Renal

CYSTIC DISEASES OF THE KIDNEY

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I. INTRODUCTION TO RENAL CYSTIC DISEASES

The renal cystic diseases are a heterogenous group of disorders which are comprised of heritable, developmental, and acquired disorders. Renal cysts are common radiographic and morphologic occurrences in clinical practice; finding the cysts is relatively easy, but identifying them and interpreting the findings are relatively difficult. One factor which has greatly limited the idenfication of renal cysts is the complicated classification systems which have been developed over the past decade. Accordingly, the radiologist may see parenchymal defects, the urologist or nephrologist may see cysts on the capsular surface, and the pathologist may see sections of a cyst from restricted points of view. Each may use a different descriptive term although each recognizes a similar pattern; in some cases each may use the same term and intend something entirely different. Hence, a standard terminology is critically needed in the area of renal cystic disease.

One obvious problem with renal cystic disease is that renal cysts are, despite their great heterogeneity, similar in many respects. Obviously, however, it is not suffice to call everything "polycystic disease". For example, some cysts are hereditary, some developmental, and some acquired; but most are lined with flattened, undistinguished epithelium. The classification of renal cysts proposed by Bernstein represents a clinical and radiographic approach to the terminology.

Before presenting a classification of renal cysts, it is important to emphasize several general points regarding cystic diseases. Cysts may arise in any part of the nephron and collecting system, but have a predeliction for the loops of Henle and for the collecting tubules and peripheral portions of collecting ducts. Nevertheless, some patterns are charactistic of certain conditions. The cysts in infants with polycystic disease of autosomal recessive type are characteristically located in the collecting tubules and ducts. Glomerular and tubular microcysts in the peripheral cortex are commonly associated with syndromes of multiple malformations. Dysplastic cysts in the peripheral cortex are commonly associated with a lower urinary tract obstruction. The tendency of microcysts to localize in the peripheral cortex seems, like a similar localization of dysplastic cysts, to hold some clue to the pathogenesis. One might ask if renal cysts in heritable syndromes are inherent in those syndromes. The answer has implications also for polycystic disease. A lesion that affects selected nephrons may be caused by exterenal factors acting through a limited period of time. A generalized vulnerability to develop cysts would be more compatible with an abnormality residing in the nephron itself. If some cystic abnormalities are indeed secondary to extrinsic factors that affect immature tubular structures secondarily, then those cysts should be regarded as developmental. Other cysts arising later in life, even in association with heritable disorders, would not in a strict sense be developmental. Cysts arising from a genetic abnormality residing within the tubular cells themselves are regarded as hereditary. It is important to remember that the renal lesions in syndromes of congenital malformations are sufficiently diverse to impair any unitarian theory of their pathogenesis.

II. EMBRYOGENESIS OF THE KIDNEY

Three distinct phases of development have occurred in the development of the human kidney. The earliest and simplest excretory organ was the pronephros, functional today only in cyclostomes and a few fish. The pronephros does serve as a provisional kidney in larval fish and amphibians, but it is replaced by the mesonephros which remains as the permanent kidney of these animals. The embryos of reptiles, birds, and mammals develop first a rudimentary and functionless pronephros and then a mesonephros (functional during a part of fetal life), whereas the final kidney is a new organ, the metanephros. The three kidneys develop overlappingly, one caudad to the other.

Each of these kidney types are composed of uriniferous tubules which have a common source of origin and arise from the mesoderm of the nephrotome (a connecting plate in the mesenchyme).

The permanent kidney of human arises far caudad in the body; it consists of an aggregate of tubules which drain into a common duct. The inert system of drainage ducts (ureter, pelvis, calyces, papillary ducts, and straight collecting tubules) is derived from a bud growing off the mesonephric duct. Each secretory unit, or nephron (Bowman's capsule, both convoluted tubules, and Henle's loop), differentiates from the substance of the caudal end of the nephrogenic cord. A collecting and secretory tubule then unite secondarily to complete a continuous uriniferous tubule (1).

This scheme is reproduced graphically below in Figure 1 and Figure 2.

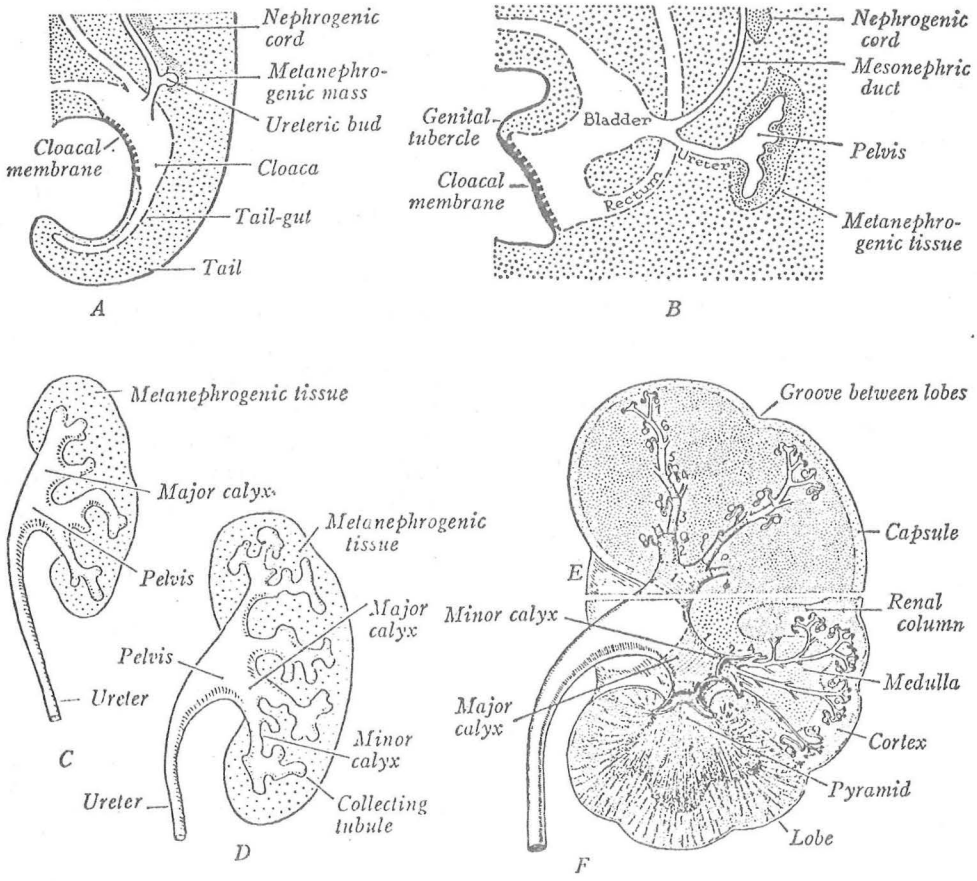


Fig. 1: ORIGIN OF HUMAN METANEPHROS AND DEVELOPMENT OF DUCT SYSTEM.

A,B: Origin and early relations.

C-F: Development of ureteric bud into the duct system.

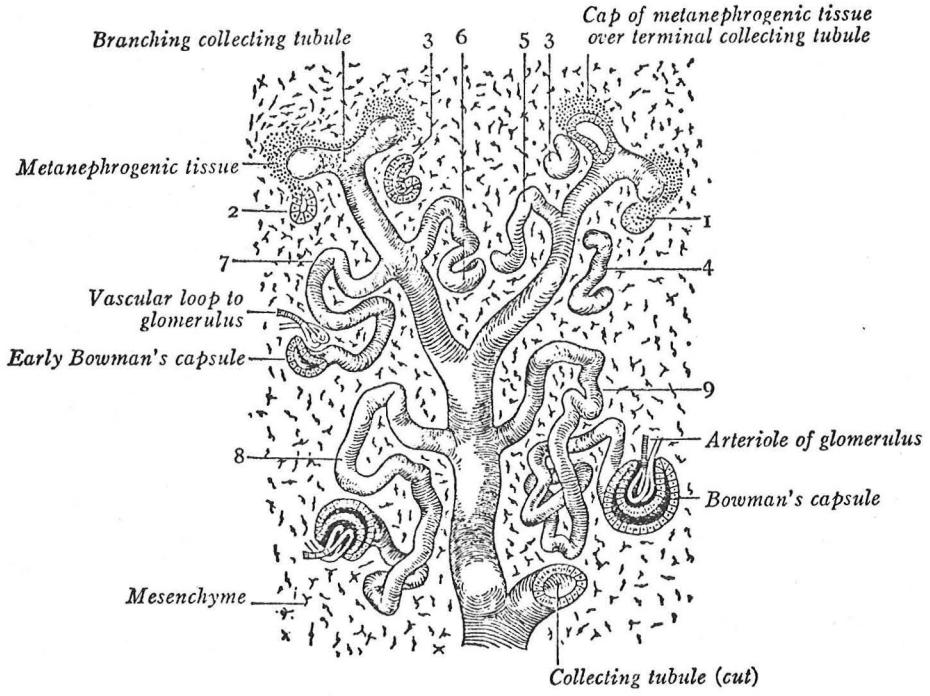


Fig. 2: LINKAGE OF NEPHRONS WITH BRANCHING COLLECTING TUBULES
Composite diagram, illustrating differentiation of nephrons and their linkage to collecting tubules.

This process has been illustrated in a slightly different manner by Osathanondh and Potter and is illustrated below in Figure 3 and Figure 4.

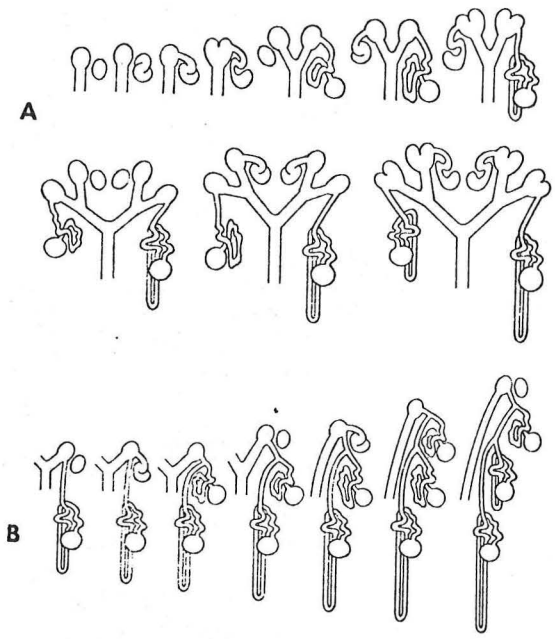


Fig. 3: KIDNEY DEVELOPMENT

A: Development of nephrons on growing collective tubules.

B: Aracade formation.

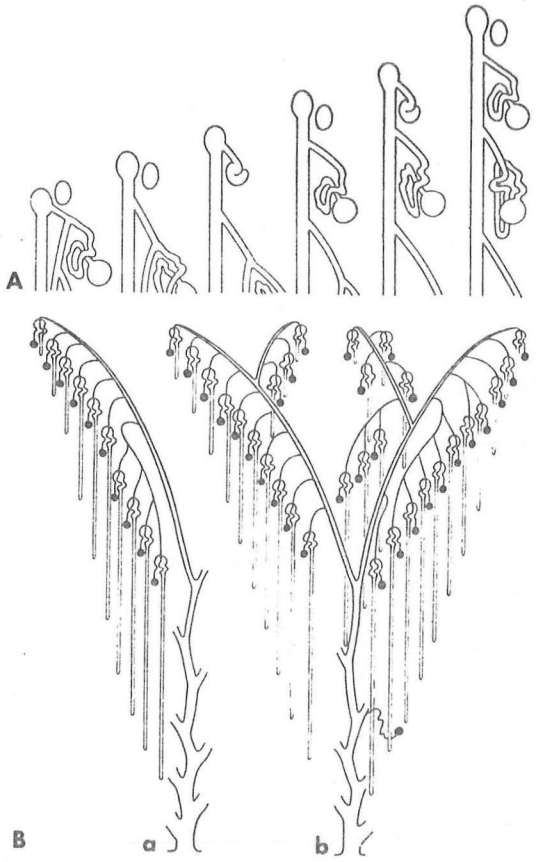


Fig. 4: FURTHER STAGES OF KIDNEY DEVELOPMENT

A: Direct attachment of distal nephrons to ureteric bud.

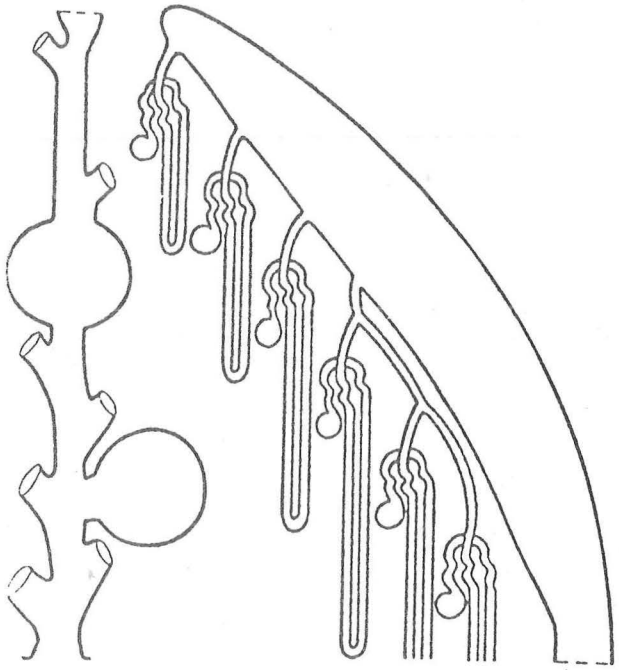
B: Arrangement of nephrons at birth: a: usual pattern
b: possible variations

The rationale for an introductory discussion of renal embryogenesis is that Osathanodh and Potter have suggested an embryogenic classification of renal cysts is possible based on microdissection studies.

Potter Type I Cystic Disease is due to hyperplasia of the interstitial portions of collecting tubules (Figure 5). This is a rare, fatal condition

Fig. 5: POTTER TYPE I (INFANTILE POLYCYSTIC DISEASE)

Lesions develops in terminal and proximal portions of collecting ducts.



of newborn infants and is termed infantile polycystic kidney disease. This is a hereditary abnormality and is transmitted as an autosomal recessive trait. Initially the ureteric bud and metanephric blastema develop normally and give rise to normal appearing nephrons. However, at some time during the last half of intrauterine life, the collecting tubules in both kidneys become altered, the proximal collecting tubules develop large sacules and diverticula while the more terminal collecting tubules become diffusely enlarged leading to Potter's term "tubular gigantism" (see Figure 5). The remainder of the nephrons are normal. It is important to stress that this is a bilateral disease with the kidneys being symmetrically enlarged at birth often filling the entire abdomen. Grossly, multiple small cysts are visible through the renal capsule representing the dilated terminal portions of the tubules. Microscopically there is no flattening of cells that could be attributed to excessive tension. Interstitial connective tissue is not increased. The intravenous urogram demonstrates marked prolongation of the nephrogram phase sometimes lasting for a week or more. Contrast medium is excreted and one can frequently identify radiating streaks of contrast material all the way from the periphery representing the dilated collecting tubules. Thus, the most striking features of this disease are the symmetrical enlargement of both kidneys, the prolonged nephrogram phase, and the streaking of contrast material seen at time of urography (3).

Originally it was believed that this condition was uniformly fatal in the newborn. It is now recognized that the prognosis depends on the number of abnormal nephrons, and in those children in whom 90% or more of the collecting tubules are involved, death occurs early in the neonatal period. Invariably the liver is abnormal in this form of cystic disease with an increase in the number and size of bile ducts as well as in the proliferation of intraductal connective tissue. Thus, a few children with only a small percentage of their renal collecting tubules involved may live into adolesence or beyond, only to die from the effects of portal hypertension.

Potter Type II Cystic Disease (Figure 6) is due to an inhibition of

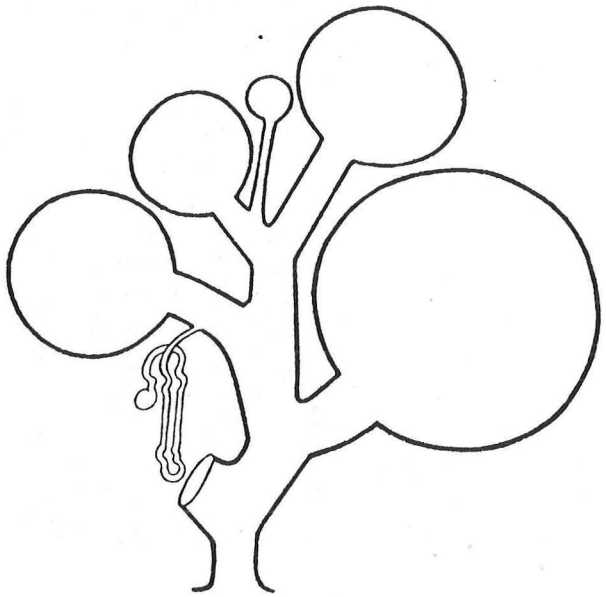


Fig. 6: POTTER TYPE II

Secondary to failure of ureteric bud to subdivide. Also called "congential multicystic kidney".

amplullary activity. On microdissection (see figure), the total number of generations of tubules derived from the ureteral bud is reduced. Instead of the normal 12 to 20 generations there are only 4 to 12. Discontinuity or obstruction of nephrons is not apparent. Tubules terminating in cysts are encircled by dense connective tissue. Proximal and distal convoluted tubules are especially prone to enlargement. Affected portions of the kidney are abnormal in development, because of inadequate function of the ampulla and a resultant failure of nephron induction. The terminal portion of the tubules then expand into cysts. Consequently, the collecting tubules have a few branches and all terminate in cysts. This disease is not hereditary; Potter has subdivided Type II disease into Type IIA which is also called "congenital multicystic kidney" disease and IIB which represents dysplastic kidneys of reduced size (aplastic or hypoplastic). Congenital multicystic kidney disease deserves special mention inasmuch as it is one of the more common causes for an abdominal mass being found in the newborn infant and must be differentiated by an urologist or a nephrologist from hydronephrosis, renal vein thrombosis, Wilm's tumor, or neuroblastoma. The multicystic kidney is invariably unilateral, but the contralateral kidney has a higher incidence of congenital disorders such as ureteropelvic obstruction. The striking feature of all dysplastic kidneys is that the involved area is completely abnormal. The nephrons are greatly reduced in numbers and rarely develop into functioning structures. The connective tissue contains the irregularly distributed variable size blood vessels, nerve trunks, and, occasionally, islands of cartilage. The liver is rarely involved. In congenital unilateral multicystic disease, the ureter is usually abnormal or atretic. Due to the absence of ampullary branching, the pelvis and calices most often fail to develop normally and the kidney fails to take on reniform shape as it does in other cystic diseases.

Potter Type III renal disease is due to multiple abnormalities of development. It is the only form of cystic disease in which normal and abnormal collecting tubules are intermixed and in which cysts of the nephrons are also present (Figure 7). This disorder is present at birth and may not come to clinical attention or cause death until some time later, depending upon the severity of the abnormality. This disorder corresponds to the clinical classification of adult polycystic kidney disease. Typically the kidneys are usually larger than normal, and cysts are present throughout the renal parenchyma and enlarge slowly during the life of the patient. This disorder will be discussed in detail subsequently.

Potter Type IV Cystic Disease (Figure 8) is due to urinary tract obstruction during development and is presumably secondary to ampullary injury resulting from obstructive uropathy. This is most often encountered in children with posterior uretheral valves or ureteroceles. In the more severe type the bladder is markedly distended, the ureters are distended and tortuous, and the kidney consist of large numbers of cysts of varying size. In milder forms, in which interference with outflow occurs later in embryogenesis and in which the obstruction can be relieved soon after birth, cysts occur only in the last one or two generations of nephrons. The cysts are usually subcapsular in location inasmuch as the youngest nephrons seem to be the most vulnerable to the effects of back pressure, and these nephrons are usually closer to the surface of the kidney (Figure 8). The extent of renal damage depends on the degree and duration of obstruction, and all structures may be normal except for the terminal portions of the collecting tubules and their associated nephrons.

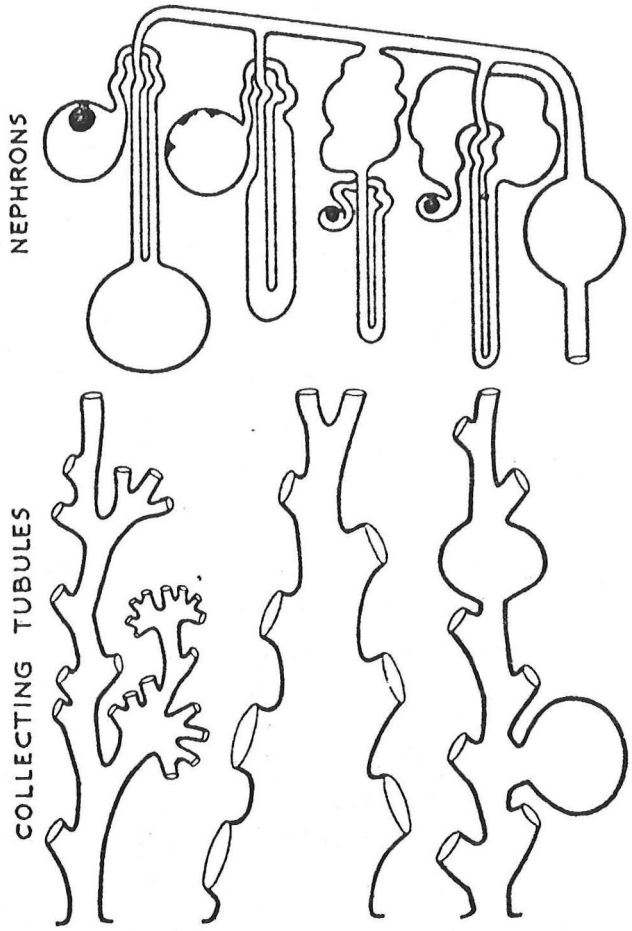


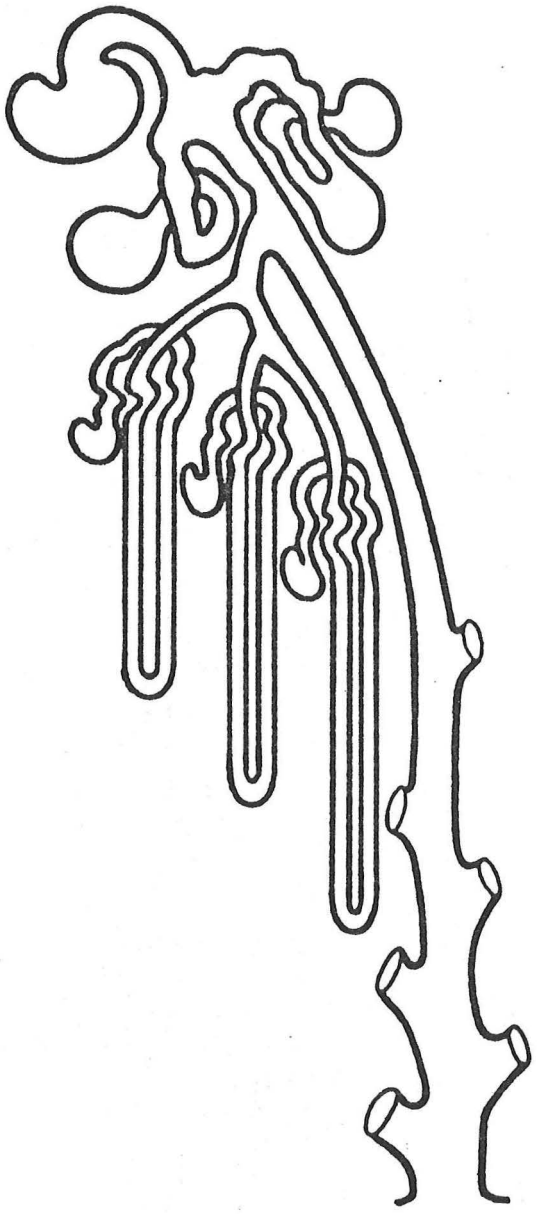
Fig. 8: POTTER TYPE IV CYSTIC DISEASE

Cysts located peripherally or in subscapsular location.

Fig. 7: POTTER TYPE III CYSTIC DISEASE

(Adult Polycystic Disease)

Both normal and abnormal collecting tubules coexist with cysts in nephron.



III. CLASSIFICATION OF RENAL CYSTIC DISEASES

The following is a comprehensive classification of cystic renal disease provided by Bernstein (4).

TABLE 1

CLASSIFICATION OF RENAL CYSTS

I. Renal dysplasia
   - A. Multicystic dyplasia
     1. Unilateral multicystic kidney
     2. Bilateral multicystic dysplasia
   - B. Focal and segmental cystic dysplasia
   - C. Cystic dysplasia associated with lower urinary tract obstruction
   - D. Familial cystic dysplasia

II. Polycystic disease
   - A. Infantile polycystic disease
     1. Polycystic disease of early infancy
     2. Polycystic disease of childhood
     3. Congenital hepatic fibrosis
   - B. Adult polycystic disease

III. Renal cysts in hereditary syndromes
   - A. Meckel's syndrome
   - B. Zellweger's cerebrohepatorenal syndrome
   - C. Jeune's asphyxiating thoracic dystrophy
   - D. Tuberous sclerosis complex and Lindau's disease
   - E. Cortical cysts in syndromes of multiple malformations

IV. Renal cortical cysts
   - A. Diffuse glomerular cystic disease
   - B. Peripheral cortical microcysts
   - C. Juxtamedullary cortical microcysts
   - D. Simple cysts, solitary and multiple

V. Renal medullary cystic disorders
   - A. Medullary sponge kidney
   - B. Medullary cystic disease complex
     1. Familial juvenile nephronophthisis
     2. Medullary cystic disease
     3. Renal–retinal dysplasia

VI. Miscellaneous parenchymal renal cysts
   - A. Inflammation and necrosis
     1. Medullary necrosis
     2. Lithiasis
     3. Tuberculosis
     4. Echinococcosis
   - B. Neoplasia
     1. Cystic degeneration of carcinoma
     2. Multilocular cystadenoma (benign cystic nephroma)
     3. Dermoid cyst
   - C. Endometriosis
   - D. Traumatic intrarenal hematoma

VII. Extraparenchymal renal cysts
   - A. Pyelogenic cyst (pelvic diverticulum)
   - B. Parapelvic cyst (lymphangiectasia)
   - C. Perinephric cyst

IV. THE MORPHOLOGY OF RENAL CYSTIC DISEASE

A. Renal Dysplasia

By conventional pathologic terminology, "dysplasia" connotes any disturbances in growth or development. In this regard, renal dysplasia designates a very broad collection of abnormalities of renal development. An acceptable definition of renal dysplasia is that it represents a disturbance

of nephrogenesis which results in the conversion of all, a segment, or multiple microscopic foci of one or both kidneys to structures which do not recapitulate any stage in normal nephrogenesis. Microscopic features include spaces lined by cuboidal to columnar epithelium unlike that of any segment of the developing nephron and encompassed by mantles of variably differentiated mesenchyme; bizarrely branching ductular structures lined by cuboid or flattened hyperchromatic epithelium, again unlike any segment of the developing nephron; and disontogenic interstitial tissue including dilated blood vessels, hematopoietic tissue, adipose tissue and most characteristically, spicules of hylan cartilage. Beyond infancy cartilagnous elements may calcify or ultimately ossify (5,6).

Microscopic features of renal dysplasia so defined are most frequently associated with unilateral malformations of the ureter, either atresia or extreme stenosis. In these circumstances, the metanephrogenic mass on the relevant side either regresses entirely or becomes totally dysplastic. Certain epithelium lined structures in the dysplastic mass very frequently undergo cystic dilatation producing a grossly or clinically appreciable multicystic mass. This phenomenon comprises the urologic syndrome of "unilateral multicystic renal disease". A less frequently recognized but nonetheless characteristic situation formerly designated renal aplasia, is that in which the renal mass on one side is represented only by a flat disc of grossly fiberous tissue which microscopically presents the features of renal dysplasia described above but lacks gross cystic dilatation of any element.

On rare occasions, total renal dysplasia may be bilateral. In these uncommon cases, the clinical manifestations resemble those of renal agenesis even with the presentation of atypical facies. Distinction from renal agenesis may not be possible clinically if dysplastic masses are not palpable in either renal fossa.

Unilateral total renal dysplasia is almost invariably a sporatic malformation. Unilateral total renal dysplasia constitutes the most common abdominal mass palpable in the newborn.

Occasionally, grossly discrete segments of one or both kidneys may present histologic features of renal dysplasia as defined above. These examples of "segmental renal dysplasia" have been associated with duplication of renal collecting systems and drainage of the supranumerary system by an ectopic ureterocele (7).

A number of other abnormalities of development may also occur in conjunction with dysplastic kidneys. Abnormalities of cardiac septation, particularly isolated ventricular septal defect; intestinal atresia, particularly duodenal atresia; and abnormalities enclosure of the neural tube, notably lumbosacral meningomyelocele, conspiculously concentrate in series of cases with unilateral renal dysplasia. This concentration of abnormalities probably exemplifies the general principle that abnormalities of ontogenesis tend to be correlated more with the period of the insult than with its nature. Table 2 lists three major syndromes of multiple malformation associated with generalized cystic dysplasia (8).

Cystic dilatation of renal glomeruli is a component of renal dysplasia, particularly that form of dysplasia which results from renal obstruction during nephrogenesis. Often in such cases glomerular cystic

dilatation is most severe in most peripheral glomeruli as if the more completely elaborated nephron of more mature units somehow suppressed whatever deleterious influence obstruction brought to bare upon shorter simpler nephrons.

TABLE 2

CYSTIC RENAL DYSPLASIA
AND
BILIARY DYSGENESIS

Meckel's syndrome	Microcephaly, posterior encephalocele, ocular abnormalities, genital abnormalities, polydactyly, cleft palate, cleft lip, gross hepatic cysts
Jeune's syndrome	Osteochondrodystrophy with dwarfism, small thorax with asphyxiation
Zellweger's syndrome	Hypotonia, high forehead, cerebral maldevelopment with pachygyria and micropolygyria, ocular abnormalities, stippled epiphyses, hypospadias and undescended testes, hepatic hemosiderosis

B. Polycystic Disease

Renal polycystic disease may be defined as familial disorders in which functionally significant portions of normally differentiated kidneys are replaced by cysts. Clinical, genetic and morphologic considerations distinguish APCD from IPCD. The latter disorder appears at present to be phenotypically and perhaps genotypically pleomorphic.

Infantile Polycystic Renal Disease

IPCD differs clinically, functionally, genetically and morphologically in its natural history from the adult form of renal polycystic disease. IPCD is less common than APCD.

Kidneys afflicted with IPCD are enlarged and may weigh as much as 100 grams a piece in a newborn infant. The kidneys maintain a renoform shape and are smooth. Malformations of the collecting system are not usually described. Small opalescent dots about 1 mm in diameter may be visible on the surface of the kidney. Microscopic examination reveals that cystic expansion is recognized grossly on the surface of the kidney are acutally enormously expanded collecting ducts that terminate beneath the renal capsule. Wedges of normally defferentiated parenchyma are interposed among these dilated spaces. Considering that the normal parenchyma is dilated in renal masses perhaps ten times normal size, normal parenchyma is probably normal in amount. As noted previously, this disorder conforms to the Potter classification of renal cystic disease Type I.

Extrarenal lesions associated with the IPCD are relatively homogeneous. All cases appear to have a diffuse lesion in the liver consisting of elaborately branching biliary ductules in the ultimate portal triads. In newborn infants, biliary ductules are embedded in immature mesenchymatous tissue which,

in older individuals, assumes the character of collagenized fibrous tissue. These epithelium lined structures are not usually recognizable as cysts. The lesion has been diffuse, involving every portal space in every completely reported case.

Renal Cystic Disease Associated With Congenital Hepatic Fibrosis

During the last two decades a clinical syndrome has gradually emerged, characterized by the insidious appearance in adolescence or young adulthood of complications of portal hypertension: abdominal swelling due to recurrent unexplained ascites, appearance of abdominal collateral venous channels, or, most characteristically and significantly and unherald bleed from ruptured esophageal varices (9). Gross paramaters of liver function are usually well preserved. The disorder appears to be familial, siblings often being involved. Pathologic examination of liver has shown variable abnormalities ranging from diffuse expansion of portal triads by proliferating biliary ductules embedded in immature mesenchyme or collagenous fibrous tissue, to multiple cystic expansions lined with billiary epithelium. There is some suggestion that the variability of hepatic lesions is age dependent or perhaps genotypically determined. Hepatic parenchyma does not typically show proliferative changes sufficient to justify the diagnosis of cirrhosis. A few patients have had pulmonary lesions, particularly pulmonary hypertensive vascular lesions. This syndrome has come to be referred to as congenital hepatic fibrosis. Few of these patients have had renal functional impairment, and detailed pathological descriptions of renal tissues from patients who present with the hepatic abnormality are hard to find. In fully half of the reported cases of congenital hepatic fibrosis the kidneys have been normal by fully competent pathological examination. Thus, the pathologic anatomy of renal cystic lesions in patients with congenital hepatic fibrosis is poorly characterized, to say the least. Frequently when tissue has been available, the renal lesion is consistent of a few thin walled spherical cysts scattered through the renal parenchyma (10). In most cases, authors tend to distinguish between IPCD which appears invariably to be associated with an hepatic lesion from congenital hepatic fibrosis in which the kidneys may or may not be cystic. Currently, congenital hepatic fibrosis is regarded as a pleomorphic, clinical pathologically defined disorder. About half of those afflicted have normal kidneys. Approximately half have an adequately characterized cystic kidneys. Of these, exceptionally prolonged survivors with IPCD contribute a few (11).

Adult polycystic disease will be discussed below.

C. Renal Cysts In Hereditary Syndromes

Renal cysts are encountered in several heredity syndromes (Table 3).

Zellweger's cerebrohepatorenal syndrome
Jeune's asphyxiating thoracic dystrophy
Autosomal trisomy syndromes, D and E
Oral–facial–digital and lissencephaly syndromes
Goldenhar's and Marden–Walker's syndromes
Ehlers–Danlos' syndrome
Congenital cutis laxa
Chromosomal translocation syndromes
Short rib–polydactyly syndromes

TABLE 3

RENAL CORTICAL MICROCYSTS IN SYNDROMES OF MULTIPLE MALFORMATIONS

Most such syndromes are associated with only minor renal involvement, usually in the form of peripheral cortical microcysts beneath the capsule and along the columns of Bertin. The lesions are trivial, not visualized radiographically, and rarely have clinical importance. The cysts are commonly localized within glomeruli and also within convoluted collecting tubules (12-14). The abnormal structures contain poorly differentiated epithelium, which imparts a primitive histologic appearance, and the cystic changes are often accompanied by both involutional and proliferative changes in the same and adjacent structures. Association of cysts with involutional changes in the peripheral cortex suggests damage to immature nephrons; the association in some instances with hypoplastic tubular segments suggests arrested nephrogenesis. The distribution of these lesions also indicates that the pathogenetic event had been limited in time, occurring relatively late in gestation. Potter has interpreted these findings on microdissection to indicate multiple abnormalities of ductular and nephronic development. The abnormality lacks a suitable terminology. The term "micro-cystic disease", used in connection with a form of congenital nephrotic syndrome, and the term "multicystic kidney", customarily used to signify a form of cystic dysplasia have both thereby been preempted. In any case, these cystic lesions should not be confused with polycystic disease.

Small cortical cysts are encountered in approximately 1/3 of infants with Tristomy D, arising within peripheral glomeruli and tubules. Cysts are less common with Trisomy E perhaps on the order of 10%, an involution and atrophy of individual nephrons are more obvious. Similar cortical microcysts have been described in association with numerous other malformations: Oral-Facial-Digital syndrome (15), Lissencephaly syndrome (16), Goldenhar's syndrome (17), Marden-Walker syndrome (18), Ehler-Danlos syndrome (19), congenital cutis laxa (20), and chromosomal translocation (21). In each of these the cysts appear to have been inconsequential, and these hardly deserve to be called polycystic disease. Small cysts have also been observed in the short rib polydactly syndromes of Majewski and of Saldino-Noonan (22). Medullary collecting ducts may on occasion also be cystic without a definite pattern (14).

In Zellweger's cerebrohepatorenal syndrome a wider spectrum of renal involvement has been observed (23). Cortical cysts are very common with a frequency of approximately 90% and with variation of tiny microcysts to gross cysts 1 cm in diameter. The larger cysts might on occasion be visible radiographically. In other cases the kidneys have undergone abnormal metanephric differentiation with generalized cystic dysplasia.

A similar spectrum of renal abnormalities has been observed in Jeune's syndrome and has been similarly interpreted (23). The abnormalities include in addition to peripheral cortical microcysts, diffuse tubular cysts and cystic dysplasia (24,25). The renal lesion in Meckel's syndrome has been a severely maldeveloped cystic dysplasia with marked nephrotic aplasia, although some early reports have included descriptions of hypoplastic kidneys (26). All three conditions have been associated with hepatic dysgenesis, an alteration in the small intrahepatic ducts resembling the lesion in infantile polycystic disease, and many cases of Meckel's syndrome had had enlarged grossly cystic livers.

The renal cystic lesion in tuberous sclerosis sits apart as a morphologically distinctive, perhaps unique abnormality (27,28). This lesion is different from and is much less common than renal angiomyolipomas, which are commonly a part

of the tuberous sclerosis complex. Large cysts are demonstrable radiographically, but their differentiation from the solid tumors may be difficult, unless arteriography is used to demonstrate demarked vascularity and abnormal blood vessels in these tumors. The cysts are lined by a remarkable epithelium of hypoplastic, eosinophilic cells that bear some resemblence to proximal tubular epithelium. The cysts can become quite large and produce renal impairment that antidates other clinical evidence of the syndrome.

A somewhat similar lesion has been found in a kidney in Lindau's disease (29,30). Cysts lined by variably hyperplastic epithelium occur in approximately 2/3 of cases and the patients are at risk of developing carcinoma. Nodular hyperplasia has also been observed within cyst walls, apparently progressing to clear cell carcinoma. The hyperplastic epithelium in Lindau's disease and in tubulus sclerosis are not exactly the same, but the malignant potential of the former raises the question of malignancy in the latter.

D. Renal Cortical Cysts

Cystic disease limited to the renal corpuscles is uncommon, and a characteristic clinical pathologic picture has not emerged. A coherent subclassification of glomerular cystic diseases is not yet apparent.

Peripheral cortical microcysts are found in cases of nonfamilial, presumably nongenetic malformations, often in association with congenital heart disease. They occur as isolated findings. They cysts are very similar to those cysts described in the discussion on heritable syndromes, involving glomeruli and tubules. Inner cortical or juxtamedullary microcysts are, of course, characteristic of one of the forms of early infantile nephrotic syndrome, which has been designated as microcystic disease.

The solitary simple cyst which can become quite large, is really a problem in differential diagnosis, and the radiographic criteria seem to be well established. Multiple cysts, particularly in middle-aged patients, do present a diagnostic dilemma: the differentiation of a nonprogressive, nonhereditary cysts from polycystic disease. This lesion will be discussed in greater detail in a subsequent section.

E. Miscellaneous Parenchymal and Extraparenchymal Cysts

Renal medullary necrosis with cavitation within the pyramid can obviously acquire the radiographic appearances of medullary cysts, and well-healed, well-epithelialized lesions look on gross and microscopic examination deceptively like ductal cysts. Nephrolithiasis with medullary necrosis can, as observed in the proceeding section, be difficult to differentiate from medullary sponge kidney complicated by a lithiasis.

Pyelogenic cysts, peripelvic cysts, and calyceal diverticulum are all synonymous, with the last being the most accurate description of the abnormality. Parapelvic cyst is often used anonymously with parapelvic lymphatic cysts and parapelvic lymphangiectasia. A perinephric cyst is a collection of fluid around the kidney known variously as hygroma perirenalis, perirenal effusion, hydrocele renalis and perirenal pseudocyst. They are in childhood usually subcapsular effusions secondary to urinary tract obstruction. They may in adults lie between the capsule and renal cortex or between the capsule and

perinephric fat. They are believed to result principally from extravasation of urine secondary either to trauma or urinary obstruction (11).

IV. ADULT POLYCYSTIC KIDNEY DISEASE

The best pathologic equivalent of APKD is a so-called Potter Type III described previously. For the purpose of this discussion it is relevant to note that Potter Type III is typified by several developmental abnormalities with abnormal calyces in a varying number of normal and abnormal tubules. Though any portion of the nephron may be involved in this disorder, the angle of Henle's loop, Bowman's space, and the collecting duct at the corticomedullary junction are most frequently affected.

A. Incidence Of Polycystic Kidney Disease

The autopsy frequency of APCD varies in different studies from 1 in 220 cases to 1 in 1,019 cases with a mean of close to 1 in 500 cases out of approximately 250,000 autopsies. The frequency of disease recognition in clinical material varies even more widely from 1 in 342 hospital admission to 1 in 4,933, with a mean of approximately 1 in 3,000. These data thus suggest that approximately 1 in 6 cases are recognized during life.

The problem is compounded further by the intrinsic inaccurcies of clinical as opposed to pathologic diagnoses. Many patients who reach old age with bilateral cystic disease and normal renal function almost certainly do not have true adult polycystic disease but rather multiple simple retention cysts.

B. Genetic And Developmental Aspects Of Polycystic Kidney Disease

The most definitive study on the genetics of polycystic kidney disease is that of Dalgaard and colleagues (31). In this study of 284 patients and families, he confirmed decisively the original suggestion of Cairns (32) that polycystic kidney disease is inherited in an autosomal dominant fashion, as opposed to the autosomal recessive inheritance of the infantile polycystic form. It also became clear from Dalgaard's study that the penetrance of the dominant polycystic disease gene is such that close to 100% of carriers will manifest the disease should they reach the age of 80. This does not mean that all patients will eventually become symptomatic from the disease, but rather that all, or nearly all, will show evidence of it morphologically. Another interesting feature is the apparent similarity in the chronologic and clinical manifestations of the disease within affected families. In view of this similarity and the highly penetrant nature of the gene it is suprising how often a positive family history cannot be elicited. In the study of Raul and Odell (33) 33% of the patients gave a definite family history and a further 25% or less convincing one. Only 10 of the 58 patients of Hatfield and Pfister (34) gave a positive family history. It is interesting that among these 10, only one patient was asymptomatic, tending to give credence to Dalgaard's contention that disease manifestations tend to remain constant within families and would thus hinder recognition in the family of an asymptomatic patient.

C. Clinical Course: Clinical Features And Natural History

The mean age of onset of polycystic kidney disease in adults is in the late 30's and early 40's, with the mean age of definitive diagnosis some five years later. There are three characteristic features of the disease

clinically-pain, abdominal swelling, and renal functional impairment. Within 6 months of the recognizable clinical onset of disease, 46% of the patients had experienced pain, 26% had palpable kidneys and in only 12% was there any evidence of chronic renal failure (35). This onset is depicted graphically in Figures 9 and 10. At any given age the risk of a patient suffering pain was greater

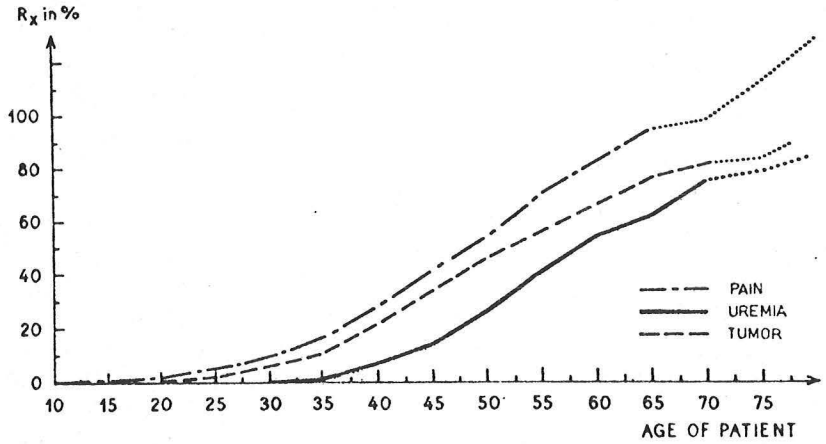


Fig. 9: RISK (ONSET) OF PAIN, UREMIA, AND PALPABLE KIDNEYS

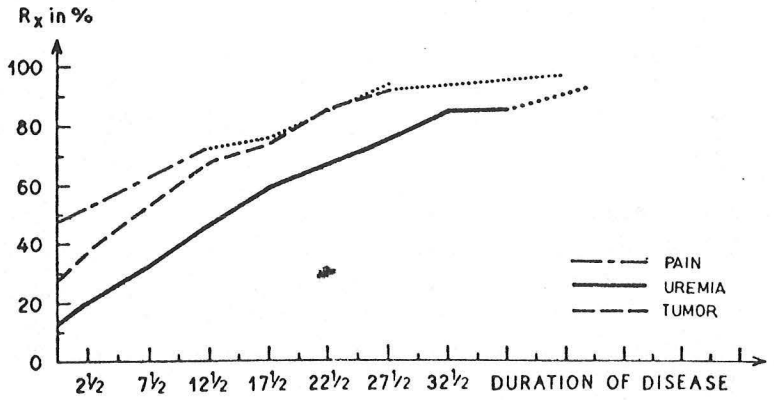


Fig. 10: RISK (ONSET) OF PAIN, UREMIA, AND PALPABLE KIDNEYS IN RELATION TO DISEASE DURATION.

than the risk of his having palpable kidneys; that in turn was greater than the risk of his having uremia. The risk of suffering from each of these features increase significantly with time. A pattern is thus established whereby pain antedates renal palpability, which itself antedates the onset of chronic renal failure.

In clinical practice it is extremely unusual for uremia to occur in patients in the absence of palpable kidneys. With repeat intravenous urograms it has been demonstrated that an increase in kidney size of greater than 2 cms was associated with a significantly greater incidence of chronic renal failure (35). In another recent study, kidney weight in symptomatic patients was almost twice that of asymptomatic patients (34). More than 50% of symptomatic patients had

at least one cyst of greater than 3 cms in diameter as opposed to only 20% of asymptomatic patients. Both of these studies support the contention that increase in cyst size is closely related to clinical symptomatology and decrease in renal function.

The mean pressure measuring the cysts in polycystic kidneys is 16 mm Hg (37) which is considerably higher than the value of 10 mmHg usually quoted for the proximal tubules in experimental animals (39). There is, however, no relationship between the size of cysts and the pressure within them (37). Gardner has proposed that cyst growth might be accounted for by the generation of osmotically active substances to the cyst contents. He detected amino acids in a number of cysts accounting for some 50-60 mOsm./Kg of cyst fluid osmolality. He felt that they might meet the necessary criteria for osmotic effectiveness in cysts (39).

Pain is the most frequent complaint voiced by patients with adult polycystic disease. It occurs in approximately 50% of the patients with this disorder. Characteristically the pain is a nagging, dull aching lumbar or lateral abdominal pain which is frequent unilateral and may radiate to the back, epigastrium or suprapubic area. Relationship to exertion and other variables is inconsistent as is the success of measures for pain relief. The theory of pain etiology suggested earlier, swelling of cysts producing pressure or stretch of the renal parenchyma or capsule, is attractive, though perhaps simplistic. Other theories for pain etiology include excessive weight of the enlarged kidney (40), pressure on adjacent organs (35, 41, 42), and traction on the renal pedicle (42). Sudden excaberation of pain may be due to hemorrhage into a large cyst or acute pyelonephritis. Persistent severe pain can be due to one of the more greatly enlarged cysts. Colicky pain is not uncommon and occurred in 18% in Dalgaard's series (31). This kind of pain is frequently the result of ureteral obstruction by a stone or blood clot, although frequently no specific cause can be determined.

Hematuria of varying severity is second only to pain in its frequency during the course of the disease, occurring in 25-50% of cases as a presenting complaint. Hematuria may be microscopic, macroscopic, intermittent, or virtually continuous. Massive hematuria may be accompained by a clot, colic, and ureteral obstruction. Though frequently precipitated by trauma or by physical exertion, its specific etiology in most cases is not clear-cut. It is also unclear why hematuria should be so much more common in polycystic disease than in other forms of renal cystic disease.

Proteinuria is without question the most frequent laboratory finding in polycystic disease, occurring in 70-90% of the patients (31, 42). In most early studies of the disease assessment ot proteinuria was quantitative only and the general conclusion was drawn that is severity was variable but usually slight. In most cases proteinuria is less than 2.0 grams per day. Of 122 patients in whom a quantitative estimation of proteinuria was made in Dalgaard's series, in only 3 was there greater than 5 grams per day (31). A minority of cases have been reported who develop the nephrotic syndrome. The coexistance of another renal disease must be considered when proteinuria is heavy.

The occurrence of renal colic from renal stones in polycystic disease is relatively common, occurring in approximately 10% of patients. The frequency

is suprising in view of the concentration defects seen in the disease and may be a reflection of anatomic distortion or of stagnation of urine. No data are available as to the chemical nature of the stones. Hamburger et al point out that the stones may contain largely uric acid and hence be translucent (43).

A palpable abdominal mass is one of the cardinal features of polycystic kidney disease. Bilateral palpable masses are present in 50-80% of the cases and a single palpable kidney in some (15-30%). Kidneys may enlarge asynchronously during the course of the disease and this probably accounts for many of the patients reported by Rall and O'Dell (44) to be suffering from unilateral polycystic kidney disease. Very rare cases of what is claimed to be true unilateral polycystic disease have been described. Typically the palpable polycystic kidney has a cobblestone consistency owing to cysts on the anterior surface, but it may feel far more smooth. In many cases the kidneys move with respiration or they may be fixed by a perirenal adhesion. Even in patients where because of tense abdominal masculature or obesity, the enlarged kidneys cannot be palpated. There is often a fullness and feeling of resistance on lateral abdominal palpation.

The problem of malignancy in PCKD is a difficult one (45) and will be discussed under complications of PCKD.

D. Complications Of Polycystic Kidney Disease

1. Cysts In Other Organs-Hepatic Involvement

A finding of cysts in organs other than the kidney is so typical of polycystic kidney disease that some authors cast doubt of a diagnosis in their absence (49). Cysts have been described in liver, pancreas, lungs, spleen, ovaries, testes, epididymis, thyroid, uterus, broad ligament, and bladder.

Of these, however, hepatic cysts are by far the most common, occurring in from 20-46% of patients. Polycystic kidney disease occurs in approximately 50% of patients with polycystic disease of the liver. Cysts in organs other than the liver occure in approximately 2% of patients. It is difficult to know if their occurrence is merely a chance finding. (Tables 4 and 5).

TABLE 4

INCIDENCE OF CYSTIC LIVERS IN PATIENTS WITH POLYCYSTIC KIDNEYS

STUDY	CYSTIC LIVERS/ POLYCYSTIC KIDNEYS	PERCENT
LeJars	-/-	27.0
Luzzatto	5/90	5.5
Johnson	11/46	24.0
Oppenheimer	4/14	28.5
Rall & O'Dell	15/46	33.0
Dalgaard	69/173	40.0
Brown	8/36	22.2
Feldman	50/169	34.3
Williams	6/8	75.0
	168/582	28.9

TABLE 5

INCIDENCE OF POLYCYSTIC KIDNEYS IN PATIENTS WITH CYSTIC LIVERS

STUDY	CYSTIC KIDNEYS/ CYSTIC LIVERS	PERCENT
Moschowitz	75/85	88.2
Comfort and Gray	13/24	54.0
Feldman	193/374	51.5
Davis	152/499	30.5
	433/982	44.0

There is a major difference in the hepatic involvement of adult and infantile polycystic disease. In infants there is fibrous cystic proliferation of bile ducts with frequently significant impairment of hepatic parenchymal function. However, in adults parenchymal architecture remains largely intact and clinical and biochemical parameters of hepatic function are typically within normal limits. The liver cysts in adults are usually asymptomatic although rarely they may appear to be a source of epigastric discomfort or biliary colic-like symptoms. Cases of hepatic failure from multiple cysts have been described, as has death from infected cysts (50,51). Both the latter complications are however, extremely rare.

2. Intracranial Aneurysm

The coexistance of intracranial aneurysms in the region of the circle of Willis was reported soon after an original description of polycystic kidney disease and has been described frequently since (61,62). Intracranial aneurysm has been found at autopsy in 16-40% of patients with polycystic renal disease. The frequency of the association is unlikely to be the result of co-existant hypertension, since intracranial aneurysm is far less common in other forms of hypertension ($\sim$ 1%), including that associated with coarctation of the aorta.

Carotid angiography is certainly not practical in every patient with polycystic disease in clinical practice. Therefore carotid angiography should be considered in only those patients where there is clinical suspicion of an intracranial lesion, or where the occurrence of an aneurysm would be of particulary dangerous prognostic significance. Patients with recurrent migraine headaches or evidence of cerebrovascular disease, and young patients who survive ruptured aneurysms should be subjected to intravenous urography as part of their workup. Tables 6-8 detail pertinent facts about this relationship.

3. Hypertension

Hypertension (> 140/90) is very common in polycystic disease, occurring in 70-75% of all patients (31,33,34). In most it is relatively mild and susceptible to hypotensive therapy. The cause of the hypertension is unclear.

TABLE 6

INCIDENCE OF POLYCYSTIC KIDNEY DISEASE IN PATIENTS WITH RUPTURED ANEURYSMS AND/OR SUBARACHNOID HEMORRHAGE (SAH)

Study	Polycystics/ Aneurysms or SAH	Percent
Suter	5/27	18.5
Brown	20/362	5.5
O'Crowley	3/38	7.8
Bigelow	24/407	5.9
Sahs	2/12	16.6
	54/846	6.4

TABLE 7

INCIDENCE OF CEREBRAL ANEURYSMS IN PATIENTS WITH POLYCYSTIC KIDNEYS

Study	Aneurysms/ Polycystic Autopsies	Percent
Suter	2/5	40
Poutasse and Gardner	3/5	60
Brown	6/36	16.6
Bigelow	3/18	16.6
	14 ~~29~~/64	19% ~~54~~.0

TABLE 8

INCIDENCE OF SUBARACHNOID HEMORRHAGE (SAH) IN PATIENTS WITH POLYCYSTIC KIDNEY DISEASE

Study	Death Secondary to SAH/ Polycystic Autopsies	Percent
Dalgaard	7/172	4.0
Brown	8/36	22.0
Bigelow	47/499	9.4
Poutasse and Gardner	2/5	40.0
	64/173	9.0

It cannot be explained merely on the basis of chronic renal disease since it occurs much more commonly than in chronic pyelonephritis with equivalent functional impairment. In one series, no specific abnormality in the renin angiotensin system was detected as the cause of the hypertension (68).

4. Acute and Chronic Renal Failure

Any sudden deterioration in renal function in a patient with polycystic disease should be considered potentially reversible until shown otherwise. In one series approximately 15% of patients developed acute reversible renal failure during the course of their disease, the majority being due to volume depletion (69). With one major exception the management of acute renal failure in polycystic disease is no different than that occurring in other forms of chronic renal failure. As mentioned previously, because of the danger of infection, bladder catherization and retrograde pyelography should be avoided and other diagnostic procedures used. The combination of acute renal failure, polycystic disease, and ascending infection is one which may be lethal. In a recent series of infected cysts in PCKD, 4 of 5 patients required surgical drainage of cysts after intravenous antibiotics failed (70).

In general patients with polycystic renal disease who develop chronic renal failure often feel better than patients with other forms of chronic renal failure. Most likely this is a reflection of the relative absence of anemia that typifies the terminal course of this disease. Erythrocytosis occurs in a variety of forms of renal disease, including polycystic disease, and is almost certainly due to increased circulating levels of erythropoietin. As polycystic disease progresses this tendency usually expresses itself as a relatively mild reduction in the hematocrit levels for the degree of renal function impairment.

Hyperchloremic acidosis is frequently described in polycystic disease and may be due to a defect in renal tubular amoniagenesis (71) recently reported to occur in the early stages of this disease. Gouty arthritis, rare in chronic renal failure despite high levels of plasma uric acid, also appears to be slightly more common in the uremic polycystic patient. It was recently documented that acute gouty arthropathy occurred in 4 of 11 adults with uremia secondary to polycystic disease (72). Many of the gastrointestinal symptoms such as nausea and vomiting which were described in early reports of the disease are in fact nonspecific reflections of end stage uremia. Hiatus hernia however, does appear to be distinctly more common in polycystic disease, presumably because of the large size of the cystic kidneys. Bailey and colleagues reported hiatus hernia in 11 of 18 uremic polycystic patients; in 4 patients who were nephrectomized the hernia disappeared (73).

5. Malignancy

The dectection of malignancy arising in polycystic kidneys presents a difficult diagnostic problem to the clinician. The clues to a malignancy in a patient with PCKD are listed in Table 9. The finding of a solid mass on ultrasound, CAT scan, or by nephrotomography warrents further investigation by renal arteriography in those cases in which malignancy is suspected.

The frequency of malignancy in PCKD is unknown. Table 10 lists the types of malignant cell types known to have had origin in PCKD. Of 11 patients

diagnosed before and after surgical exploration, 6 presented with hematuria and 5 with weight loss and abdominal pain (45). None of the patients presented with lymphadenopathy or hilar enlargement.

TABLE 9

CLUES TO THE PRESENCE OF MALIGNANCY IN PCKD

1. New onset of bleeding after a long asymptomatic period.
2. Intrarenal calcification.
3. A discrepancy in renal size.
4. Solid mass by ultrasound, CAT scan, or nephrotomography.
5. Unexplained weight loss, fever, night sweats.

TABLE 10

MALIGNANT CELL TYPES IN PCKD

1. Renal cell carcinoma (majority of cases- may be unilateral or bilateral, unicentral or multicentral).
2. Angiomyosarcoma (74).
3. Fibrosarcoma
4. Malignant cyst adenoma (45).
5. Transitional cell carcinoma (75).

The association of PCKD and neurofibromatosis has also been made, although infrequently (76). A better-known association is that of renal cell carcinoma, polycystic kidneys, and von-Hippel-Lindaa disease (77). Hence, patients with PCKD should be screened for neurocutaneous manifestations, such as cystic tumors in the posterior fossa.

6. Infections In Polycystic Kidney Disease

From 50-75% of all patients with polycystic disease develop urinary tract infection of varying severity during the course of their illness (42,35,46), 35% of the patients studied by McLamara had evidence of severe pyelonephritis (47). The patients afflicted are more commonly women and the clinical manifestations vary from asymptomatic pyuria to those of typical pyelonephritis and pyonephrosis. Apart from the direct morbidity and mortality of these complications, it is possible that infection also plays an important role in the deterioration of renal function seen in the disease. Overt pyelonephritis and pyonephrosis is certainly not an uncommon event during the course of polycystic disease. Intra-renal infection may accelerate the duration of renal function in this order (47).

With regard to susceptibility to intrarenal infection, it has been shown that in experimental models of renal cystic disease intravenous injection of 10-6 E. coli organisms resulted almost universally in frank pyelonephritis, whereas intrarenal infection was rarely observed in control rats subjected to the same bacterial challenge (48). This enhanced vulnerability to renal infection, which likely occurs as a consequence of structural derangement leading to intrarenal obstruction, it is obvious that procedures increasing the risk of either ascending or hematogenous renal infection (i.e., bladder catheterization and cystoscopy), should be avoided. Retrograde pyelography should likewise be avoided in polycystic disease since necessary clinical information can usually be obtained by intravenous urography and ultrasonography except in rare cases. Once an intrarenal infection is established, there is considerable risk of bacteremia. In a recent series of infected cysts in PCKD, 4 or 5 patients required surgical drainage after I.V. antibiotics failed (70).

In a recent report of cyst fluid antibiotic concentrations in PCKD, proximal (n=61) and distal (n=16) nephron antibiotic concentrations were compared (78). Proximal cysts are defined as those cysts with a cyst fluid: serum sodium ratio $\geq$ 0.9; distal cysts are those with a ratio $\leq$ 0.2 (79). As shown in Figure 11, the majority of cysts punctured were proximal. As indicated

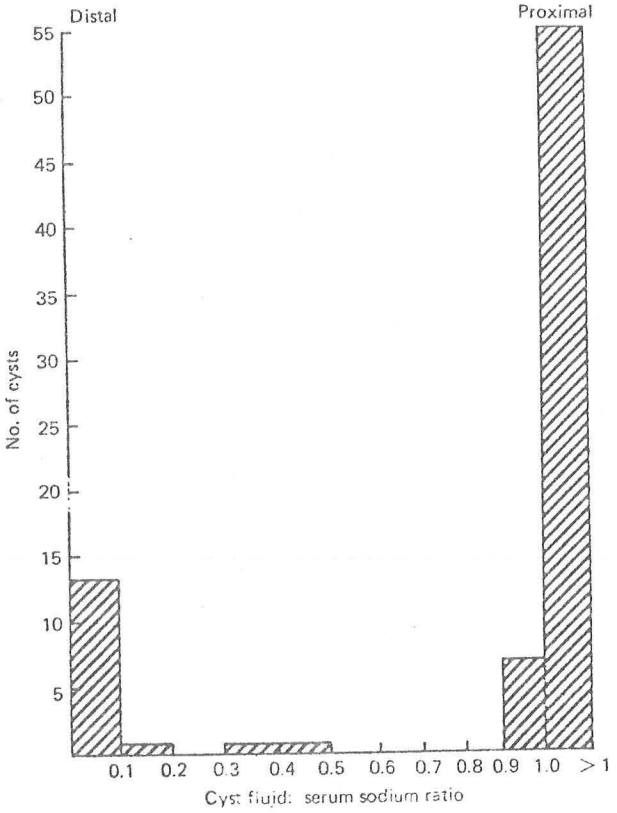


Fig. 11: PROFILE OF 79 ASPIRATED CYSTS

in Tables 11 and 12, relatively low cyst to serum levels of gentamicin (26%), cepharin (19%), and ticarcillin (12%) were observed. This concentration was unrelated to the creatinine clearance in any patient. In general, higher antibiotic concentrations were observed in proximal cysts. Thus, these results help to explain the poor clinical response to antibiotics seen in many PCKD patients with cyst infections. Further, gentamicin and ticarcillin provided the best cyst antibiotic levels.

TABLE 11

CONCENTRATIONS OF ANTIBIOTIC LEVELS
BETWEEN PROXIMAL AND DISTAL CYSTS

Drug	C_{Cr}[a] ml/min	In serum μg/ml	In cyst[b] μg/ml	Ratio of cyst:serum
Gentamicin				
patient 1	<5	3.1	1.3 (4)	0.42
patient 5	106	1.8	0.46 (9)	0.26
patient 6	<5	2.0	0.62 (20)	0.31
Cephapirin				
patient 2	15	105.0	15.5 (3)	0.15
patient 1	<5	27.0	10.6 (31)	0.39
patient 5	106	6.3	1.7 (9)	0.27

[a] No relationship between the creatinine clearance (C_{Cr}) and the cyst drug levels is apparent.

[b] Numbers in parenthesis indicate number of cysts sampled.

TABLE 12

COMPARISON OF ANTIBIOTIC LEVELS BETWEEN
PROXIMAL AND DISTAL CYSTS

Drug	No. of patients	In serum μg/ml	In cyst fluid[a] μg/ml Proximal	Distal
Gentamicin	3	2.3	1.04 (19)	0 (14)
Tobramycin	2	3.7	0 (2)	0 (3)
Cephapirin	3	46.0	8.1 (42)	38 (1)
Ticarcillin	1	400.0	135.0 (7)	0 (13)

[a] Numbers in parentheses indicate number of cysts punctured.

E. Tubular Function In Polycystic Kidney Disease

Studies of tubular function have been performed in a number of recent studies. Martinez-Maldonado and colleagues demonstrated a defect in maximal urine osmolality (Umax) in patients with PCKD and renal insufficiency and family members with cysts but without renal insufficiency (80). Family members without demonstrable cysts had normal Umax. Urinary dilution was normal

in all groups of patients. The authors concluded that the presence of cysts in medullary collecting ducts caused this early abnormality in renal function; and that the normal diluting capacity indicated that the ascending limb of Henle's loop functioned normally. Thus, a defect in Umax is the earliest sign of tubular dysfunction in patients with PCKD.

A defect in urinary amonium excretion and urinary acidification has also been reported in PCKD patients with moderate ($Cl_{CR} \simeq 70$ ml/min) renal functional impairment (81). Heiseman et al (82) have recently reported solute composition, volume, and hydrostatic pressure in cysts from 8 patients with PCKD. Irrespective of the degree of renal impairment, proximal cysts had sodium, potassium chloride, hydrogen ion, creatinine, and urea values virtually equal to their respective sera, whereas distal cysts had sodium and chloride concentrations lower and potassium, hydrogen ion, creatinine, and urea concentrations greater than serum (see Figure 12 and Table 13). Transmural hydrostatic pressures were similar in proximal and distal cysts and were not different from normal intratubular pressures. These studies support the view that cysts are derived from massively dilated segments of nephrons and collecting tubules that qualitatively maintain their basic solute transport functions throughout the life of the patient.

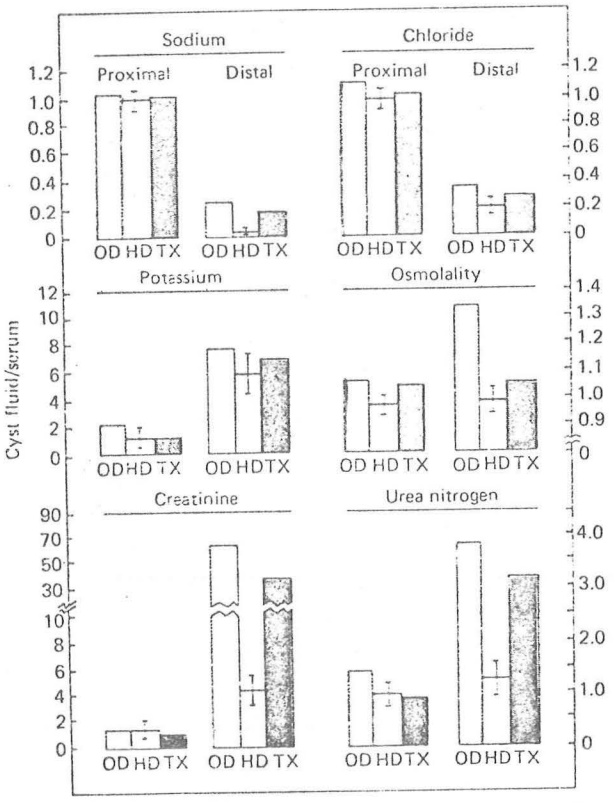


Fig. 12: CYST FLUID/SERUM RATIOS IN PROXIMAL AND DISTAL CYSTS

HD = hemodialysis patient
TX = transplant patient
OD = organ donor patient

	Proximal *mmoles/liter*	Distal *mmoles/liter*
Na	138	4.8
K	5.1	25.3
Cl	96	18.3
PO_4	5.1	15.1
Ca	3.9	4.0
Glucose	5.8	14.1
Urea	25	32.9
Creatinine	1.7	4.3
"Hippurates"	2.8	1.4
Total	*283.4*	*120.2*
Osmolality, *mOsm/kg*	290	301

TABLE 13
NOMINAL COMPOSITION OF CYST FLUIDS IN AZOTEMIC PATIENTS

F. Treatment Of Polycystic Kidney Disease

Control of high blood pressure forms the major cornerstone of conservative treatment in polycystic patients, just as it does in other forms of chronic renal disease. Although there is no documentation of improvement of prognosis with control of blood pressure, the known effect of hypertension in the progress of the disease makes such treatment mandatory. Generally hypertension is relatively mild and amenable to standard drug regimens. The importance of prevention of infection has already been discussed, but deserves reiteration. The other measures designed to treat polycystic patients are similar to the treatment of other illnesses which result in chronic renal failure.

Particular attention should also be made of chronic drug regimens patients with chronic renal insufficiency are placed on. In this regard, analgesic medications, particularly non-steroidal anti-inflammatory agents, should be used with caution (83).

Indications for nephrectomy (Table 14) in polycystic patients include neoplasia, intractible bleeding, tubuerculosis, and, rarely, prior to transplantation.

TABLE 14

INDICATIONS FOR NEPHRECTOMY IN POLYCYSTIC KIDNEY DISEASE

1. Intractable bleeding
2. Neoplasia
3. Infection (Pyonephrosis, Tuberculosis)
4. (Rarely) Pre-Transplantation

G. Dialysis In Polycystic Disease

The complications of regular hemodialysis in 34 patients with polycystic disease reported by Lazarus et al (84) were not different from those of dialysis patients in general. Mild hypertension was common, but was easily controlled by maintaining an optimal extracellular volume and in no case was the hypertension severe enough to require a nephrectomy. There was, however, an increase in the incidence of gross hematuria and urinary tract infection which could be directly related to the underlying polycystic disease (84). Bilateral nephrectomy was required in two of the three patients with severe urinary tract infection and four of the patients with gross hematuria. In 4 patients hematuria was sufficiently severe to require additional blood transfusion and regional heparinization on dialysis; this problem became less severe with time. Despite these specific problems the kidney should be left in situ whenever possible. Removal of the kidneys led to a significant fall in hematocrit from a mean of 30.1% to 23.6% in the patients in the group studied by Lazarus; and the resultant increase in transfusion requirements is an obvious disadvantage. Fluid management is significantly facilitated in patients on dialysis

with kidneys in situ who continue to pass urine. The presence of extrarenal cysts seems to provide no source of problems during long-term dialysis.

In agreement with these observations, Chester et al (95) have noted that, in contrast with other types of renal disease leading to renal failure, patients with PCKD on dialysis have higher hematocrits (Figure 13), lower blood pressures (Figure 14), and improved survival on dialysis.

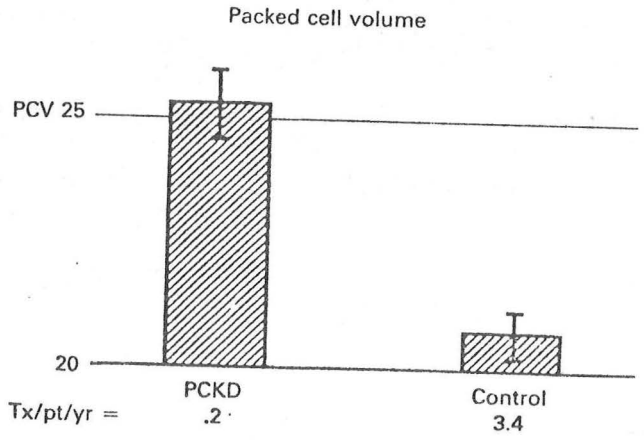
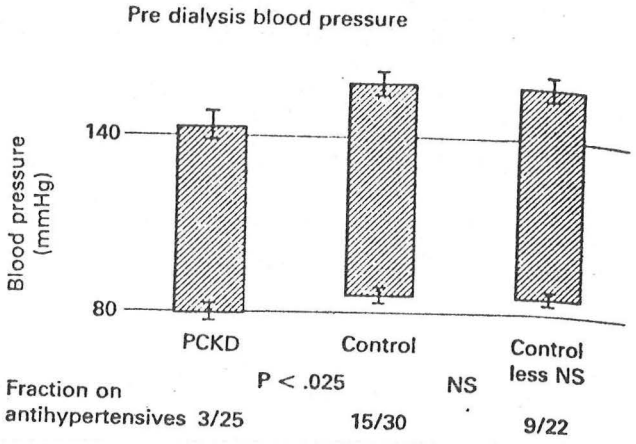


Fig. 13: HEMATOCRITS OF PCKD PATIENTS VS CONTROLS ON DIALYSIS

Fig. 14: BLOOD PRESSURES OF PCKD VS CONTROL PATIENTS ON DIALYSIS



H. Transplantation And Polycystic Disease

No major differences are seen in survival rates of patients with polycystic disease compared to patients with pyelonephritis or glomerulonephritis. (Figure 15). In the patients reported by Lazarus and colleagues (84) there did appear to be a high transplant rejection rate which was thought to be due to difficulty in obtaining suitable family donors and hence the reliance on cadaveric kidneys with the worst prognosis. The presence of extrarenal, particularly hepatic cystic disease, did not influence survival or present unusual problems. Specifically, the use of immunosuppressive drugs is not associated with increased laboratory or clinical evidence of altered liver functions or hepatitis.

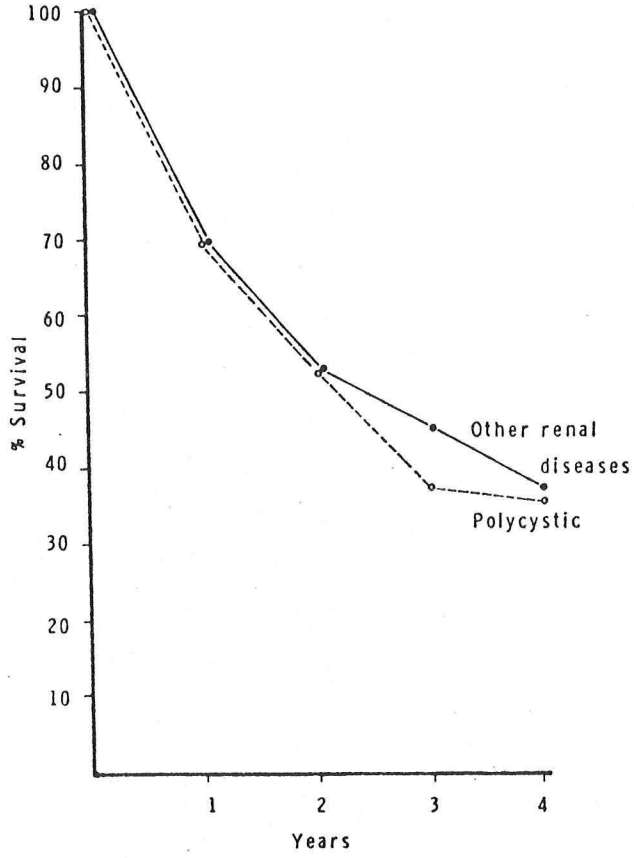
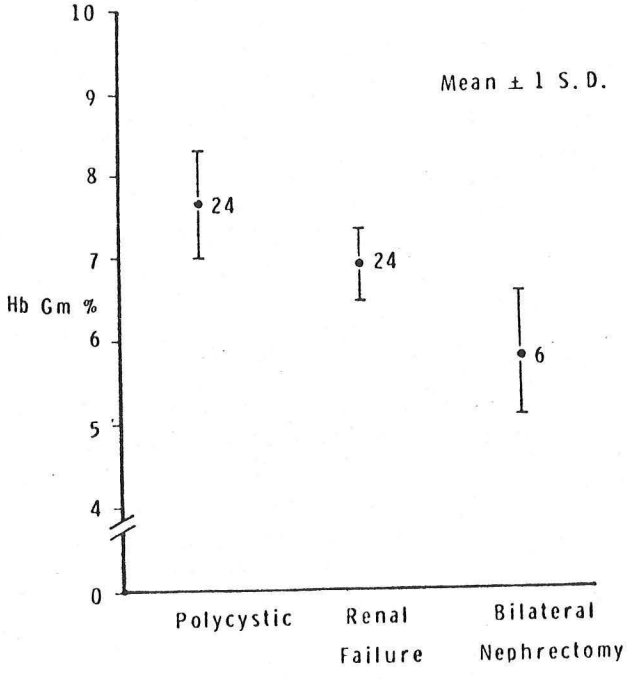


Fig. 15: PATIENT SURVIVAL AFTER TRANSPLANTATION

PCKD VS CRF

Pretransplant nephrectomy is not usually required in polycystic patients (96). In those patients not suffering from hematuria or urinary tract infection leaving the kidney in situ appears to be both safe and desirable (96). A fall in hematocrit was obviated in the nonnephrectomized group, and no particular problems were encountered during the transplantation procedure owing to the mass of the kidney. (Figure 16).

Fig. 16: MEAN HEMOGLOBIN CONCENTRATIONS IN PCKD, CRF, AND Nx PATIENTS PRIOR TO TRANSPLANT



Similar results have been recently reported by Michael et al (85) in 6 patients transplanted without prior nephrectomy. None of the patients had evidence of pretransplant infection, though one patient developed severe pyelonephritis in the post transplant period and required bilateral nephrectomy.

I. Early Diagnosis And Genetic Counseling In Polycystic Disease

The occurrence of polycystic kidney disease in approximately 1 out of 500 people makes it one of the most frequent of genetic disorders. Though the dominant inheritance of the gene and the pattern of its inheritance is well-established, its delayed onset and varied expressiveness makes genetic counseling difficult. The problem has recently been considered in depth by Fialkow (86). The typical question that might be asked by an asymptomatic patient of a polycystic parent is what are the chances of developing the disease and transmitting it. First, the probability that the patient carries the disease must be determined. To estimate this a 50% chance that the gene was carried at birth has to be modified for the fact up to the time of inquiry he has not developed manifestations of the disease. Were the patient 80 years old one could confidently say that the gene was absent since all carriers manifest the disease in some form by this age. At an intermediate age, however, this probability is difficult to assess, though the data of Dalgaard referred to earlier are of some help. The chances of just transmitting the disease to offspring are 50% of the chances of carrying the gene. Should children already be affected the patient is by necessity carrying the gene and the probability at birth that additional children carry the disease is 50%.

Lack of a family history does not exclude PCKD in symptomatic patients; when initially diagnosed, 25-50% of patients may be unaware of another case in the family (87). If present in another family member, the pattern of onset of PCKD is remarkably constant within families, a fact which helps in counseling. Characteristic pyelographic abnormalities are usually a first step to making the diagnosis. (Table 15). Ultransonography is now regarded as sensitive and specific as pyelography with nephrotomography in picking up asymptomatic carriers (87,88). Combing ultrasonography with nephrotomography probably offers the greatest

TABLE 15

COMMON PYELOGRAPHIC ABNORMALITIES IN PCKD

1. Round lucencies
2. Enlargement and scalloping of the renal outline
3. Caliceal elongation and distortion
4. Flask-shaped or bowl deformity of the calix
5. Displacement of longitudinal axis of the kidney

resolution of suspected lesions (89). No false negatives were observed with comparisons of ultrasonography to nephrotomography (see Tables 16 and 17).

TABLE 16

NUMBER OF POTENTIAL GENE CARRIERS WITH A POSITIVE DIAGNOSTIC TEST FOR APKD (ULTRASONOGRAPHY) PER AGE GROUP

Age group (years)	Investigated (no.)	Positive ultrasonography (no.)	%
< 10	2	0	0
11 - 20	20	3	15
21 - 30	20	11	55
> 30	10	3	30
TOTAL	52	17	33

Computerized axial tomography has also been utilized with success (87). In summary, by combining ultrasonography with a test of urinary concentrating ability, a sensitive and non-invasive diagnostic approach is achieved. Nephrotomography and CAT scans, are other useful diagnostic procedures, but have the disadvantage of radiation exposure.

TABLE 17

COMPARISON OF RESULTS OBTAINED WITH SONOGRAPHY AND IVP IN 43 PERSONS WITH A 50% RISK OF BEING A CARRIER OF THE APKD GENE

		Sonography Positive	Negative	Total
IVP	Positive	15	0	15
	Negative	1	27	28
	Total	16	27	43

J. Prognosis In Patients With PCKD

Four of the larger studies report life expenctancy from the onset of the first symptoms as between 4 and 13 years. This life expectancy is considerably reduced for patients over 50 years of age. The survival figures can be broken down further to take into account features of the disease. For example, in Dalgaards' series, 91% of the women and 70% of the men were alive 2¼ years after the kidneys were first palpated and 7% of the men and 3% of the women were alive 2½ years after the onset of uremia, though the criteria for diagnosis of uremia were not clearly defined. A similar relationship to the stage of the

disease has been described by Simon and Thompson (90). These data tend to confirm the concept of disease progression discussed earlier.

The life expectancy after the onset of uremia varies from 2-4 years in a large series, but these figures do not express the frequently observed observation that many uremic polycystic patients may have a particularly prlonged course. Hypertension, as stressed earlier, plays a very significant role in determining prognosis and, in the experience of Hamburger et al (91), it was the normotensive uremics only who could anticipate prolonger survival. The combination of hypertension with uremia or intracranial aneurysm is a particularly malignant one as life expectancy is 15 years less in hypertensive patients than in normotensive patients with these complications. These statistics do not take into account the optimism engendered by the role of dialysis and transplantation for polycystic patients, nor do they take into account the number of asymptomatic patients who have the disease. 32 of 58 patients reviewed by Hatfield and Pfister (92) were entirely asymptomatic.

V. JUVENILE NEPHRONOPHTHISIS AND RENAL MEDULLARY CYSTIC DISEASE

A. Introduction

In 1962 Stauss (93) drew the attention of North America to 18 cases of renal disease with characteristics sufficiently consistent to suggest a definite entity: anemia of insidious onset, a paucity of abnormalities on routine urinalysis, a defect in urinary concentrating ability, renal sodium wasting, and progressive renal failure terminating in early death. The post-mortem hallmark of the entity was small cortical medullary and medullary cysts in kidneys that were shrunken and scarred. Strauss labeled the condition cystic disease of the renal medulla. In 1964 Winberg (94) pointed out that with the possible exceptions of genetic transmission and renal cyst formation that features of the entity were shared by a group of cases reported from Europe under the title, "Familial Juvenile Nephronophthisis". Winberg suggested that the two conditions were the same. Subsequently most authors, including Strauss, agreed.

Two decades later much about the entity still remains unsettled. There are questions that concern the number of its genetic variants, the importance of medullary cysts to its diagnosis, and the characteristics that may typify it. Answers to these basic questions have been difficult to come by. This syndrome is not encountered frequently by any single nephrologist or a medical center. Subtle differences in presentation and evolution challenge the efforts to characterize and classify the disease. Thorn et al and Smith and Graham (97, 98) published what was generally regarded to be the first reported cases of a nephronophthisis-cystic renal medella complex. A search of the ensuing literature by Gardner (99) reveals at least 63 papers which described 238 individuals who presented with most or all of the characteristic symptoms and signs of a nephronophthisis-cystic renal medella complex. Both the awareness and recognition of the complex are increasing. Titles under which the syndrome appears in the literature are several and are listed in Table 18. Of the 238 reported cases 108 are male and 130 are female. This difference between the sexes are not different.

TABLE 18

SYNONYMS FOR MEDULLARY CYSTIC DISEASE

1. Juvenile Nephronophthisis
2. Cystic Disease of The Renal Medulla
3. Congenital Cysts of The Renal Medulla
4. Microcystic Disease of The Renal Medulla
5. Uremic Sponge Kidney
6. Fanconi's Nephronophthisis
7. Salt-Losing Nephritis
8. Renal-Rentinal Dysplasia
9. Polycystic Kidney (Medullary Type)
10. (Erroneously) Medullary Sponge Kidney

Sixty-seven propositus are described in which the family history is documented and positive for renal disease. There are reports of 29 additional individuals whose family histories are documented but are negative for renal disease. Finally, 13 case reports have appeared in which no family history is mentioned and from which, therefore, no conclusions concerning heredity can be drawn. Of the 67 families in which there is reasonable well-documented evidence of genetic transmission, a recessive pattern of inheritance is documented or seems likely in 56; a dominant patter has occurred in 11 of these 67 families.

The mortality of the disease is difficult to assess with precision; however this renal disease is terminated fatally or the need for dialysis or kidney transplantation in 155 of 238 instances. Most reports describe affected Caucasians or do not mention race, 1 black is reported.

B. Clinical Manifestations Of Medullary Cystic Disease

Polyuria, enuresis, and polydypsia are described in over 80% of the well-documented cases. In descending order of frequency, manifestations include: weakness and pallor in more than 60%; short stature and retarded bone growth in more than 40% (confined almost completely to reports of children and adolescents); no complaints in asymptomatic relatives of affected subjects; about 15% nausea and vomiting; bleeding, convulsions, and some signs of azotemia 10%. At the time of their initial reported work-up 82 of 110 patients or 75% were azotemic with blood urea nitrogens in excess of 30 mgs % or creatinines greater than 1.5 mgs %. Hypertension (a pressure greater than 140/90 mmHg) is documented in 28 cases of 110, or 31% of those in which blood pressures were measured. Arterial hypertension has been reported to disappear with the onset of renal sodium wasting.

Anemia (usually of the normochromic-normocytic type) is also a frequent feature of this disease. The degree of anemia correlates with the degree of renal failure in most cases. Urinary findings are traditionally considered scant in patients with this syndrome. 32% of azotemic patients had no protein, no blood, and no formed elements in their urines. An additional 61% had 1

or more of these abnormalities, but almost always present in small amounts: 1-2+ proteinuria, a few red or white blood cells, and occasionally hyaline or granular casts. However, significant urinary abnormalities can be encountered. Kyle (100) reported a case with 2.9 grams per day of protein uria- a degree of abnormality that is rare. Proteinuria of such extent probably should be considered a sign of other renal disease until proven otherwise.

Sodium handling by the kidney has been studied in approximately 35 cases of this disease. Sodium wasting was demonstrated in 24 of the cases and was not present in 11 cases. Salt wasting does not appear to depend on cyst formation.

C. Renal Pathology

A majority of reports in which renal pathology is described documents cysts in the medullary and cortical medullary regions of the kidney. Cysts elsewhere are not described, in contrast with polycystic kidney disease. Overall, kidneys are shrunken and scarred; microscopically they resemble those seen in chronic pyelonephritis. A nonspecific interstitial inflammation has often been observed histologically in medullary cystic disease. Other studies describe interstitial fibrosis in hyperplastic epithelium but no inflammatory cells. Clinical infection appears to be remarkably uncommon in this disorder and is not a major factor in the inevitable development of chronic renal failure.

Retinitis pigmentosa was observed in 7 cases from 3 families and accompaniment of medullary cystic disease. Retinal degeneration and cataracts have also been reported. Some investigators have noted the higher incidence of red or blond hair as an increased finding in patients with the nephronophthisis-cystic renal medullar syndrome. Adults with medullary cystic disease prior to the appearance of severe azotemia must be informed that the disease is likely transmitted as an autosomal dominant so that at least 50% of the future offspring are likely to be affected. Also, if living donor renal transplantation is being considered, genetically related potential donors must be screened carefully for signs of the disease. With juvenile nephronophthisis, the parents of affected children must be informed of the chances that future offspring of this marriage will also develop the disorder (25%), transmitted as a recessive trait.

D. Genetic Variance

Evidence supporting transmission of the nephronophthisis-cystic renal medella complex as an autosomal recessive trait is strong. There is also evidence to suggest recurrence of heterozygous state among recessive families. At least 10 instances among 4 families are reported in which the discovery of a urinary concentrating defect in one of the parents or siblings of affected offspring has raised the question of a heterozygous state. None of these individuals has been studied intensively and one always can question the results of a urinary concentrating test in which the margin for error by patient or laboratory is large. A clear difference in ages and onset and death exist depending upon the mode of inheritance. Dominantly inherited disease appears later and results in later death (Figure 17). The relationship between age and onset and mode of inheritance results in death in early

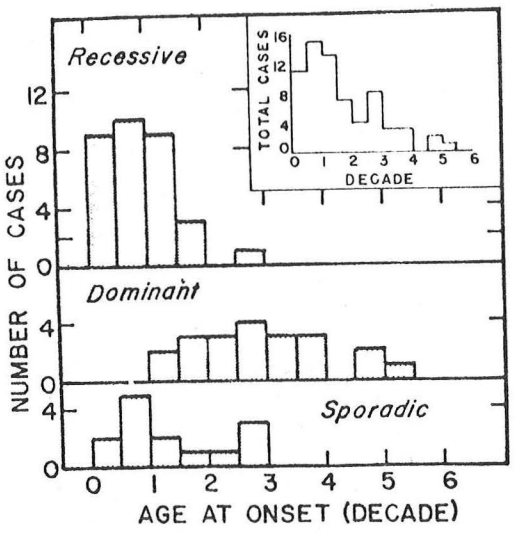


Fig. 17: AGE OF ONSET BY MODE OF INHERITANCE

years whereas dominant inheritance manifests itself in the latter decades of life. The nephronophthisis-cystic renal medulla complex has been reported in twins, evidently as the result of both recessive and dominant transmission. Juvenile nephronophthisis and adult medullary cystic disease have been reported to occur in the same families. Gardner reports that the average age at presentation of juvenile nephronophthisis is 10.5, with an average time to death or hemodialysis of 4.4 $\pm$ 1.5 years. He reports that the average age of onset of adult medullary cystic disease is 28.4 years, with a remarkably short period of 3.3 $\pm$ 0.8 years to either death or dialysis. The difference in apparent duration of the disease may reflect the greater likelihood of earlier diagnosis in the juvenile form because of obvious growth retardation.

VI. MEDULLARY SPONGE KIDNEY

A. Introduction

This disorder was described histologically as early as 1908 and radiographic features were first appreciated in 1938 (101,102). A decade later medullary sponge kidney was elevated to the rank of a clinical entity with distinctive radiographic and histologic features by Cacchi (a urologist) and Ricci (a radiology student). Over the next 25 years over 600 cases of medullary sponge kidney were reported in the world's literature. The term medullary sponge kidney is appropriate only because of common usage such as first application by Cacchi and Ricci, certainly not on the basis of anatomic resemblence to a sponge. More precise terminologies such as "precalyceal cannicular ectasia" or "cystic dilatation of renal collecting tubules" have been proposed.

B. Histopathology

Dilatation of collecting ducts may be apparent only microscopically or may be readily visible on gross examination as multiple cystic cavities up to 7.5 mm in diameter may be seen in one, a few, or all pyramids. Tubular

dilatation and cyst formation are strictly confined to medullary pyramids, especially to their inner papillary portions. The ectasia never progresses peripherally beyond the corticomedullary junction. The cortical columns of Bertin are normal in gross and microscopic appearance unless involved by changes of contiguous pyelonephritis or atrophy consequent to longstanding calculi and/or ureteral obstruction. The involved kidney is normal in size in most cases. Mildly ectatic collecting tubules may retain normal collumar epithelium in their intrapapillary portions, and high cuboidal epithelium in more proximal intramedullary regions. Increasing degrees of tubular dilatation produce cystic cavities often 1 to 3 mm and occasionally 5 mm in diameter; cysts usually communicate proximally with collecting tubules and distally with papillary ducts or directly with the corresponding minor calyx. Other factors which may influence the micropathology of the medullary sponge kidney are interstitial nephritis from longstanding obstruction of stones and analgesic addiction originating during initial painful episodes of urolithiasis. A distinctive pattern of intracavitary concretions clustered toward the papillary apices is apparent on microradiography of excised renal tissue, even in the 50% of medullary sponge kidney patients without evidence of nephrocalcinosis on conventional x-rays. Calculi may erode through cyst walls or widened papillary ducts, passing into the renal pelvis as free calculi. When analyzed, calcium phosphate stones predominate, though calcium oxylate and ammonium magnesium phosphate calculi have been seen.

C. Diagnosis

The diagnosis of sponge kidney is essentially radiographic (Table 19). Though the picture is variable, a sufficient number of principles exist to allow prompt recognition of this entity by the experienced radiologist or clinician. On excretory urography diagnostic alterations are limited to medullary pyramids - the renal cortex is normal. Ectatic medullary tubules and cysts may fill with contrast media on initial films prior to calyceal opacification. There is a persistance of medullary opacification throughout the examination, including delayed films. 77% of these cases are bilateral and multiple pyramids are involved in the majority of cases seen. Linear radiations ("paint brush" sign) consistent with tubular dilatation is also a helpful diagnostic feature. Calculi are clinically present at some time in about 60% of symptomatic cases and nephrocalcinosis is present to some degree in 40 to 60% of cases. Generally this takes the pattern of a spherical densely radiopaque cluster of opacification not more than 5 mm in size and located within ectatic ducts and cysts.

Long term radiographic follow-up indicates that the pattern of pyramidal opacification tends to remain constant in many individual cases, that evolution in the number and size of renal calcifications is the most common documented alteration, but that a small percentage develop radiographic features of pyelonephritis and/or hydronephrosis which appear as sequelae when complicating stone passage and infection supervene. Of 17 patients followed radiographically from 5 to greater than 20 years by Extrum and colleagues (101) only one demonstrated new cavities in previously uninvolved papillae, 2 revealed new cavities where previous concretions were present, and 3 demonstrated an increase in the size of stone-containing cysts. The limited evidence available would indicate that progressive ductular ectasia may occasionally occur especially as a consequence of extrusion of enlarging calculi. Clinical and experimental

data imply that tubular dilatation does not necessarily follow intratubular microcalculus formation, however.

TABLE 19

RADIOGRAPHIC FEATURES OF MSK

Constant	
Plain film	Normal sized or slightly enlarged (30%) kidneys
Excretory urography	Diagnostic alterations limited to medullary pyramids, especially papillary portions; absence of *cortical* cysts, calcifications, atrophy
	Ectatic medullary tubules/cysts fill with contrast media on initial films, prior to calyceal opacification
	Urographic pyramidal pattern visualized without ureteral compression, but frequently more distinct following this maneuver
	Persistence of medullary opacification throughout examination, including delayed films (after calyceal emptying)
	Constancy of urographic pattern on repeated examinations, except for the occasional sequelae of calculus migration, obstruction or infection.
Retrograde pyelography	Ectatic tubules/cysts either fail to fill or fill less prominently than with excretory urography
Nephrotomography	Usually fails to contribute to detail
Angiography	Noncontributory (usually normal)
Variable	
	77% bilateral; 23% unilateral
	Involvement of one pyramid (2%), a few pyramids (34%), multiple pyramids (36%), or all pyramids (27%)
	Urographic pyramidal opacifications may present multiple appearances: papillary blush (see text), linear radiations consistent with tubular dilatation, various cystic forms (Table 2). The pattern may be uniform within each involved pyramid and among all involved pyramids, or, more frequently, may present a morphologic mixture.
	Free calculi; clinically present at some time in about 60% of symptomatic cases
	Nephrocalcinosis: present to some degree in 40–60%; generally spherical, densely radiopaque, clustered within one or many papillae, minute to 5 mm in size, and located *within* ectatic ducts/cysts
	Enlargement of involved pyramids (about 50% of patients) with or without flattening of corresponding minor calyx
	Noncommunicating cysts beneath calyceal mucosa may present "blistered" appearance of small rounded radiolucent defects at papillary apices
	Radiographic signs of complicating pyelonephritis, ureteropyelocaliectasis, impaired urographic excretory capacity or "nonfunction" may be present

Calcifications are an acquired complication in sponge kidney. The radiographic picture of sponge kidney is usually characteristic unless

complicated severely by recurrent infection, stone formation, and by the sequellae of passage of calculi. Further it should be recalled that sponge kidney may coexist with any of the following: reports in literature documenting a few examples of sponge kidney complicated by renal tuberculosis, hyperparathyroidism, distal renal tubular acidosis, and papillary necrosis. An interesting recent report from this institution (104) documents the presence of absorptive hypercalciuria in 17 patients with sponge kidney and nephrolithiasis.

D. Incidence

The overall incidence of sponge kidney in the population is unknown. A urographic incidence of 0.5% has been established by some authors and, based on intravenous pyelography, an overall incidence of 1 in 20,000 has been proposed. This probably is an underestimant of the true incidence of this illness. The sexes appear to be equally involved and no obvious racial preponderance is apparent from the review of the literature. The average patient is diagnosed and in his 4th or 5th decade, though many are diagnosed in their 6th and 7th and a few in their 8th decades. A few cases in childhood have been well-documented. A symptomatic interval of 5 to 7 years prior to diagnosis is not unusual and may extend up to 30 years in some cases.

E. Clinical Characteristics, Course And Prognosis

It is generally concluded that sponge kidney per se is asymptomatic. Complicating calculus formation and infection are responsible for the great majority of presenting symptoms: ureterocolic or loin pain in roughly 50-60%; gross hematuria in 10-18%; urinary tract infection varying symptomatically from local uretheral or bladder symptoms to frank pyelonephritis in 20-33%. Smaller numbers of patients that had this diagnosis established as incidental findings at the time of intravenous urography for other conditions (hypertensive screening, abdominal tumors, etc) or during an investigation of the cause microscopic hematuria, still pyuria, limited proteinuria, or enuresis.

Although the clinical course is highly variable, at some time up to 1/3 of symptomatic cases in the literature have experienced recognizable urinary tract infection, roughly 30% have experienced gross hematuria, and approximately 60% have passed stones. Nephrocalcinosis is usually the most important manifestation of this disease. Hypertension does not occur in a proportion greater than in the general population. While asymptomatic intervals are the rule for a large number of patients, others present with recurrent clinical episodes of frequent stone passage and pain and hematuria and require hospitalization or urologic evaluation repeatedly.

An estimate derived from the literature would be that in as many as 10% of the patients with symptomatic sponge kidney the long-term prognosis would be regarded as poor. These are patients with chronic pyelonephritis complicating recurrent calcareous episodes, espically those with retained free concretions.

F. Renal Function

A decrease in GFR as assessed by creatinine clearance or inulin

clearance is reported to be present in 10 to 20% of patients. Chronic medullary dysfunction might be suspected from the anatomic lesion and its complications. Compromised concentrating ability is the rule, hypercalciuria is frequent (see ref. 104), diminshed acidification is occasionally noted, and 1 study suggests sodium reabsorption may be less than optimal in may patients with sponge kidney (105). Impaired concentrating ability was documented in 15 of 22 patients with bilateral sponge kidney and 18 of 21 patients investigated by another author. Urinary dilution is usually unimpaired. The impairment in acidification mechanisms does not occur in ever case in sponge kidney. Several different types of acidification abnormalities have been described in these patients, including distal renal tubular acidosis and incomplete renal tubular acidosis (106). Some are patients who have been shown to have isolated defects in ammoneogenesis. Coexistance of sponge kidney with complete distal renal tubular acidosis in an additional 3 patients. Defects in achievable hydrogen gradients, tritratable acidity or ammonia productions relate to primary tubular epithelial cell dysfunction per se in sponge kidney, or, more likely may reflect the effects of progressive complicating interstitial nephritis, a chance inheritance to unrelated disorders, or conceivably, though unlikely, primary renal tubular acidosis with secondary tubular dilatation due to calcareous disease.

G. Treatment

In 1966 Pyrah (107) developed a rationale for therapy in medullary sponge kidney disease. In his classification, Group I consists of patients with the characteristic urographic appearance of medullary sponge kidney, but free of urinary tract calcification. Usually free of symptoms or presenting infrequent signs of urinary infection or hematuria, these patients are encouraged to consume a high normal sodium and water intake to reduce the possibility of infection and calculous formation, to undergo routine urinalysis and culture at least yearly and immediately upon the onset of urinary symptoms so that antibiotic treatment may be instituted if appropriate, and to have abdominal films every 3 years to detect onset of complicating nephrocalcinosis. The prognosis for a middle age patient presenting in Group I would be considered excellent. A young patient diagnosed initially in Group I could progress to Group II or III with time.

Group II patients demonstrate pyramidal nephrocalcinosis in addition to the typical urographic changes of medullary sponge kidney. They are intermittently symptomatic, particularly during urinary tract infections, and occasionally present with hematuria. Erosion of a medullary calculus into the renal pelvis advances such a patient into Group III, at least temporarily until the stone is passed or removed. In addition to the recommendations of Group I, Group II patients require an insured high fluid intake in attempt to prevent further deposition of calcium salts and to limit complicating urinary tract infections. Chronic suppressive therapy with antibiotics may be necessary to give if intermittent infection continues to appear in these patients. The effectiveness of dietary calcium restriction, therapy with oral sodium cellulose phosphate, magnesium, and other agents which are designed to limit stone formation in this disorder is unknonw. Testing of renal function in yearly intervals is advised.

Group III patients encompass those patients with free calculi, who are

often symptomatic (hematuria, renal pain, ureteral colic, superimposed infection) despite the usual clinical course of spontaneous passage of the symptomatic calculus. Prolonged conservative therapy with frequent followup with urine cultures and renal function is preferred, as outlined previously for Group I and Group II patients. Especially close observation is required at times of symptoms. Spontaneous passage of a stone should be followed by careful evaluation for presence of infection. Failure to pass a calculus within a reasonable period of time, especially if it is 5 mm or greater in size or if accompanied by infection may well require lithotomy.

H. Pathogenesis

Most authors consider medullary sponge kidneys to be a congenital anomaly present at birth in its fully developed form. Although a few well-documented cases in infants and children have been noted, it is customary for the diagnosis to be made in adulthood as secondary calcareous or infective complications emerge. Several associations with other congenital malformations (see Table 20) have been made. The possibility of tissue degeneration later in life cannot be excluded (e.g. progressive dystrophy of collecting tubules analagous to cystic degeneration of mucus membranes of the urinary tract, etc.).

TABLE 20

CONDITIONS REPORTED IN ASSOCIATION WITH MSK

CONDITION	CAUSE	NUMBER OF CASES REPORTED
Ehler-Danlos syndrome	Hereditary	4
Congenital hemihypertrophy	Occasionally hereditary	17
Congenital pyloric stenosis	Congenital	1
Polycystic renal disease	Hereditary	10
Pyeloureterocystitis cystica	Congenital or acquired	16
Renal ectopia, malrotation, horeshoe kidney, ureteral duplication, bifid ureter calcyceal diverticula, megaureter	Congenital	Many
Renal arterial fibromuscular dysplasia	Acquired	1
Parathyroid adenomata	Acquired	5
Distal renal tubular acidosis	Hereditary or acquired	8

Stating that dilated collecting tubules are present prior to birth and are congenital does not define the etiologic basis for this defect, for a variety of physical, chemical or genetic influences could contribute to dysembryoplastic development. Intrauterine crystalline obstruction by urinary calcium salts or by uric acid crystals with residual collecting tubular dilatations subsequent to their dissolution would seem unlikely,

especially in view of the disparity between the frequency of uric acid deposits and the rarity of tubular ectasia in stillborn infants. The occasional association with heritable disorders of connective tissue raises the possibility of sponge kidney representing the renal expression of more generalized abnormalities of connective tissue in some cases. Other physical, chemical, or genetic factors may contribute to the most often cited pathogenic mechanism: dysplastic cystic dilatation of the first few generations of the metanephric duct arborizations within nephrogenic tissue early in embryonic development. Indeed, as proposed by Morris et al (108), the radiographic appearance of sponge kidney may reflect a heterogenous mixture of disease processes.

Though most cases of sponge kidney occur sporadically, genetic transmission has been suggested by 9 families with two or more involved members. A total of 29 hereditary cases of sponge kidney includes five pairs of siblings, three examples of involvement of two successive generations, and a family with 6 members with this diagnosis. Sponge kidney was well-documented in 3 generations in another family and was at least suggestively present in a total of 8 individuals spanning 5 generations. Estimation of the true frequency of genetic influences would require radiographic examination of all relatives of patients with sponge kidney disease in light of the probably asymptomatic or minimally symptomatic nature of this disorder.

A summary of differentiating features of adult polycystic disease, medullary cystic disease, and sponge kidney is provided in Table 21.

TABLE 21

CLINICAL DIFFERENCES AMONG THREE COMMON CYSTIC DISORDERS OF THE HUMAN KIDNEY

Diagnostic Criterion	Nephronophthisis–Cystic Renal Medulla	Polycystic Kidney Disease	Medullary Sponge Kidney
Flank pain	Usually absent	Usually present	Present only if complicated
Hypertension	Unusual	Frequent	Unusual
Hematuria[b]	Absent until azotemic	Often present	Present, if complicated (as with stone)
X-ray findings	Small kidneys	Large kidneys Cysts	Normal to large kidneys Papillary cavitations
	No calculi	Calculi	Medullary calcifications
Impaired glomerular filtration after onset	Frequent	Frequent	Absent unless complicated
Age at death	1st–4th decade	<5 or >50 yr	Normal life-span
Familial incidence	>75% of cases	>75% of cases	<20% of cases

VII. SIMPLE CYSTS

Some difficulty entails the choice of the diagnostic term to designate the cystic lesion most frequently encountered in autopsy practice. At least 50% of adults older than 50 years have, at autopsy, one or more grossly

recognizable cysts of the renal parenchyma. Sometimes designated "cortical", these cysts appear in the medella as well as the cortex. Although often designated serous their contents are not serous. Frequently called solitary, these lesions are as commonly multiple as solitary. And finally, even though they are called simple cysts their pathogenesis is probably far from simple.

Simple cysts vary in size from the limit of the naked eye perception to many cm in diameter. They are usually spherical and thin-walled (unless secondarily altered), and contain fluid with gross and chemical features of an ultrafiltratrate plasma. The cysts may contain as much as 3.5 liters of fluid; the record amount of fluid contained by a single cyst is reported to be 23 liters (110). Microscopically the lining of simple cysts is characteristically low cuboidal epithelium to attenuated flattened nondescript epithelium. Papillary projections, multicellular layers, etc. are not characteristic. Other morphologic features represent the results of complications of the basic lesion. Simple cysts may contain recent clotted or altered blood ultimately assuming the consistency of putty streaked with cholesterol clefts. In complicated lesions, the capsules may become thickened by the addition of laminated fibrous tissue about the epithelial lining. If a cystic renal lesion of this sort contains blood there is about 1 chance in 3 that the lesion is carcinoma. Practically always these are cystic cancers rather than cancers arising in a cyst.

Table 22 lists the diagnostic approach to the asymptomatic renal mass lesion as detailed by Clayman et al (111). Non-operative use of nephrotomography, sonography, arteriography, and cyst puncture have yielded acurrate diagnoses in a high percentage of cases, without false negatives.

TABLE 22

DIAGNOSTIC APPROACH TO THE ASYMPTOMATIC RENAL MASS: QUALITY CONTROL

Varible	Operative Evaluation (%)	Nonoperative Evaluation (%)*
Accuracy:	97	97
False positive	3	3
False negative	0	0
Mortality	0.71	0.07
Serious complications	1.6	1.03
Minor complications	19.0	5.4
Nephrectomy due to complication	1.6	0.28

* Includes intravenous pyelography, nephrosonography, cyst puncture & renal angiography

Figure 18 provideds an orderly diagnostic approach to the asymptomatic renal mass as proposed by these authors (111).

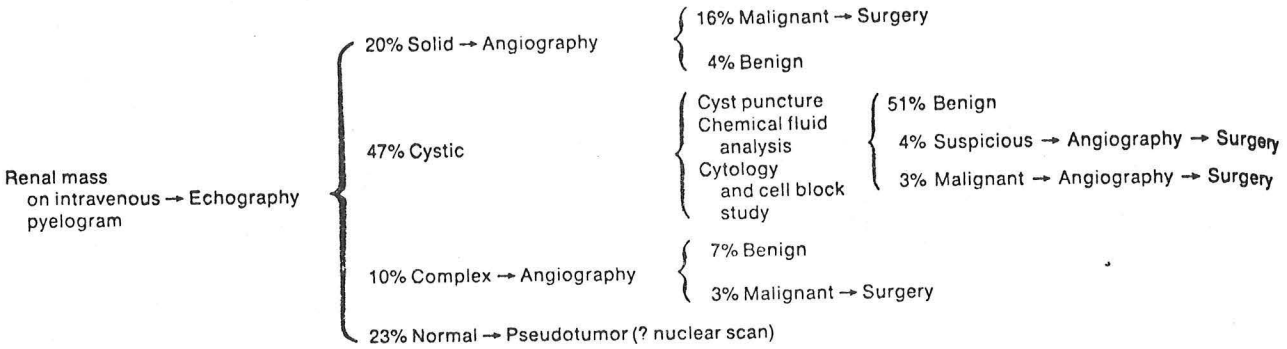


Fig. 18: DIAGNOSTIC APPROACH TO THE ASYMPTOMATIC RENAL MASS

This schema suggested by Clayman et al does not incorporate the major impact of computed tomography (CT) on the radiographic diagnosis of the renal mass lesion. With the use of CT, the diagnostic accuracy approaches 100% and is minimally invasive (112-3). A series of strict CT criteria have been developed to enhance the diagnostic accuracy of renal masses. They are listed in Table 23 below:

TABLE 23

CT CRITERIA OF RENAL MASS LESIONS

SIMPLE CYST
1. Homogeneous, low attenuation value (near water density).
2. An indiscernable wall.
3. Sharp delineation from surrounding parenchyma.
4. Lack of enhancement following intravenous contrast.

RENAL MALIGNANCY
1. Attenuation coefficient dose to that of renal parenchyma and often heterogeneous.
2. Definite contrast enhancement, usually less than the normal parenchyma. Transient marked enhancement can be seen during the vascular phase after bolus injection.
3. An unsharp interface with the surrounding parenchyma.
4. Secondary characteristics such as:
   a. Enlargement of renal vein or regional lymph nodes.
   b. Nodular areas of soft-tissue attenuation within the perinephric space, gross invasion of the inferior vena cava, or involvement of main renal vein.

In a recent study (114) of 815 renal masses evaluated applying the above criteria, 60 (7.4%) did not fit criteria for cyst or neoplasm. In

these indeterminate cases, ultrasound and needle aspiration were diagnostic in 84%. Thus, only 9 patients out of the total of 815 (1%) did not have a diagnosis established non-invasively before surgery. In this study, angiography was not diagnostically useful in these indeterminate lesions; hence, these authors propose CT scanning as the major radiographic tool with a diagnostic yield in about 93% of patients. The remainder of patients then may have ultrasound with or without cyst puncture to pick up another 6%.

References

1. Arey LB: Developmental Anatomy. WB Saunders Co., Philadelphia, PA, 1974, pp 295-301.

2. Osathanondh V, Potter EL: Development of Human Kidney as Shown by Microdissection-3 Parts. Arch Path 76:271, 1963.

3. Potter EL: Normal and Abnormal Development of the Kidney. Chicago: Year Book Medical Publishers, 1972.

4. Bernstein J: A Classification of Renal Cysts. In Cystic Diseases of the Kidney. Ed. by KD Gardner Jr., John Wiley and Sons, New York. pp 7-31, 1972.

5. Ericsson NO, Ivemark, BI: Renal Dysplasia and Pyelonephritis in Infants and Children: Part I. Acta Pathol 66:255, 1965.

6. Ericsson NO, Ivemark BI: Renal Dysplasia in Pyelonephritis in Infants and Children: Part II. Primitive Ductules and Abnormal Glomeruli. Arch Pathol 66:264, 1958.

7. Newman LB, McAlister WH, Kissane J: Segmental Renal Dysplasia Associated with Ectopic Ureteroceles in Childhood. Urology 3:23, 1974.

8. Bernstein J, Brough AJ, McAdams AJ: The Renal Lesion in Syndromes of Multiple Congenital Malformations: Cerebrohepatorenal Syndrome; Jeune's Asphyxiating Thoracic Dystrophy; Tuberous Sclerosis; Meckel's Syndrome. In 5th Conference on the Clinical Delineation of Birth Defects, Birth Defects: Original Article Series. Vol X/4:35, New York: The National Foundation, 1974.

9. Anon: Case Records of the Massachusetts General Hospital. Weekly Clinicopathological Exercises. N Engl J Med 290:676, 1974.

10. Liberman E, Salinas-Madrigal L, Gwinn JL, Brennan LP, Fine RN, Landing BM: Infantile Polycystic Disease of the Kidneys and Liver: Clinical, Pathological and Radiological Correlations and Comparisons with Congenital Hepatic Fibrosis. Medicine (Baltimore) 50:277, 1971.

11. Kissane JM: Morphology of Renal Cystic Disease. KD Gardner Jr., John Wiley and Sons, New York, 1971.

12. Potter EL: Normal and Abnormal Development of the Kidney. Chicago: Year Book Medical Publishers, 1972.

13. Bartman J, Barraclough G: Cystic Dysplasia of the Kidneys Studied by Microdissection in a Case of 13-15 Trisomy. J Pathol Bacteriol 89:233, 1965.

14. Mottet NK, Jensen H: The Anomalous Embryonic Development Associated with Trisomy 13-15. Am J Clin Pathol 43:334, 1965.

15. Doege TC, Thuline HC, Priest JH, Norby DE, Bryant JS: Studies of a Family with the Oral-Facial-Digital Syndrome. N Engl J Med 271:1073, 1964.

16. Dicker H, Edwards RH, ZuRhein G, Chou SM, Hartman HA, Opitz JM: The Lissencephaly Syndrome. In 1st Conference on the Clinical Delineation of Birth Defects, Birth Defects: Original Article Series. Vol V/2:53, New York: The National Foundation, 1969.

17. Caramia G, DiBattista C, Botticelli A: La Sindrome di Goldenhar: Descrizione di un Caso Con Malformazioni Cardiovascolair, Agenesia Del Polmone Destro E Situs Viscerum Inversus. Minerva Pediatr 22:362, 1970.

18. Marden PM, Walker WA: A New Generalized Connective Tissue Syndrome. Am J Dis Child 112:225, 1966.

19. Imahori S, Bannerman RM, Graf CJ, Brennan JC: Ehlers-Danlos Syndrome with Multiple Arterial Lesions. Am J Med 47:967, 1969.

20. Kaye CL, Fisher DE, Esterly NB: Cutis Laxa, Skeletal Anomalies and Ambiguous Genitalia. Am J Dis Child 127:115, 1974.

21. Talvik T, Mikelsaar A-V, Mikelsaar R, Kaosaar M, Tuur S: Inherited Translocations in Two Families (t(14qt;10q-) and t(13q-;21qt)). Hamangenetik 19: 215, 1973.

22. Spranger J, Grimm B, Weller M, Weissenbacher G, Hermann J, Gilbert E, Krepler R: Short Rib-Polydactyly (SRP) Syndromes, Types Majewski and Saldino-Noonan. Z Kinderheilk 116:73, 1974.

23. Bernstein J, Brough AJ, McAdams AJ: The Renal Lesion in Syndromes of Multiple Congenital Malformations: Cerebrohepatorenal Syndrome; Jeune's Asphyxiating Thoracic Dystrophy; Tuberous Sclerosis; Meckel's Syndrome. In 5th Conference on the Clinical Delineation of Birth Defects, Birth Defects: Original Article Series. Vol X/4:35, New York: The National Foundation, 1974.

24. Cremin BJ: Infantile Thoracic Dystrophy. Br J Radiol 43:199, 1970.

25. Shokeir MHK, Houston CS, Awen CF: Asphyxiating Thoracic Chondrodystrophy: Association with Renal Disease and Evidence of Possible Heterozygous Expression. J Med Genet 8:107, 1971.

26. Opitz JM, Howe JJ: The Meckel Syndrome (Dysencephalia Splanchnocystica, the Gruber Syndrome). In 1st Conference on the Clinical Delineation of Birth Defects, Birth Defects: Original Article Series. Vol V/2:167 New York: National Foundation, 1969.

27. Elkin M, Bernstine J: Cystic Diseases of the Kidney:Radiological and Pathological Considerations. Clin Radiol 20:65, 1969.

28. Engstrom N, Ljungqvist A, Persson B, Wetterfors J: Tuberous Sclerosis with a Localized Angiomatous Malformation in the Ileum and Excessive Albumin Loss into the Lower Intestinal Tract:Report of a Case. Pediatrics 30:681, 1962.

29. Wenzl JE, Lagos JC, Albers DD: Tuberous Sclerosis Presenting as Polycystic Kidneys and Seizures in an Infant. J Pediatr 77:673, 1970.

30. Chonko AM, Weiss SM, Stein JH, Ferris TF: Renal Involvement in Tuberous Sclerosis. Am J Med 56:124, 1974.

31. Dalgaard OZ: Bilateral Polycystic Disease of the Kidneys. A Follow-Up of Two Hundred and Eighty Four Patients and Their Families. Acta Med Scand Suppl 328, 1957.

32. Cairns HWB: Heredity in Polycystic Disease of the Kidneys. Q J Med 18:359, 1925.

33. Rall JE, Odel HM: Congenital Polycystic Disease of the Kidney: Review of the Literature and Data on 207 Cases. Am J Med Sci 218:399, 1949.

34. Hatfield PM, Pfister RC: Adult Polycystic Disease of the Kidneys (Potter Type III). J Am Med Assoc 222:1527, 1972.

35. Dalgaard OZ: Diseases of the Kidneys. In Strauss MB, Welt LG eds. Boston: Little, Brown, p 1223, 1971.

36. Lalli AF, Poirier VA: Urographic Analysis of the Development of Polycystic Kidney Disease. Am J Rad 119:705, 1973.

37. Bjerle B, Lindqvist B, Michaelson G: Pressure Measurements in Renal Cysts. Scand J Clin Lab Invest 27:135-138, 1971.

38. Deen WH, Roberston CR, Brenner BM: Glomerular Ultrafiltration. Fed Proc 33: 14, 1974.

39. Gardner KD: Composition of Fluid in Twelve Cysts of a Polycystic Kidney. N Engl J Med 281:985, 1969.

40. Braasch WF, Schacht FW: Pathological and Clinical Data Concerning Polycystic Kidney. Surg Gynecol Obstet 57:467, 1933.

41. Braasch WF, Schacht FW: Pathological and Clinical Data Concerning Polycystic Kidney. Surg Gynecol Obstet 57:467, 1933.

42. Simon HG, Thompson GT: Congenital Polycystic Disease. A Clinical and Therapeutic Study of 366 Cases. J Am Med Assoc 159:657, 1955.

43. Hamburger J, Richet G, Crosnier J, Funck-Brentano JL, Antoine B, Ducrot H, Mery JP, DeMontera H: Nephrology II. Philadelphia, WB Saunders, p 1070, 1968.

44. Rall JE, Odel HM: Congenital Polycystic Disease of the Kidney: Review of the Literature and Data on 207 Cases. Am J Med Sci 218:399, 1949.

45. Kumar S, Cederbaum AI, Pletka PG: Renal Cell Carcinoma in PCKD: Case Report and Review of the Literature. J Urol p24:758, 1980.

46. Oppenheimer GD: Polycystic Disease of the Kidney. Ann Surg 100:1136, 1934.

47. McNamara JJ: Pyelonephritis in Polycystic Disease of the Kidney. Am J Surg 109:178, 1965.

48. Bricker NS: Experimental Polycystic Disease and Susceptibility to Pyelonephritis. In Metcoff, J. ed. 14th Annual Conference on the Kidney. Boston:Little, Brown, 1963.

49. Hatfield PM, Pfister RC: Adult Polycystic Disease of the Kidneys (Potter Type III). J Am Med Assoc 222:1527, 1972.

50. Katzen NG: Fatal Hepatic Polycystic Disease. Br Med J 1:839, 1964.

51. Wrong O: A Case of Polycystic Disease of the Liver and Kidneys. Br Med J 4:1356, 1965.

52. Oppenheimer GD: Polycystic Disease of the Kidney. Ann Surg 100:1136-1158, 1934.

53. Moschowitz E: Non-parasitic Cysts (Congenital) of the Liver, with a Study of Aberrant Bile Ducts. Am J Med Sci 131:674-699, 1906.

54. Rall JE, Odel HM: Congenital Polycystic Disease of the Kidney: Review of the Literature and Data on 207 Cases. Am J Med Sci 218:399-407, 1948.

55. Dalgaard O: Bilateral Polycystic Disease of the Kidneys. Acta Med Scand Suppl 328, 158:13-255, 1957.

56. Brown RAP: Polycystic Disease of the Kidneys and Intracranial Aneurysms. The Etiology and Interrelationship of these Conditions: Review of Recent Literature and Report of Seven Cases in Which Both Conditions Coexisted. Glasgow Med J 32:333-348, 1951.

57. Williams JA, Price JDE: Liver Cysts in End Stage Uremia Due to Polycystic Kidney Disease. Can Med Assoc J 102:856-857, 1970.

58. Comfort MW, Gray HK, Dalhin DC, et al: Polycystic Disease of the Liver: A Study of 24 Cases. Gastroenterology 20:60-78, 1952.

59. Feldman M: Polycystic Disease of the Liver. Am J Gastroenterol 29:83-86, 1958.

60. Davis CR: Non-parasitic Cysts of Liver. Am J Surg 35:590-594, 1937.

61. Borelius J: Zur Genese und Klinischen Diagnose der Polyzystischen Degeneration der Nieren. J Nord Med Ark 34:1, 1901.

62. Dunger R: Zurlehre von der Cystenniere, mit Besorderer Berucksichtigung. Beitr Pathol Anat 35:445, 1904.

63. Suter W: Das Kongenitale Aneurysma der Basalen Gehirnarterien und Cystenieren. Schweiz Med Wochenschr 79:471-476, 1949.

64. Bigelow NH: The Association of Polycystic Kidneys with Intracranial Aneurysms and Other Related Disorders. Am J Med Sci 225:485-494, 1953.

65. O'Crowley CR, Martland HS: The Association of Polycystic Disease of the Kidneys with Congenital Aneurysms of the Cerebral Arteries. Am J Surg 43:3-9, 1939.

66. Sahs AL, Keil PG: Subarachnoid Hemorrhage Caused by Ruptured Intracranial Aneurysm. Am Heart J 26:645-661, 1943.

67. Poutasse EF, Gardner WJ, McCormack LJ: Polycystic Kidney Disease and Intracranial Aneurysm. J Am Med Assoc 145:741-744, 1954.

68. Anderson RJ: Unpublished Report.

69. Funck-Brentano JL, Vantelon J, Lopez Alvarez R: Les Accidents Evolitifs de la Maladie Polykystique des Reins: 154 Observations Personelles, Presse Med 72: 1583, 1964.

70. Waters WB, Hershman H, Klein LA: Management of Infected Polycystic Kidneys. J Urol 122:383, 1979.

71. Hamburger J, Richet G, Crosnier J, Funck-Brentano JL, Antoine B, Ducrot H, Mery JP, DeMontera H: Nephrology II. Philadelphia, WB Saunders, p1070, 1968.

72. Newcombe DS: Gouty Arthritis and Polycystic Kidney Disease. Ann Intern Med 79:605, 1973.

73. Bailey GL, Griffiths H, Lock JP, Hampers CL, Merrill JP: Gastrointestinal Abnormalities in Uremia. Abstr Am Soc Nephrol p 5, 1971.

74. Lowsley OS, Curtis MS: The Surgical Aspects of Cystic Disease of the Kidney. J Am Med Assoc 127:1112-1119, 1945.

75. Ahmann TH, Wurster JC, Ceccarelli FE: Transitional Cell Carcinoma in Bilateral Multiple Renal Cystic Disease. J Urol 109: 179, 1973.

76. Siegelman SS, Zavod R, Hect H: Neurofibromatosis, Polycystic Kidneys, and Hypernephroma. N Y State J Med 71:2431-2433, 1971.

77. Christoferson LA, Gustafson MB, Petersen AG: Von Hippel-Lindau Disease. J Am Med Assoc 178:280, 1961.

78. Muther RS, Bennett WM: Cyst Fluid Antibiotic Concentrations in Polycystic Kidney Disease:Differences Between Proximal and Distal Cysts. Kid Internat 20:519, 1981.

79. Grantham JJ: Polycystic Renal Disease, Chapter 30, In Diseases of the Kidney Ed by Earley LE, Gottschalk CUS, Boston, Little, Brown and Co., p1132, 1979.

80. Martinez-Maldonado M, Yium JJ, Eknoyan G, Suki WN: Adult Polycystic Disease: Studies of the Defect in Urine Concentration. Kid Internat 2:107, 1972.

81. Preuss H, Geoly K, Johnson M, Chester A, Kliger A, Schreiner G: Tubular Function in Adult Polycystic Kidney Disease. Nephron 24:198-204, 1979.

82. Huseman R, Grady A, Welling D, Grantham J: Macropuncture Study of Polycystic Disease in Adult Human Kidneys. Kid Internat 18:375, 1980.

83. Henrich WL, Blachley JD: Renal Failure with Prostaglandin Inhibitors. Sem in Nephrol 1:57, 1981.

84. Lazarus JM, Bailey GL, Hampers CL, Merrill JP: Hemodialysis and Transplantation in Adults with Polycystic Renal Disease. J Am Med Assoc 217:1821, 1971.

85. Mitchell TS, Halpez TA, Gitter RF: Renal Transplantation: Selective Preliminary Bilateral Nephrectomy. J Urol 109:796, 1973.

86. Fialkow PJ: Genetic Counselling in Renal Disease. The Kidney. 6:3, 1973.

87. Chester AC, Geoly K, Schreiner GE, Preuss H: Early Diagnosis of Polycystic Kidney Disease. Am Fam Pract 23:175, 1981.

88. Rosenfield AT, Lipson MH, Wolf B, Taylor KJW, Rosenfield NS, Hendler E: Ultrasonography in the Pre-symptomatic Diagnosis of Dominantly Inherited (adult-onset) Polycystic Kidney Disease. Radiology 135:423, 1980.

89. Hogewind BL, Veltkamp JJ, Koch CW, Graeff J: Genetic Counseling for Adult Polycystic Disease. Ultrasound a Useful Tool in Pre-symptomatic Diagnosis. Clin Genetics. 18:168, 1980.

90. Simon HB, Thompson GT: Congenital Polycystic Disease. A Clinical and Therapeutic Study of 366 Cases. J Am Med Assoc 159:657, 1955.

91. Hamburger J, Richet G, Crosnier J, Funck-Brentano JL, Antoine B, Ducrot H, Mery JP, DeMontera H: Nephrology II. Philadelphia, WB Saunders, p 1070, 1968.

92. Hatfield PM, Pfister RC: Adult Polycystic Disease of the Kidneys (Potter Type III). J Am Med Assoc 222:1527, 1972.

93. Strauss MB: Clinical and Pathological Aspects of Cystic Disease of Renal Medulla. Ann Intern Med 57:373-381, 1962.

94. Winberg J: Correspondence. Am J Dis Child 108:566, 1964.

95. Chester AC, Argy WP, Rakowski TA, Schreiner GA: Polycystic Kidney Disease and Chronic Hemodialysis. Clin Neph 10:129, 1978.

96. Williams G, Mitcheson HD, Custro JE: Transplantation for Polycystic Kidney Disease. Urol 12:628, 1978.

97. Thorn GW, Koepf GF, Clinton M Jr: Renal Failure Simulating Adrenocortical Insufficiency. N Engl J Med 231:76-85, 1944.

98. Smith CH, Graham JB: Congenital Medullary Cysts of the Kidneys with Severe Refractory Anemia. Am J Dis Child 69:369-377, 1945.

99. Gardner KD: Juvenile Nephronopthesis and Renal Medullary Cystic Disease. In Cystic Diseases of the Kidney, ed by KD Gardney Jr, John Wiley and Sons, New York, NY. pp174-185, 1974.

100. Kyle VN: Medullary Cystic Disease of the Kidneys: Report of a Family. Can J Surg 16:1-6, 1973.

101. Ekstrom T, Engfeldt B, Lagergren C, Lindvall N: Medullary Sponge Kidney. Stockholm:Almqvist and Wiksell, 1959.

102. Lenarduzzi G: Reperto Pielografico Poco Commune (Dilatazione Delle vie Urinarie Intrarenali.) Radiol Med 26:346-347, 1939.

103. Kniper JJ: Medullary Sponge Kidney. In Cystic Diseases of the Kidney, ed by KD Gardner Jr., John Wiley and Sons, New York, NY, pp151-171, 1974.

104. O'Neill M, Bresla NA, Pak CYC: Metabolic Evaluation of Nephrolithiasis in Patients with Medullary Sponge Kidney. JAMA 245:1233, 1981.

105. Granberg PO, Lagergren C, Theve NO: Renal Function Studies in Medullary Sponge Kidney. Scand J Urol Nephrol. 5:177-180, 1971.

106. Kumagai I, Matsuo S, Kato T: A Case of Incomplete Renal Tubular Acidosis (Type I) Associated with Medullary Sponge Kidney Followed by Nephrocalcinosis. J Urol 123:250, 1980.

107. Pyrah LN: Medullary Sponge Kidney. J Urol 95:274-283, 1966.

108. Morris RC, Yamauchi H, Palubinskas AJ, Howenstine J: Medullary Sponge Kidney. Am J Med 28:883-892, 1965.

109. Goldman SH, Walker SR, Merigan TC Jr., Gardney KD Jr., Bull JMC: Hereditary Occurrence of Cystic Disease of the Renal Medulla. N Engl J Med 274:983-991, 1966.

110. Fish GW: Large Solitary Serous Cysts of the Kidney. Report of 32 Cases Including Two Cases Cured by Aspiration and Instillation of 50 Percent Dextrose Solution. J Am Med Assoc 112:514, 1939.

111. Clayman RV, Williams RD, Fraley EE: The Pursuit of the Renal Mass. N Engl J Med 300:72, 1979.

112. Sagel SS, Stanley RJ, Levitt RG, Geisse G: Computed tomography of the kidney. Radiology 124:359, 1970.

113. McClennan BL, Stanley RJ, Melson GL, Levitt RG, Sagel SS: CT of the cyst: Is cyst aspiration necessary? Am J Roent 133:671, 1979.

114. Balfe DM, McClennan BL, Stanley RJ, Weyman PJ, Sagel SS: Evaluation of renal masses considered in determinate on computed tomography. Radiology 142:421, 1982.