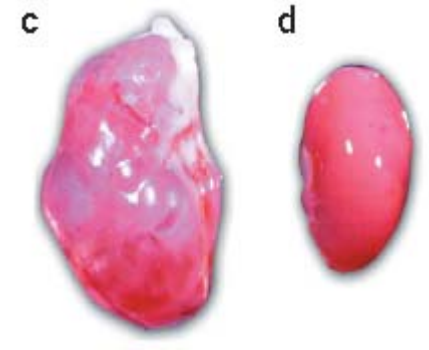
V_2 RECEPTOR ANTAGONISM



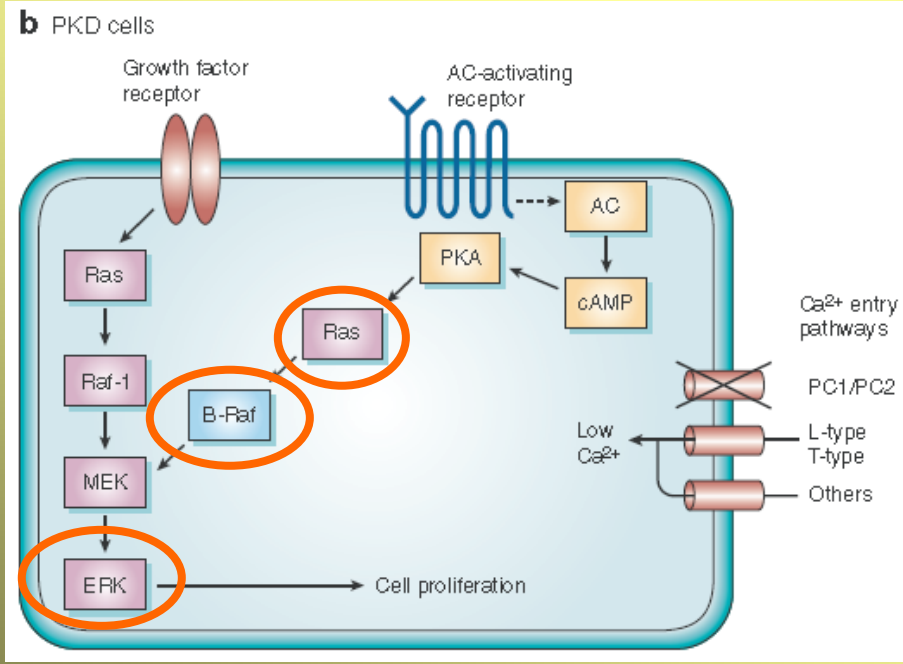


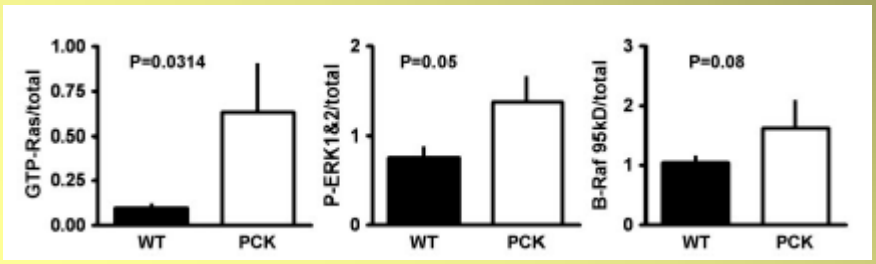


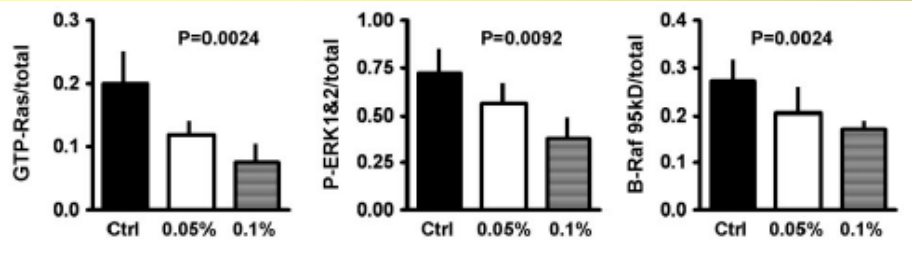


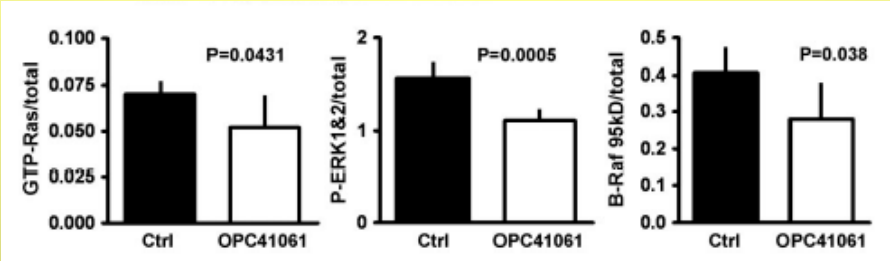


MAP KINASE CASCADE AND V_2-RECEPTOR ANTAGONIST









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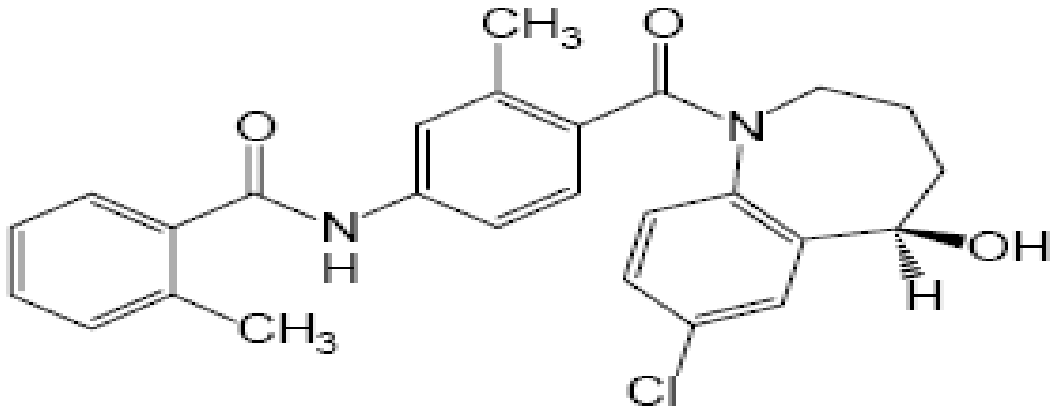
CONCLUSIONS

- ENDOTHELIAL CELL PROLIFERATION AND FLUID SECRETION NECESSARY FOR RENAL CYST FORMATION IN HERITABLE CYSTIC KIDNEY DISEASE RESULTS FROM ALTERED CA HOMEOSTASIS AND INCREASED CAMP SIGNALING
- V2 RECEPTOR ANTAGONISTS DECREASE INTRACELLULAR CAMP
- V2 RECEPTOR ANTAGONISTS ARE ATTRACTIVE AS THERAPY BECAUSE OF THEIR RENAL SELECTIVITY
- V2 RECEPTOR ANTAGONISTS CAN BE SAFELY ADMINISTERED BASED ON PRECLINICAL AND CLINCAL DATA IN OTHER DISEASES (CHF, CIRRHOSIS)

TOLVAPTAN

Chemical structure:



Other name:	OPC-156
INN, USAN:	Tolvaptan
Molecular formula:	$C_{26}H_{25}ClN_2O_3$
Molecular weight:	448.94
Appearance:	OPC-41061 is a white crystalline powder.

TOLVAPTAN INTERACTION WTH V_1 & V_2 RECEPTORS

- ANTAGONISM TO AVP BINDING:
  - UP TO 300-FOLD INCREASE CONCENTRATION FOR V_1 RECEPTORS
- PLATELET AGGREGATION (MEDIATED BY V_{1a})
  - INHIBITS AVP-INDUCED AGGREGATION BUT NOT ADP-INDUCED AGGREGATION
  - TOLVAPTAN DOES NOT INDUCE AGGREGATION
- DOSE DEPENDENT INCREASE IN URINE VOLUME AND DECREASE IN URINE OSM
  - NO TOLERANCE
  - PARTIAL AGONISTIC WAS NOT DEMONSTATED
- CORRECTS HYPONATREMIA IN MODELS OF CIRRHOSIS, CHF, HYPONATREMIA

TOLVAPTAN STUDY

Primary Objective:

- Evaluate long-term efficacy of tolvaptan in ADPKD through rate of renal volume change (%) for tolvaptan-treated compared to placebo-treated subjects

Secondary Objectives:

- Evaluate long-term efficacy of tolvaptan in ADPKD through a composite of ADPKD progression clinical markers (ie, hypertension, renal pain, albuminuria and renal function)
- Evaluate long-term efficacy of tolvaptan in ADPKD using single clinical markers of ADPKD progression
- Evaluate long-term safety of tolvaptan through standard clinical measures
- Evaluate pharmacokinetic (PK), pharmacodynamic (PD) and exploratory parameters for tolvaptan in ADPKD

TOLVAPTAN STUDY

- PHASE 3 TRIAL
- PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-ARM TRIAL IN PATIENTS WITH APCKD
- 1200-1500 SUBJECTS STUDIED FOR UP TO 36 MONTHS
- SUBJECTS STRATIFIED FOR GFR, RENAL SIZE AND HYPERTENSION

HALT/PKD STUDY

- TO EXAMINE THE EFFECT OF INTENSIVE RAAS BLOCKADE AND BLOOD PRESSURE CONTROL ON PROGRESSION OF APCKD
- 2 PARALLEL STUDIES:
  - A. CKD I-II DESIGN- 2X2 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-MASKED STUDY COMPARING ACE-I MONOTHERAPY vs ACEI + ARB AND STANDARD BP CONTROL vs LOW BLOOD PRESSURE. PRIMARY OUTCOME IS CHANGE IN KIDNY SIZE OVER 5 YEARS
  - B. CKD III DESIGN- 2X1 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE MASKED STUDY COMPARING ACE-I MONOTHERAPY vs ACEI + ARB AND STANDARD BP CONTROL. PRIMARY OUTCOME IS RATE OF PROGRESSION OF RENAL FAILURE (50% REDUCTION IN MDRD eGRF, DDT) OVER 5 YEARS
- STUDY A: n = 550; STUDY B: n = 470

THANKS FOR YOUR ATTENTION

THE SMILE