1947

# Polycystic kidney diseases : pathogenesis and clinical aspects

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# POLYCYSTIC KIDNEY DISEASE:

# PATHOGENESIS AND CLINICAL ASPECTS.

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Senior Thesis
Presented to The College of Medicine
University of Nebraska
Omaha, 1947

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## PATHOGENESIS

Polycystic kidney disease is a condition which is characterized by widespread cystic transformation in one, or more commonly, both kidneys. It is now generally accepted that the disease may be placed on a congenital maldevelopment basis, in which there is a strong hereditary tendency and common association with congenital anomalies in other portions of the body. Numerous theories have been advanced as to the exact etiology of the condition, but before going into these a brief review of the embryology of the kidney will be given.

In the development of the human kidney three sets of organs are formed during embryonic life. These are the pronephros, mesonephros, and metanephros, the latter of which will develop into the adult organ. All three types have a common origin, namely the nephrogenic cord, which is a division of the intermediate cell mass, lying just lateral to the mesodermal segments. All three types are structurally similar, having a glomerular tuft system, and an excretory duct system, which discharges wastes from the body. Because of the importance of the metanephros, its development will be considered in detail.

The metanephros is the last of the group to develop, the other two eventually disappearing after their function is taken over by the caudally developing metanephros. The metanephros arises in part from a portion of the nephrogenic cord which has separated caudally. The rest of the organ develops from the ureteric bud which is an outgrowth from the mesonephric duct, i.e., the main

excretory duct of the mesonephros. A detailed account of the changes and transformations in shape and anatomical relations of the gross features of the developing kidney is not necessary in this paper. It is necessary, however, to understand the development and changing relations of the individual unit, or nephron.

The ureteric bud will form the pelvis, calices and collecting tubules of the kidney. At an early age it develops as an outgrowth from the mesonephric duct and pushes into the metanephrogenic tissue which has separated from the nephrogenic cord. This latter portion will form the secretory tubules and Bowman's capsule. At the sixth week of the embryo, the primitive renal pelvis flattens from side to side and two primary tubules, or definitive major calices, bud out from its walls. These tubules in turn give rise to secondary tubules, which in turn give rise to tertiary tubules, and so on, until a maximum number of twenty generations of tubules have been formed at birth. The higher orders of tubules will form the straight collecting tubules of the adult kidney.

Meanwhile, the metanephrogenic tissue is developing in relation to the collecting tubules. This tissue condenses about the end of each collecting tubule into a spherical mass, the anlage of the secretory tubule. The solid mass thus formed becomes converted into a vesicle, and elongated and twisted into an S-shaped secretory tubule, lying in close proximity to the adjacent collecting tubule. It must be noted at this stage that there is no direct connection between the secretory and col-

lecting tubules. Eventually one end of the secretory tubule will become indented by blood vessels, forming the glomerulus and Bowman's capsule; the other end will unite with the blind end of the adjacent collecting tubule. (Arey 1942) (Kiebal & Mall 1912)

It is at this stage in the development of the kidney that is important as regards the etiology of polycystic kidney disease. In 1923, Kampmeier made a series of examinations on 26 human embryos and foetus, ranging in age from six weeks to five months. He was able to trace the development of the nephron and the progress of cyst formation throughout successive embryological stages. The theory that evolved through this work as to the etiology of polycystic kidney disease is now regarded as the most substantial. (Bell 1935) (Anderson 1944) (Boyd 1938)

As stated above, the ureteric bud will form the collecting tubules and the metanephrogenic tissue forms the secretory, or uriniferous tubules. At birth the uriniferous tubules discharge into collecting ducts of the tenth or higher orders only, whereas ducts of a lower order do not become a functioning part of the adult kidney. What happens to the uriniferous tubules and the collecting ducts of a lower order has been a matter of speculation, but it has been assumed that the uriniferous tubules become detached from ducts of lower orders and become attached to ducts of higher orders; or that with elongation, progressive sprouting and outgrowth of the collecting tubules, the uriniferous tubules migrated peripherally. (Kiebel & Mall 1912)

Kampmeier in his study of the progressively developing kidney made several very important observations, He found that with the sprouting of the primary collecting ducts, the metanephrogenic tissue is carried away from the primitive renal pelvis. Isolated fragments, however, remained behind near the pelvis, and during the seventh week develop normally into spheres and vesicles, and occasionally into tubules. At no time, however, is there any communicating connection between these primary order uriniferous tubules and the primary collecting ducts. There is only occasional glomerulus formation in these tubules and histological differentiation is rare. These definitely represent an abortive attempt at tubule formation, and Kampmeier's observations establish the fact that they never become functional. Their importance is only that they are still present in a five month foetus, an age at which one would expect them to have disintegrated, since they are not to assume function. They may undergo cystic degeneration and become of importance, clincally.

Uriniferous tubules of the second order begin to develop in a six week embryo and are quite precocious in development in comparison to tubules of the first order. Also, in contrast to first order tubules, second order tubules are very well differentiated and look very much alike, also closely resembling the tubules of higher orders. During the S-shaped stage of development most of these tubules connect with the corresponding second order collecting ducts, thereby completing the functional

unit. Somewhat later, they develop a diverticulum extending from the point of junction with the collecting tubule to the blind end of the collecting ducts of a higher order. This subsequently forms a communication with the fourth or fifth collecting ducts and the early communication with second order ducts is lost. Thus the shifting relations between uriniferous tubules and collecting ducts is explained. (Kampmeier 1923)

The fate of these secondary tubules was accurately traced by Kampmeier. With further differentiation the tubules become fully developed, functioning units, but at some time between the third and fifth month cystic degeneration occurs. The connection with the collecting duct is lost and the tubule becomes enlarged and cystic. The epithelium is flattened and squamous in character. Bowman's capsule is dilated and the glomerulus projects into the cavity as separate tufts of capillaries. Normally, these cysts will disappear after attaining a variable size. In some the epithelium degenerates and the cyst simply disappears; in others the cyst is compressed and obliterated by the growth of surrounding parenchyma.

It thus becomes obvious that the human kidney normally passes through a period of development which is characterized by numerous cystic renal tubules, and it is easy to see that an arrest of normal progress at this stage could result in persistent numerous cysts, and consequently the production of polycystic kidney disease. (Kampmeier 1923)

Assuming Kampmeier's theory on the nature of the development of polycystic kidneys to be the most accurate, a brief review of other, previous theories will be given. Virchow was one of the first to give an explanation of polycystic kidney disease. He ascribed the condition as being due to obstruction of the tubules by uric acid and lime infarcts, later modifying the theory by saying that it was the irritation of these substances during intrauterine life, causing atresia and obliteration of the collecting tubules. This conclusion was reached partly by his observation that there was a great increase in connective tissue in the renal pyramids in cases of polycystic kidney. The connective tissue found in cystic kidneys actually however is fine, fibrillar, and cells are few in number, (Moschowitz 1906), and not at all like the dense fibrous tissue formed as the result of inflammation. Virchow, in propounding his theory, which, perhaps because of his fame, had many followers, had not taken into consideration that the ratio of connective tissue and differential epithelium is high in embryonic kidneys, and that the normal ratios in normally developing kidneys is not reached until nearly full term. Therefore, it apparently passed unobserved to Virchow that the connective tissue which he saw was very embryonal in nature and probably of no pathological significance.

Unsatisfied with Virchow's theory, Brigidi and Severi in 1880 introduced a new theory. They thought that polycystic kidneys were the result of new-growth formation and termed the condition a multilocular adenocystoma. They received many supporters of

this theory, based on the observations that there were epithelial sprouts into surrounding tissue, increased number of layers of epithelium and proliferation of epithelium, and pseudo-papilliferous formations in many of the cysts. However, it was later shown by Busse and Dunger that epithelial elements are not increased, but actually reduced in cases of polycystic kidney disease. They also found that most of the observations upon which Brigidi and Severi based their theory were not sound, and that they could be demonstrated in the normally developing embryonic kidney.

An important fact which previously had passed unnoticed was at this time brought to light. Why the great incidence of apparently unrelated congenital malformations of other parts of the body in patients suffering from polycystic kidney disease? Von Mutach was the first to suggest that the lesion might be on a non-development or embryonal basis. Shattock, in 1886, thought the condition was due to persistence of the wolffian body which became cystic and in turn caused compression and cystic dilatation of the ducts. Hildebrand in 1894 first explained the condition on an embryological basis, theorizing that there was failure of connection between the secretory and collecting portions of the urinary tubules, with the result that the secretory portions became dilated. (Moschowitz 1906) Thus developed the theory that the disease was on a congenital basis gained many supporters, and is the prevailing theory today, but the exact nature of this

maldevelopment was not brought to light until Kampmeier made his very fine studies in 1923.

Having developed a satisfactory theory for the origin of polycystic kidney disease, and having noticed the common association with other congenital, inherited anomalies, stress was laid on the possible inheritance of the disease. Cairn in 1925, investigated and reported the occurrence of this condition in three successive generations of a family, comprising a total of forty-two individuals. In this family there were definitely eight and probably ten, cases of the disease. That would mean that at least 19% of the family were afflicted, which considering the rarity of the disease, would be too great an incidence to attribute to coincidence. On the contrary, it would be much in favor of a hereditary basis for the disease. In addition, Cairn substantiated his report by reviewing the literature on 23 other instances where polycystic kidney disease occurred more than once in a family. Six cases occurred in a family during three generations, totaling sixty individuals. In eleven other families the disease could be traced through two generations. In the remaining eleven familes, polycystic kidney disease was present in more than one individual of the same generation. (Cairn 1925)

Cairn doubts that "isolated" cases of the disease do occur, and suspects that the condition is invariably inherited. This cannot be definitely proven, but because of the variety of, or lack of, symptoms in many cases which go undiagnosed, or are incidental findings at autopsy, it is quite possible that the

disease was present in preceding generations when an "isolated" case is reported. The disease is not sex-linked and no consanguinity was recored in Cairn's review. Associated hereditary anomalies were also found in high incidence in these series of cases, such as hereditary myopia and accessory digits, either in combination with polycystic kidney disease, or alone. (Cairn 1925) Other congenital anomalies include hare-lip, cleft palate, meningocele, spina bifida, and perhaps more significant, other local anomalies of the uro-genital tract such as hypospodia, atresia, and absence of ureter, double vagina, and absence of the bladder. There is also fairly frequent association with congenital cysts of the liver and pancreas. (Moschowitz, 1906)

In 1937 Gordon and Trasoff reported a family in which six of seven children showed evidence of renal disease. Four of the six had clinical and radiological evidence of polycystic kidney disease. In addition, the father died at the age of forty-two of "chronic nephritis" and the mother suffered several years from an undiagnosed renal disease. It is perhaps significant that the parents were related in this case, being uncle and niece. (Gordon and Trasoff 1937) As stated above, the reports by Cairn would indicate that consanguinity was not a predominant factor. It has been shown, however, that inbreeding of rats after exposure to x-ray, can produce whole litters in which a variety of congenital kidney anomalies can be found, varying from polycystic kidneys to complete absence of kidneys. (Lewis 1946)

It may be generally said that small, isolated cysts of no clinical importance can be found in the majority of adult kidneys, and with a very thorough post mortem examination from a large number of autopsies transition forms ranging from true polycystic kidneys to solitary cysts could be found. Only the true polycystic kidney will be considered.

The polycystic kidney generally maintains its normal shpae, with proportional increases in size. Because of the increased weight, they are usually displaced caudally, and the intestines may be forced medially and anteriorly. On gross examination, the external surface is seen to be studded with rounded, elevated areas, variable size, corresponding to the underlying cysts which on section give the kidney a honey comb appearance. Between the cysts, variably sized areas of normal renal tissue may be seen, the amount dependent on several factors, namely the extent and progress of the disease, the amount of compensatory hypertrophy and the portion of kidney being examined. The greatest amount of normal tissue is normally to be found in the subcapsular area. Both the cortex and medulla are filled with cysts and it is usually impossible to differentiate between the two zones. Herxheimer in 1906, reported a case in which there were no cysts in the medulla, and Shaeffer in 1922 reported a case in which the cysts were found at the cortico-medullary junction, and no where else. Also, in one of Bell's series of unilateral cases in a new-born, and in one of his subclinical cases, only one pole of the kidney was filled with cysts.

Bell says that frequently the cysts will communicate with the calices, but this is probably a secondary communication as a result of rupture due to increasing pressure in the cyst; a primary communication would not be in agreement with the prevailing theory of origin of the cysts. (Kampmeier 1923) (Boyd 1938) The cysts are filled with a watery fluid, usually clear, but often highly colored, as a result of hemorrhage. Disintegrating blood gives a kaleidoscopic picture of color varying from red to purple to green and yellow. (Smith & Gault 1938) Occasionally the cysts will be small and numerous and give the kidney a spongy texture.

One of the prominent microscopic features which Bell found in his examinations of the kidneys of new-born infants with the disease is the great increase of interstitial connective tissue, which varies from loose areolar tissue to dense fibrous tissue, most common in the medullary area. As the disease progresses this tissue becomes more prominent and tends to compress the glomeruli and tubules and undoubtedly plays a large part in the production of symptoms of progressive renal insufficiency.

Another conspicuous feature is the reduction of glomeruli and tubules. Only a few collecting tubules can be found in the medulla. Normal glomeruli and convoluted tubules can usually be found only in small islands in the subcapsular zone. Hyalinized glomeruli are rare in infants (Bell), but is a common feature in adults with the disease. (Smith & Gault 1938) In infants the arteries and arterioles show no significant changes.

In Bell's series of cases in which death was due to extra-renal causes and in which there were only slight, if any renal symptoms, certain microscopical features were found to be promient. Normal renal tissue is abundant, with small areas of atrophy usually found only between the cysts, which though numerous, are small. Arteries and arterioles seem to vary in appearance from normal to those found in hypertension.

In the more important series of adult cases in which renal symptoms are the prominent findings, the following pathology is found. Normal renal parenchyma is markedly reduced and interstial connective tissue increased. Hyalinization of the glomeruli is prominent, and tubules are atrophic and markedly reduced in number, sometimes being large and dilated. Arteries and arterioles often show marked medial degeneration and thickening, with fibrosis and narrowing of the lumen. The vascular changes are often extensive enough per se to cause renal damage and probably play an important role in the progress of the disease. The cysts themselves, which predominate in the gross examination of the polycystic kidney, usually do not vary much in microscopic appearance. The epithelium is low cuboidal, and where pressure is great becomes greatly flattened and resembles squamous epithelium. (Boyd 1938) or endothelium. (Bell 1935)

The arteriole disease in polycystic kidneys differs from that of typical arteriosclerosis, which shows intimal and subintimal changes, in that here the media is affected and the intima is normal. (Bell 1935)

## CLINICAL ASPECTS

Polycystic kidney disease is important clincally to both physician and surgeon, and has assumed some importance to the obstetrician who may see it in the newborn, where it may be a factor, occasionally, in obstructed labors. In fact, one of the earliest accounts of the disease was given about 1700, by Littre, who described a case which had obstructed labor. (Oppenheimer 1934) In another case of a twenty-four year old female, two pregnancies ended in obstructed and difficult labor, as a result of enlargement of the abdomen of the babies. Both babies died within a few hours after birth, and an autopsy on the second one revealed polycystic kidney disease. (Denton 1933) As to its incidence, there are varying reports. In over 22,000 autopsies, Bell found forty-four cases, or a ratio of 1 - 509. In another series the ratio was 1 to 1,019 autopsies and 1 - 3,523 clinically. (Braasch & Shacht 1933) These figures are not, however, a true indication of the incidence of the disease, as many cases probably pass unnoticed when death is due to other causes. Actually, the condition, though uncommon, is not rare, and should be kept in mind by the physician when any case resembling a chronic nephritis presents itself, especially when the presenting symptoms are pain and hematuria. The patient's condition may resemble that of a patient with primary arteriosclerosis (malignant hypertension) or one with late chronic glomerulonephritis. (Randall 1932)

Various classifications of the disease have been made. Clinically the disease may be classified into two main groups: those cases which occur in the new-born and those that occur in adult life. In the new-born form, associated congenital anomalies are very common, but are uncommon in the adult type. (Hausmann 1940 ) About thirty percent of cases are found in the new-born resulting in stillborn infants or death within the first years of life. (Boyd 1938) If the infant survives two to three years, renal rickets or renal dwarfism may be present. (Hausmann 1940 ) The other group is the remaining sixty to seventy percent of cases which occur in adult life, with the age of forty being the average age of onset of symptoms. (Osler 1944) In Bell's review of forty-four cases, he found that four cases were unilateral, seven cases were subclinical and thirty-three cases were advanced typical bilateral polycystic kidney disease. Of these four cases, eight cases were in stillborn infants and another six cases in infants under six months. The remaining thirty cases were in individuals over one year of age, with very few cases in the span of years from infancy to adult life, and the greatest percentage of cases becoming manifest during the fifth decade. Bell made the following classification of cystic kidney disease.

I. Cystic Disease (True polycystic kidneys.

A. Bilateral cystic disease.

1. Clinical (Large kidneys
(Normal sized kidneys.
(Hypoplastic kidneys.

2. Subclinical.

B. Unilateral cystic disease.

1. Large kidney.

2. Hypoplastic kidney.

3. Partial cystic degeneration.

II. Large solitary cysts.

III. Multiple small cysts associated with contracted kidneys.

Only true polycystic kidneys will be considered in this paper.

Tow, in 1925, reported that in children there is a triad of symptoms, plus frequent association with other congenital anomalies. This triad is, (1) bilateral abdominal tumors from birth; (2) signs of chronic nephritis; (3) enlarged heart. (Tow 1925) In the adult form the symptoms are quite variable, as will be seen later. One investigator divides the adult disease into three forms: (1) the uremic form, in which signs of uremia are present and the patient is usually in extremis. Death will most likely occur in eight to twenty-eight days; (2) Bright's form, in which the patient has typical symptoms of chronic glomerular nephritis and will probably live for many years, and, (3) the surgical form. In this last form pain and hematuria are the prominent symptoms and great relief may be obtained from surgical procedures. The average length of life after symptoms appear in this type is about three years. (Randall 1932)

In Oppenheimer's series of cases (Oppenheimer 1932) in which sixty cases were reviewed between the years 1911 to 1932, fourteen came to post mortem and offered ample material for examination. One of these was in a new-born, six months old, which died following a nine day illness in which the symptoms were those of nasopharyngitis and pneumonia. Post mortem examination revealed polycystic kidneys, as well as left ventricular hypertrophy and fatty infiltration of the liver. The remaining fifty-nine cases were of the adult type. Thirty seven of the patients were males, and twenty-two were females. This shows a predominance of male patients, but this finding has not been substantiated by the investigations of other series of cases. (Bell 1935) (Braasch and Schacht 1933) The age of the majority of patients when first seen ranged from thirty-five to fifty-five, the average age being forty-one and one-half years. The probable explanation for the rarity of cases between newborn and adult periods of life is that there is a large margin of safety as regards functional renal tissue, and a considerable amount of destruction must occur before renal symptoms appear. (Oppenheimer 1934) There is also the possibility that hypertrophy of renal tissue during youth and early adult life provides the necessary amount of renal tissue to maintain normal function. (Bell 1935) The age group in Oppenheimer's series was as follows:

| Age | No. of Cases. |
|---|---|
| 1 - 19 yrs | 0 |
| 10 - 19 yrs | 0 |

| Age | No. of Cases |
|---|---|
| 20 - 29 yrs | 2 |
| 30 - 39 yrs | 14 |
| 40 - 49 yrs | 17 |
| 50 - 59 yrs | 18 |
| 60 - 69 yrs | 8 |
| Total | 59 |

At the time Oppenheimer made his review, twenty-six of the fifty-nine patients were known to be dead, with the average age at death being fifty years. The earliest death was at the age of twenty-six years, and the latest death was at the age of sixty-eight years.

Of this group there were no unilateral polycystic kidneys, but Oppenheimer reviewed two cases in which microscopic examination of both kidneys revealed only unilateral involvement. Six of the cases were discovered accidentally, at operation, at post mortem, or on the finding of a symptomless mass in the abdomen. Thirteen cases had signs of hypertensive cardio-renal disease and seven cases were suggestive of renal neoplasm. Fifteen cases showed frank signs of polycystic disease, and the others had signs of pyelonephritis, hydronephrosis, or vague abdominal symptoms as vomiting, distress, constipation or distention. Nine cases had symptoms, signs and x-ray evidence of renal calculi.

The common symptoms in this group were loin pain, abdominal pain, hematuria, nocturia, weight loss, vomiting, and tumor mass in the abdomen. Both kidneys were enlarged and palpable in thirty-

nine cases, one kidney only in ten cases, and neither kidney enlarged and palpable in fifteen cases, and the heart was enlarged in nineteen cases. Fourteen cases showed peripheral arteriosclerosis. The following blood pressure changes were recorded:

| | | |
|---|---|---|
| 200 mm Hg | Systolic pressure or over | 13 cases |
| 160 - 200 mm Hg | Systolic pressure | 16 cases |
| 140 - 160 mm Hg | Systolic pressure | 9 cases |
| 120 - 140 mm Hg | Systolic pressure | 5 cases |
| 100 - 200 mm Hg | Systolic pressure | 6 cases |
| Not recorded | | 10 cases |

The highest reading was 272/112, and in relation to age, twenty-eight cases showed hypertension. By correlating blood pressure with renal function tests, Oppenheimer was able to conclude that hypertension was associated with impairment of renal function and vice versa, except in cases where cardiac failure or vascular collapse was present.

In sixteen cases with renal insufficiency, fourteen showed anemia with an average hemoglobin of 63%. The cause of the anemia may be a disturbance in hematopoeisis (Oppenheimer - after Brown and Roth 1934), or to the hematuria which is so common in polycystic kidney disease. (Hausmann 1940) Fifteen cases were diagnosed by retrograde pyelography, and three cases by exretion pyelography.

Braasch and Schacht, in 1933, reviewed 193 patients which came under observation at the Mayo Clinic. Of these cases, eighty-five had been operated on for renal complications occurring with

polycystic kidney disease, or had been operated on for other abdominal pathology, and whose condition was discovered at that time. Necropsy records were available in nine cases, and surgical records and specimens were available in ten cases.

Braasch and Schacht found a much lower incidence of the disease than did Bell (see above). They found that if symptoms did not appear in infacy, they were withheld until the third decade, or more commonly until the fourth or fifth decade. Forty-six percent of their series was in this age group and they found that symptoms may not occur until the sixth or seventh decade, their oldest patient being sixty-nine years old before symptoms appeared.

Of seventy-four patients reported dead, thirty percent died within two years of the onset of symptoms. Fifteen percent died within two to four years and the remaining fifty-five percent lived five to twenty years with two exceptions; one patient lived twenty-three years, and another lived thirty-six years. The life expectancy depends largely on the amount of functioning renal tissue, which in this disease depends on the number and size of the cysts, and the pressure exerted by them on surrounding tissue.

Braasch and Schacht found that the symptoms were quite variable. They may be gradual in onset, or very sudden, with rapid development of uremia and early death. A cerebral vascular accident may be the first indication of disease, or the patient may have progressive signs of hypertension. Cardiac decompensation with dyspnea and edema occasionally occurs. Weakness, malaise

headache, and gastric distress are very frequent findings.

Of the subjective symptoms in this series of cases, pain was present in a large number, varying from a dull ache to a severe pain in the lumbar or lateral abdominal regions. Gross hematuria was found in sixty-six of the patients and was found to be brought on frequently by exercise. Microscopic hematuria was present in eighty-five patients. In fifteen percent of the patients dysuria and polyuria were present. Nausea and vomiting occurred in fifty cases, and loss of weight was present in one hundred fifteen cases. Profound weakness was present in forty cases. These investigators found a correlation between cases with a poor prognosis and the extend of weakness and weight loss.

Objective findings revealed bilateral kidney enlargement in one hundred fifty one cases. Unilateral enlargement occurred in thirty cases, and no enlargement in twelve cases. It was usual to find one kidney larger than the other. The largest kidney which they observed was found to weigh 7,284.0 gm. The normal kidney weight is 115.0 to 170.0 gm. (Gray's Anatomay 1943

There was a definite association between polycystic kidney disease and hypertension. The average age of this group was forty-three years, and considering a blood pressure over 145 mm. Hg. systolic and 90 mm Hg diastolic, as an indication of hypertension, aixty-one percent were found to be hypertensive. Of the patients reported dead seventy-one percent had hypertension

and a control group made up of patients of same age and sex who had pyelonephritis, had only twenty-six percent hypertensives. Fifty-two percent of the patients dead and who had hypertension were under fifty years of age. Fifty-seven per cent of the entire group showed retinal sclerosis or retinitis, or both.

In fifty-six percent of the patients, the hemoglobin was below 70 % of normal, and in forty-two percent of the cases the erythrocyte count was below 4,000,000. Forty percent showed a urine specific gravity below 1.010, and albumin in small amounts was found in one hundred-eighty patients. Eleven percent had casts, and pus cells were present in ninety-four percent. Blood urea was elevated in the majority of cases, sometimes over 200 mgm %. Normal is 12 - 15 mgm %. (Kracke - Parker 1940), and renal function was impaired in sixty-seven percent as determined by dye excretion tests. (Braasch and Schacht 1933)

In 1943, Yardumian and Ackerman reported on ten cases ranging in age from new-born to old age. Of these, three presented signs of kidney pathology which apparently was precipitated by an upper respiratory infection. Five had complaints of hypertension. One case had signs of renal insufficiency and another had as the presenting symptom, an abdominal mass. Physical examination revealed abdominal masses in five of the ten cases; two bilateral and three unilateral. No gross hematuria was observed but the urine was usually loaded with pus cells. Seven of the patients were anemic. Five of the ten cases died of uremia, in addition to one new-born which died four hours after birth. The diagnosis was confirmed by pyelography in eight of the ten cases.

(Vardumian and Ackermann 1943)

Another case was reported in which the patient died from cerebral hemorrhage, associated with arteriosclerosis and hypertension. Polycystic kidney disease and a cystic liver were found at autopsy. (Oosting 1944)

The diagnosis of polycystic kidney disease is usually not difficult. The presenting symptoms of pain, hematuria, abdominal mass, and signs of renal insufficiency should lead one to suspect the condition, especially when bilateral masses are present. Polycystic kidney disease is about the only condition which will give bilateral renal enlargement. (Piersol 1928) Any case of chronic nephritis should be considered as a possible case of polycystic kidney disease. (Randall 1932) Occasionally the diagnosis may be obscure and the disease has been called the "great imitator of renal diseases". (Dooley 1940) In one case symptoms were present for twelve years before a diagnosis was made. (Berardi 1944) It is therefore possible that the diagnosis may be difficult to make unless the disease is fairly well advanced and destruction of renal tissue extensive. The main differential diagnosis is from tumors of the kidney, and from other renal pathology such as hydronephrosis, the late stages of glomerulonephritis, and from other forms of cysts which may be due to occlusion of tubules as a result of infection. (Lazarus 1937)

One of the greatest aids in the diagnosis of polycystic kidney disease has been the use of x-ray. A characteristic appearance can be found in the majority of cases. Lobulation of the kidney

outline can usually be observed in a plain film. A more characteristic and definite picture is obtained by use of intravenous or retrograde pyelography. Various distortion of the renal pelvis can be observed, there being general enlargement with lengthening and compression. Clear cut crescentic indentations in the pelvis as the result of projection of adjacent cysts, is the usual finding, and is pathognomonic of polycystic kidney disease. Bilateral findings are almost invariably present, and differentiate the condition from a neoplasm. (Shanks, Kerley and Twining 1938) Renal function is usually sufficient to outline the kidney architecture when pyelography is used. Otherwise retrograde pyelography must be used. An accurate diagnosis in the living patient depends almost entirely on pyelography. (Pillmore 1946)

The treatment of polycystic kidney disease is divided into medical and surgical forms of treatment. In general, medical treatment is the most important and consists of careful management of the patient's food and water intake, and regulation of habits, similar to patients with chronic nephritis. (Lewis 1946) Surgical treatment should be reserved only for the complications of the disease, in which case it may be used to great advantage. Among the surgical procedures used are Rovsing's multiple puncture, decapsulation, and in rare cases, nephrectomy. The first nephrectomy for polycystic kidney disease was done by Bardenheur in 1882, and in 1911, Rovsing developed the technique of multiple

puncture of the cysts, a procedure which is still widely used. (Ezickson 1936) Nephrotomy or ureterolithotomy may be required in cases with calculus. (Lazarus 1937)

The indications for surgery are, (1) severe hemorrhage; (2) pain; (3) infection; (4) calculus; and (5) impending uremia. (Ezickson 1936) The causes of the complications of polycystic kidney disease are due to interference with normal drainage from pressure of the cysts on surrounding parenchyma, or on the ureter; and to increased pressure within the cysts which causes pain and exposes the blood vessels to laceration.

Calculi are best treated surgically because of the danger of infection with repeated cystoscopic manipulation. The stone may be small enough to pass spontaneously. Infection is usually of the infected hydronephrosis or pyonephrosis type and when a badly infected kidney is present, nephrectomy may have to be resorted to in order to save the patient's life. Hemorrhage is a common complication and when extensive, is an indication for nephrectomy. It can usually be controlled however, by conservative measures, such as rest and transfusions. For pain, decapsulation and Rovsing's multiple punctures are the usual procedures of choice. Impending uremia may be thwarted by puncture of the cysts and relief of tension. (Lazarus 1937)

It has generally been decided that nephrectomy will bring out the disease in the remaining kidney. (Lazarus 1937) It is obvious, however, that in definitely unilateral disease, nephrectomy would effect a complete cure. Several such cases have been described in which recovery was apparently complete. (Ravich 1937)

(Wakely 1930) At any rate, it is the best procedure to be more conservative in the vast majority of cases. A nephrectomy should only be done when there is an extreme emergency, as in persistent suppuration or uncontrollable hematuria. (Oppenheimer 1934) Low and Croakley in 1944 said that surgery of any kind during the last decade would lead to disaster. (Low & Croakley 1944)

As the disease progresses, hematuria becomes a predominant symptom. Renal parenchyma becomes more and more destroyed and ranal function decreases. Nitrogenous products accumulate in the blood stream with eventual development of uremia, coma, and death, which is the ultimate fate of all patients with the disease unless they die sooner of another cause. (Low & Croakley 1944)

## CONCLUSIONS

From this study of polycystic kidney disease, it is possible to draw a number of conclusions.

1. The disease is definitely congenital in origin, and is the result of failure of disappearance of normally developing cysts in the embryonic kidney.
2. There is a strong hereditary tendency and the disease can definitely be traced through several generations in a family. It cannot be stated that it is invariably inherited.
3. There is a frequent association with other congenital and inherited anomalies.
4. The disease almost invariably involves both kidneys, but one kidney may be involved to a much greater extent than the other. Undoubtedly, unilateral cases do occur and several have been reported.
5. The disease generally appears in two age groups, namely, infancy and in adults, with but few cases in the years between the two age groups.
6. Symptoms are variable, and depend largely on the extent of destruction of renal parenchyma. The disease often presents symptoms of chronic nephritis. Other common symptoms are hematuria, pain, gastric disturbances. Kidney enlargement, unilateral or bilateral, is one of the commonest findings. Renal function is definitely

impaired as determined by renal function tests, and there is a fairly constant association with hypertension.

7. Diagnosis is usually easy but at times may be difficult. The most frequent differential diagnosis must be made between neoplasm and chronic nephritis. Pyelography is one of the most valuable aids to diagnosis.

8. Treatment is necessarily medical, except for certain complications, as uncontrollable hematuria, infection, pain, calculus, or impending uremia where surgery must be used. Procedures most commonly employed are Rovsing's multiple puncture, decapsulation, and pyelotomy or ureterolithotomy for calculus. Nephrectomy is reserved only for rare cases where it may prove life saving. Nephrectomy almost always results in development of the disease in the remaining kidney.

9. The prognosis is invariably poor, as this is a progressive disease, and ultimately, pressure of the cysts and destruction of renal tissue leads to renal insufficiency.

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