# POLYCYSTIC DISEASE OF THE KIDNEYS WITH SPECIAL REFERENCE TO ITS CLINICAL FEATURES, RADIOLOGICAL DIAGNOSIS AND GENETIC NATURE.

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To Kina,

who has given so much.

# PREFACE

The greater part of the radiological and genealogical investigations of this work, was carried out while I was practising in partnership with Dr. F.C. Malherbe of Swellendam. He was always willing to shoulder the extra work and responsibilities of a busy general practice to allow me the freedom to carry out this work. I am deeply indebted to him for this and for all that working with him has meant to me.

The work on this project was continued during the last two years, while I was a member of the staff of the Department of Anatomy of the University of Stellenbosch Medical School. This was only possible on account of the considerate attitude of Professor J.F. van E. Kirsten, head of this department, who has allowed me all the desired time to continue out the project. I am at a loss to express, adequately, my appreciation for this and all the assistance he has given me in other ways.

The one person who has been a constant help, from the very beginning, and who has done much to make it possible, is Dr. P.J.M. Retief. He arranged for many of these patients to be examined radiologically at a time when I was too far away from Cape Town to do it myself, and with no facilities to carry out such studies locally. I am grateful to him for this and for the friendship which has developed through this association.

I wish to thank Professor J.G. Thomson and the staff of the Department of Pathology of the University of Cape Town for permission to use their records and for the hospitality shown to me when I worked with them.

To Professor A. Kipps of the Department of Bacteriology of the University of Cape Town I am grateful for arranging for the serological typing of the blood of a group of patients, to be carried out in his department. At the same time, I wish to express my gratitude to Drs. M. Sacks and G. Davis for the interest shown in this work and enthusiasm in carrying out the serological work.

All those colleagues who examined patients on my behalf or answered letters about patients, did much to lighten a difficult task. I would like to mention in particular Dr. P.S. Olivier, who examined several patients in Johannesburg.

/Dr.....

Dr. J.N. de Klerk showed a keen interest in the radiological features of these patients and his opinion about them was a great help.

Permission to use the records of Groote Schuur Hospital was granted by the Superintendent, Dr. J.G. Burger. Access was obtained to the records of the Peninsula Maternity Hospital through the kind permission of Professor J.T. Louw and Matron A.D. East. I am grateful to all of them for these privileges.

Most of the radiological studies were carried out at the Woodstock- and Conradie Hospitals and I am most grateful to the Superintendents of these institutions for allowing this. In this respect I would also like to thank Miss. F. Duncan of the Department of Radiology of the Woodstock Hospital, who was always willing to arrange for pyelographic studies to be carried out, even at very short notice.

Mrs. G. Glickman of the Medical School Library of the University of Cape Town, made it possible to collect the literature, sometimes from obscure sources, on the subject of polycystic kidney disease. Her help has been of inestimable value; to her and to Miss. A. Rabe, I express my sincere gratitude for all the trouble they have taken on my behalf.

A number of my friends had the task of helping me with translation of articles from foreign languages. Translations from Italian were done by Professor C.G.S. de Villiers, from French by Miss. W. Dorst, Mrs. Y. van Oudenhove and Mr. J.E.K. de Vynck, from Spanish by Contesse Dr. M.J.C. de Raville and from Scandinavian languages by Mr. R.M. Braae. I am deeply indebted to all of them for their patience and willingness to assist at all times.

I gladly acknowledge the advice and aid in the statistical matters given by Prof. D.E.W. Schumann of the Department of Economics, University of Stellenbosch.

My thanks to Mr. N.H.F. Harington of the Department of Anatomy of the University of Stellenbosch for the photographic work and his assistance in innumerable matters of a technical nature.

I am grateful to Dr. O. Spohr of the Photographic Department of the Jagger Library, University of Cape Town, for shouldering the responsibility for the reproduction of this work.

/The.....

The work done by Miss. H.I. le Roux, in typing this work and preparing the tables cannot be estimated. I am more than indebted to her for her patience and for all the hard work she has put into the preparation of this manuscript.

Last of all I wish to thank the patients and other members belonging to the family that was investigated. Only with their co-operation was it possible to carry out this work.

J.C. de Villiers.

Department of Anatomy,
Stellenbosch.
December, 1958.

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# S E C T I O N  I

## INTRODUCTION AND GENERAL FEATURES.

# INTRODUCTION

This work on polycystic disease of the kidney commenced while the author was engaged in general practice in Swellendam, in the South Western Cape from 1953-1956.

Within a period of a year three patients, suffering from this disease, were seen. They were questioned about their family-relationship but they denied any such association. It was regarded as highly unlikely that three patients with a relatively rare disease, should be found in a population of about 4,000 adults without a familial relationship existing between those patients. The genealogy of each patient was worked out and when this information was brought together, it was found that they were fairly closely related.

This was the first experience that the information obtained from a patient about his family may not be reliable, not even in a small, fairly closed community.

As the family became known to the author the members were systematically investigated for polycystic kidney disease and an attempt was made to determine how many individuals were affected and in how many generations.

As the work progressed and more information was gained it became clear that many questions were in need of elucidation

/in.....

in this disease.

The work was later extended to include patients from Groote Schuur Hospital, Cape Town and also information obtained from the Department of Pathology of the University of Cape Town Medical School.

Various clinical aspects were investigated and in this respect more specifically the problem of early diagnosis. The detection of the disease in the latent phase was considered to be of great importance in giving marital advice, in giving a prognosis and in life insurance work. The early radiological features of the disease were given special attention.

The possibility of detecting the carrier state of this disease by means of gene-linkage with other inherited characteristics was also investigated.

Although there were only a limited number of infants in this series the difference between the congenital and adult form of polycystic kidneys has been emphasized.

The clinical records of patients are not given in full as this would only add to the bulk of the work without providing essential information. When features of interest were noted the clinical findings about such a patient is given in detail.

/We.....

We have had no experience with the treatment of polycystic kidneys other than by conservative means and this subject is not discussed in the present work.

MATERIAL AND METHOD

The members of the family in which polycystic kidneys occurred, formed the main group of patients in the present series.

After the genealogy of the family had been worked out, clinical examination of as many members of the family as possible was carried out.

All patients residing in the Swellendam-Heidelberg-Bredasdorp area, were personally examined by the author.

When a personal visit was impossible, letters were written to these persons and arrangements were made to have them examined by their private doctors. If they were willing, radiographic examination was arranged at the nearest hospital with facilities for adequate pyelographic examination.

As there were no X-ray facilities available in the Swellendam area, members of the family were brought to Cape Town by the author in groups of 4 or 5 for intravenous pyelography. In all about ten such journeys were made.

Hospital records of patients alive or deceased belonging to this family were traced.

/During.....

During 1958 all the members of the family, who were known to have polycystic kidneys were traced and re-examined. Some of the patients in the earlier stages of the disease who were doubtful cases had their intravenous pyelograms repeated to determine the development of the disease in its earliest phases by radiological means.

Forty members of the family had their blood typed serologically to attempt to establish linkage between polycystic kidneys and the blood-group factors and some were also investigated for the secretor property.

Taste ability for phenylthiocarbamide (P.T.C.) was also tested in these forty individuals.

It is realised that these patients belonging to one family do not present unselected groups. Most have the disease in an early or asymptomatic stage and secondly, if an intra-family correlation exists, they may show features which may not be applicable to the disease occurring in the population as a whole.

The fact that this selection of earlier cases does exist, has the advantage that the earlier stages of the disease can be followed with relative ease in such a family.

In order to obtain a more representative group of patients the records of patients admitted to Groote Schuur Hospital during the period 1940-1957 (incl.) were searched for cases of

/polycystic.....

polycystic kidney disease.

The post-mortem records of the Department of Pathology of the University of Cape Town Medical School for the years 1926-1957 (incl.) were also searched for cases of polycystic kidney disease. The records of the Peninsula Maternity Hospital for the years 1950-1957 were searched for cases of this disease in pregnant females. Admission records of the New Somerset Hospital were consulted for information on the earlier generations of the family with this disease.

HISTORICAL NOTE

In the sixteenth century Felix Plater (1536-1614), professor of anatomy at Basel, made observations on cystic kidney and liver. About a century later Giovanni Morgangi (1682-1771), professor of anatomy at Padua, found cystic kidneys in several cadavers which he dissected. He found these "hydatids" to be single or multiple. He also quoted Harvey and Willis as having made similar observations (Castiglioni, 1941).

The disease was also described by Alexis Littre (1658-1725) in a foetus (Boinet et al, 1903). In 1753 Laurentius Heisters described a foetus in which the kidneys were completely replaced by cysts. He thought these cysts to be

/due.....

due to obstruction to outflow of urine (Buttner, 1936). The disease was also described by Otmar Heer in 1790, also in a foetus (Boinet et al, 1903).

It is of interest that in its earliest stages of our knowledge, the disease was far more frequently described in infants than in adults so that Adamkiewicz (1843) thought it to be far more common in infants. This was probably because far more infants came to autopsy than adults.

During the 19th century the number of reports on this disease steadily increased and more and more cases were also reported in adults.

The literature on the subject of polycystic disease before 1900 is quite impressive. It deals mostly with case reports as curiosities and with various speculations as to its possible aetiology. Records of 41 inaugural lectures and theses on the subject of cystic kidneys were found in the literature before 1900.

The first observation on the familial occurrence of polycystic disease of the kidneys was made by Meckel in 1822 when he described the disease in 2 siblings. During the 19th century several reports of the familial occurrence of the congenital type of the disease were made by Adamkiewicz (1843), Bruckner (1869) and Virchow (1855).

/The.....

The first description of the familial occurrence of the disease in adults was by Lauenstein (quoted by Sieber, 1905) but the first author to emphasize the importance of heredity on this condition was Steiner (1899). The disease was a rarity, comparatively speaking, at the turn of the century although Dunger (1904) could collect 212 cases reported in the literature up to that time.

The diagnosis clinically was difficult and early diagnosis impossible. Hektoen (1892) could find only 3 cases of the adult form of the disease diagnosed during life. David et al (1900) could find only 14 examples of the diagnosis being made clinically.

With increasing awareness of the disease and recognition of its various guises it came to be diagnosed more frequently and this process of recognition in vivo was greatly advanced by the use of radiography and more specifically, retrograde pyelography which was first used for the diagnosis of polycystic disease of the kidney in 1913 (Adrian et al).

With the improvement in radiographic technique and the introduction of safe contrast media for excretory urography, polycystic kidneys have become a condition which is diagnosed with a fair degree of certainty on clinical and radiological grounds.

## DEFINITION AND DESCRIPTION OF POLYCYSTIC KIDNEYS

True polycystic disease of the kidney has been known under so many different names that, in the past, considerable confusion has arisen as to its meaning and the exact nosological entity indicated by the name: polycystic kidneys. Names such as congeries of cysts, cystic degeneration of the kidney, conglomerate cysts of the kidney, cystic metamorphosis of the kidney, bilateral polycystic kidney, congenital polycystic kidney and multilocular cystadenoma of the kidney have all been applied to this disease by different authors.

The concept that all cystic kidneys share the same underlying pathological mechanism but differ in the severity in which the process reveals itself did far more to confuse a difficult subject than to clarify it.

### Definition

In the fully developed form of this disease a kidney is found, in which, the normal tissue is almost completely replaced by thin-walled cysts of varying size and often of varying colour but the organ as a whole retains its characteristic renal shape.

This type of kidney lesion usually occurring bilaterally is that with which we are concerned in the present investigation.

/A.....

A few points about the pathology of this lesion may be in need of elucidation.

Bilaterality

We are not concerned here with a clinical estimation of unilaterality as this is well known to be unreliable, no matter what method of examination is employed (palpation, pyelography or even manual examination at operation). Older reports on the unilateral occurrence of polycystic kidney in clinical material can, therefore, be disregarded as only those with follow-up studies are of value. Those who did carry out follow-up studies, showed that many of the presumably unilateral cases eventually proved to have bilateral lesions (Barnett, 1917; Meltzer, 1924). If only those cases are considered where autopsy had been done and one kidney was found to be normal on macroscopic and microscopic examination, a more reliable impression is gained of unilaterality. The typical lesion as defined above has been found in such studies (Sieber, 1905; Bell, 1935).

Thiele (1952) collected a series of cases of polycystic kidneys reported by various authors in post-mortem material and found 87 unilateral cases (7.9%) in comparison to 1014 bilateral cases.

/Many.....

Many of the instances of unilateral cases reported in infants have been examples of multicystic kidney disease (Lynch et al, 1937; Schwartz, 1936; Herxheimer, 1906).

This may be the reason why Marcel (1954) found that unilaterality was more commonly found in a series in which infants are included.

Even in adults, confusion has arisen due to inadequate differentiation between polycystic kidneys, multicystic kidneys and multilocular cysts (Thomas, 1929).

Polycystic kidney on the one side and a hypoplastic kidney on the other side has been described (Oppenheimer, et al, 1949; Roscher, 1933; Fuss, 1933).

A solitary kidney affected with typical polycystic disease has also been found (Coombes, 1909; Brown, 1951; Frankson, 1955; Carlson, 1946).

Comment

We are left with the question: Does this really prove that the disease does occur unilaterally?

If we believe that adults with polycystic kidneys have always had cysts in their kidneys which only begin to develop at a later age, then a microscopically normal kidney at post-mortem proves that this kidney is normal and would have remained so.

/If.....

If, on the other hand, it is believed that the lesion in polycystic kidneys in adults is of the nature of an obiotrophy, then a normal kidney on one side may merely indicate that cystic degeneration has not yet commenced on that side. Therefore, the pathological finding of a unilateral polycystic kidney disease can only indicate the state of affairs at the time of death and no means are known, as yet, to indicate whether that normal kidney would have remained so. It is of interest that Israel (1901) stated that the disease is always bilateral, even if only potentially so in apparently normal kidneys. For all practical purposes, true polycystic kidneys must be considered as always being bilateral.

Size of the kidneys

Most authors are in agreement that the kidneys are enlarged in the vast majority of patients (Davis, 1925; Bell, 1950; Goldstein, 1951).

Bilateral hypoplastic cystic kidneys may also occur and these may be small or near normal in size (Rosenow, 1911; Ask-Upmark, 1929; Baumann, 1931; Bell, 1950).

The patients described by Thorn et al (1944) and Voth (1949) had kidneys of normal size and died in the third decade.

The great increase in size of these kidneys usually results in their lower situation than normal organs and they may exert

/considerable.....

considerable pressure on surrounding viscerae which, in turn, may lead to complications.

Shape

In the fully developed lesion the kidney retains its shape due to a proportional increase in all dimensions but the finer structural details are lost.

Surface

The irregular surface is due to the bulging of cysts of various size under the capsule.

In congenital polycystic kidneys the same irregular surface may be seen or else all cysts may appear to be of the same size or else no cysts may be seen, except an isolated one or two in cases with predominantly medullary cysts.

Capsule

This may be adherent, strip with difficulty and tear into the cysts. The capsule may be adherent to surrounding tissues due to previous inflammatory processes or haemorrhage.

Cut surface

Cysts are distributed throughout the entire kidney in the adult form of the disease. There is loss of cortico-medullary definition. The cysts are rounded and very little

/normal.....

normal renal tissue may be seen between them. Coalescence of cysts may be observed. Communication between pelvis and cysts are rarely seen. In congenital polycystic kidneys, cysts may only be found in the cortex or medulla or cortico-medullary junction. There is a far wider variation in the appearance of the kidneys in this type of polycystic disease.

Cyst contents

This varies in consistency, colour and nature. The contents may be fluid, semifluid or solid and is derived from blood, uriniferous secretion and tissue degeneration. A thick sebacious-like material containing fat, cholesterol and albumin may be found or serous fluid of urinary nature and fresh blood may fill the cysts. The variations in colour are due to altered blood pigment. Cysts with infected contents may be present. Calcification may be found within cyst contents or in the walls of cysts.

Histological findings

(a) Adult type: (See figs. I and II). The histological picture varies with the stage of the disease. The advanced case may show almost complete destruction of all normal renal tissue, with only scattered glomeruli and tubules in the septa between cysts (see fig. I). This great reduction of functionally

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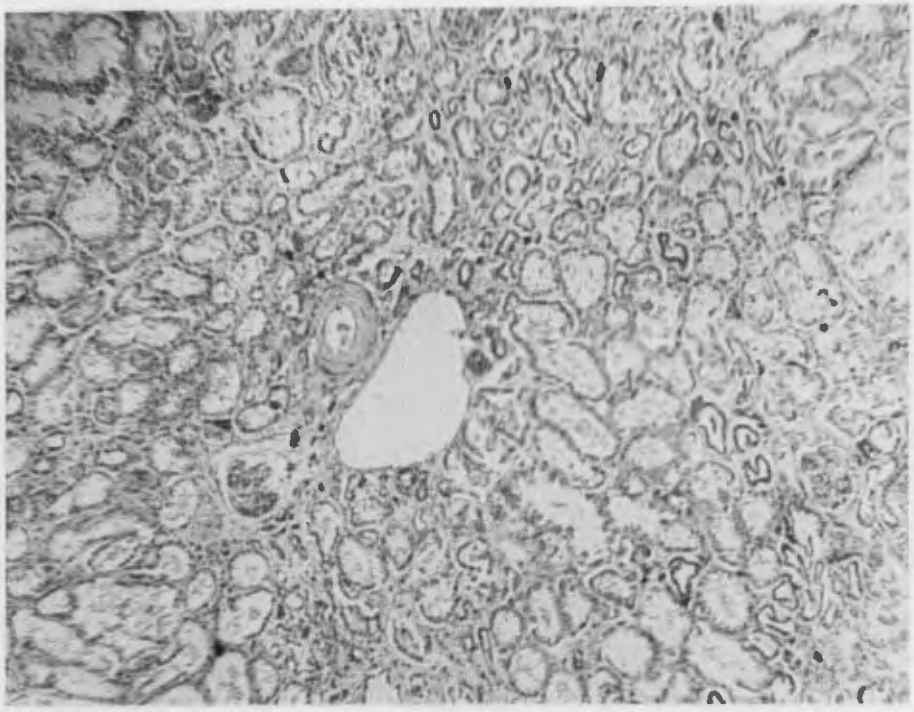

FIGURE I

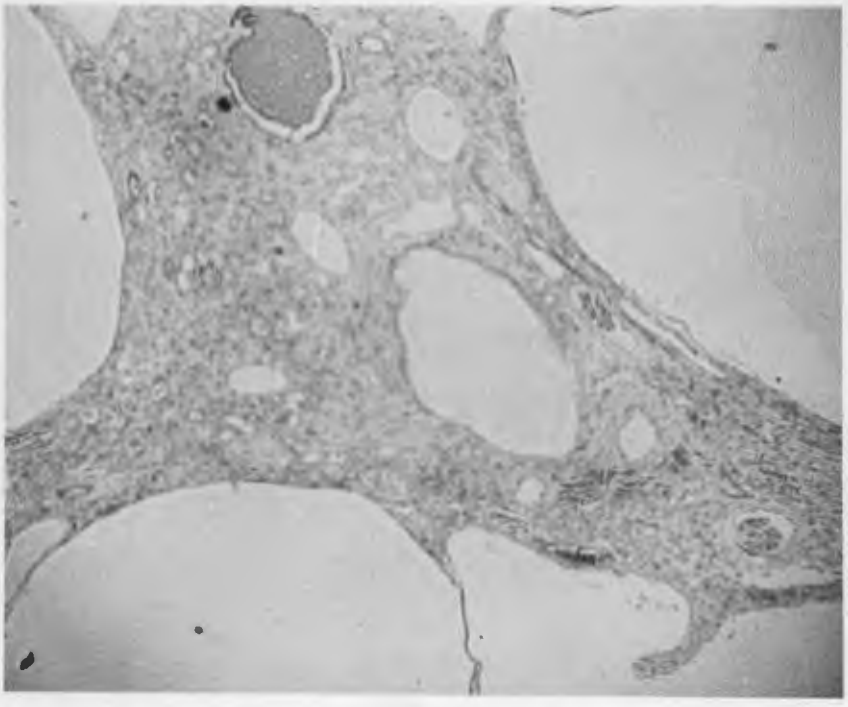

FIGURE II

able tissue, in an individual who has lived to a fairly advanced age, has always been a source of wonder to observers.

In the less advanced case proportionally larger amounts of renal tissue are found but secondary changes may be well marked in blood vessels and glomeruli (See fig. II).

The intervening renal tissue may be normal or show signs of infection or of chronic nephritis (Podgurski, 1930; Reaves, 1942). Hyalinised glomeruli are frequently found.

There may be a considerable increase in interstitial connective tissue.

The cysts may be lined by cuboidal or flattened epithelium or an epithelial lining may be entirely absent.

(b) Congenital type: (See figs. III, IV and V). The variation in the macroscopic and microscopic features displayed by the kidneys grouped together under this heading is far greater than that shown by the adult type of polycystic kidney (Boinet et al, 1903; Halbertsma, 1931; Campbell, 1951; Potter, 1952).

An attempt at classification of these lesions have been made by Potter (1952) -

I Kidneys showing no increase in interstitial connective tissue

(a) The cysts are formed by dilated tubules and glomerular capsules. The kidneys are enlarged and show cysts of about the

/same.....

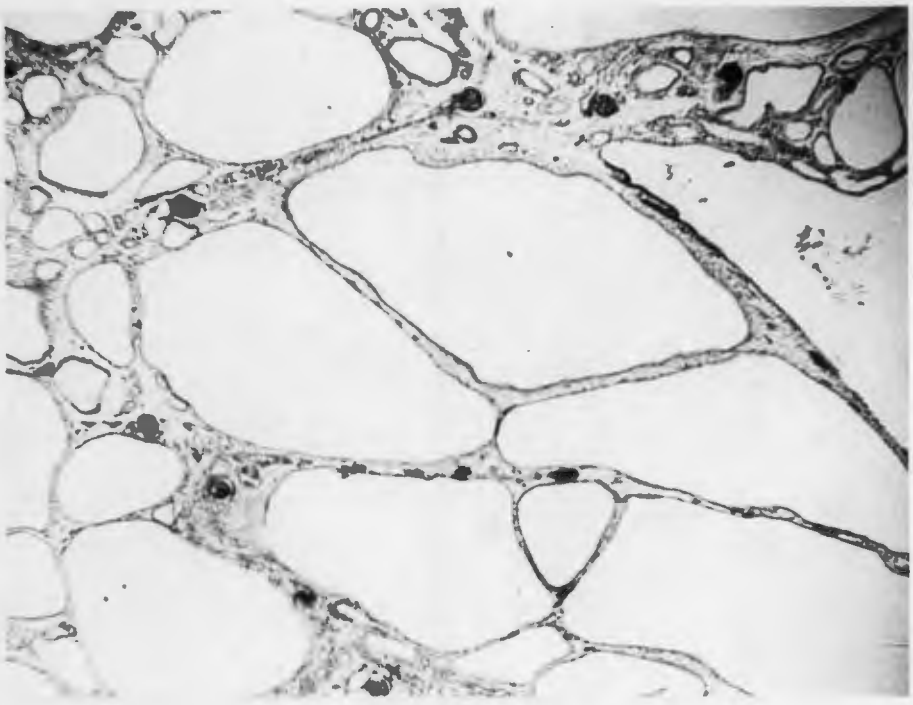

FIGURE III

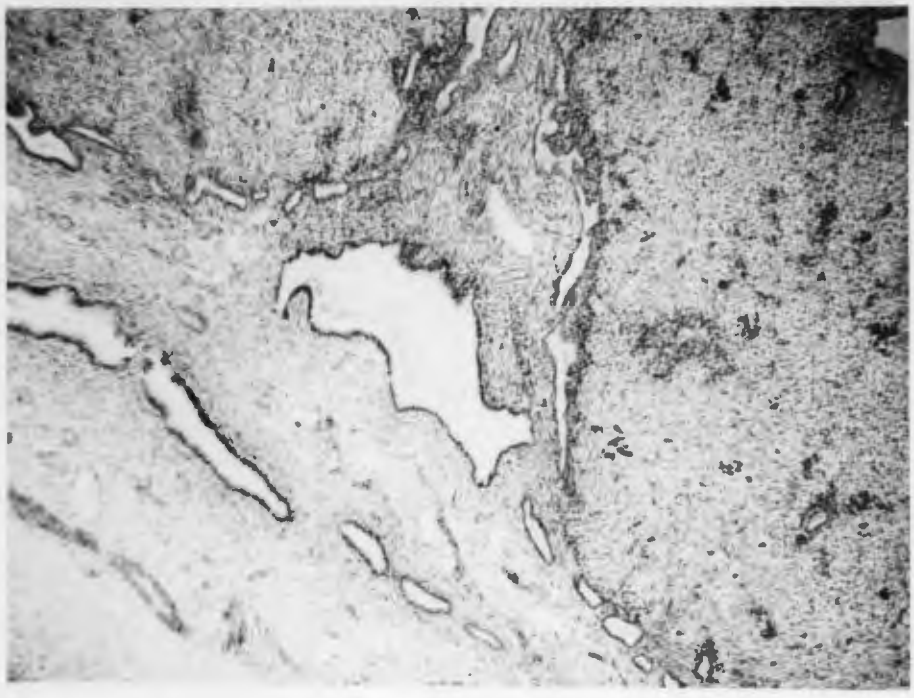

FIGURE IV

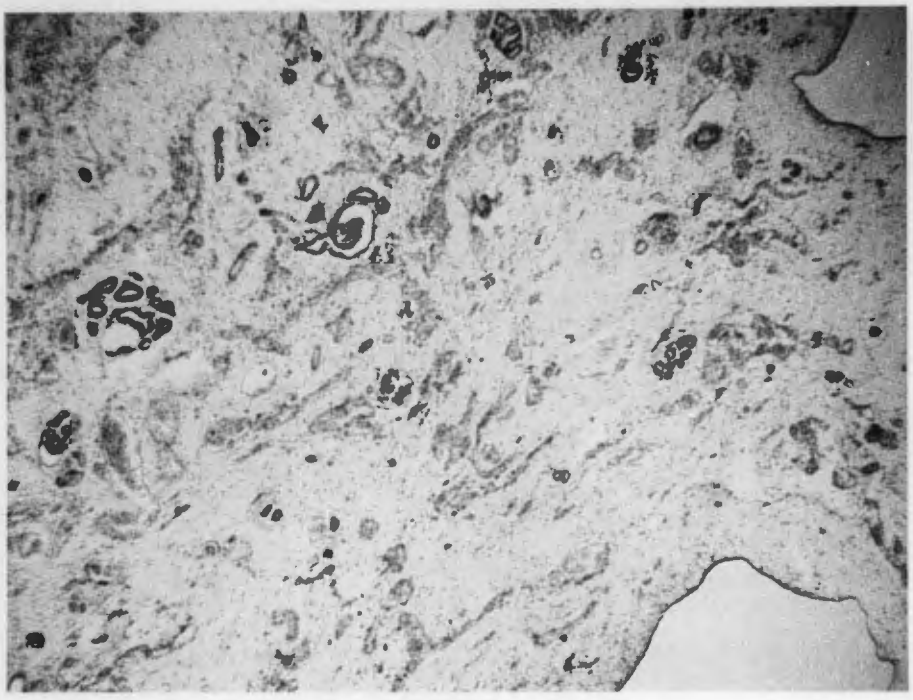

FIGURE V

same size evenly distributed throughout the entire kidney. This type associated with bile duct proliferation was found in two siblings by this author.

We found one example of this type of lesion (see fig. III). The liver also showed a marked bile duct proliferation as described by Potter (see fig. IV).

(b) Cysts formed only by dilated Bowman's capsules without increased interstitial connective tissue. Such cases have been described by Roos (1941) and Henneman (1945).

No example of this type of lesion was found in our series.

II Kidneys showing a marked increase in interstitial connective tissue

The picturespresented in these cases are more variable than in group I. Cysts vary in number and size and kidneys may be asymmetrically involved. In these kidneys there may be a large amount of connective tissue and scattered through this are cysts of varying size and a few normal renal elements and even cartilage and haemopoietic tissue (see fig. V). This lesion has earlier been described by Berner (1913) and Forssman (1913).

Cysts confined to the medulla have also been noted (Smith et al, 1945). (See fig. VI).

Comment

The histological picture is so varied in the infantile

/form.....

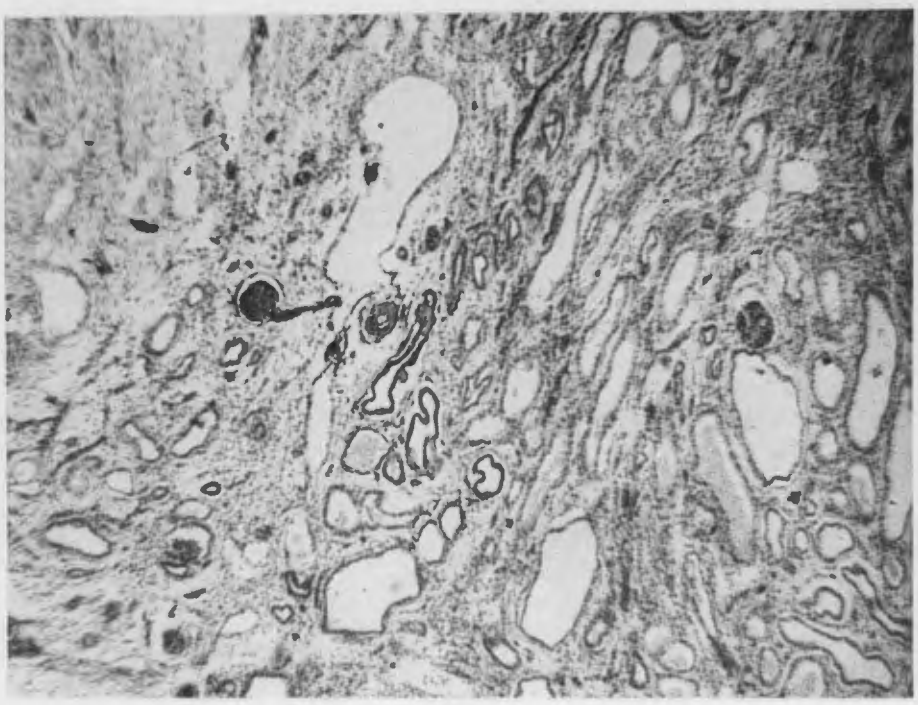

FIGURE VI

form that one has considerable doubt whether this disease is really a single entity. Potter (1952) suggested that the first type of lesion described by her i.e. the kidney without an increase in interstitial tissue may be the one which usually occurs in siblings with polycystic kidneys.

The other type has, however, also been found in members of a sibship (Forssman, 1913).

It is a fact that no equivalent of the spongy type of kidney found in infants occurs in adults.

Figure VII is added at this stage as it may be of interest.

This is a section of the kidney of a foetus of 4 months, whose mother (C. v/d V. - V 43) had polycystic disease of the kidney and developed severe toxaemia of pregnancy, on account of which the pregnancy had to be terminated. The few isolated dilated tubules may be of no significance especially if the work of Kampmeyer (1923) is accepted. It is considered to be most unlikely that this is the earliest lesion of polycystic kidney disease.

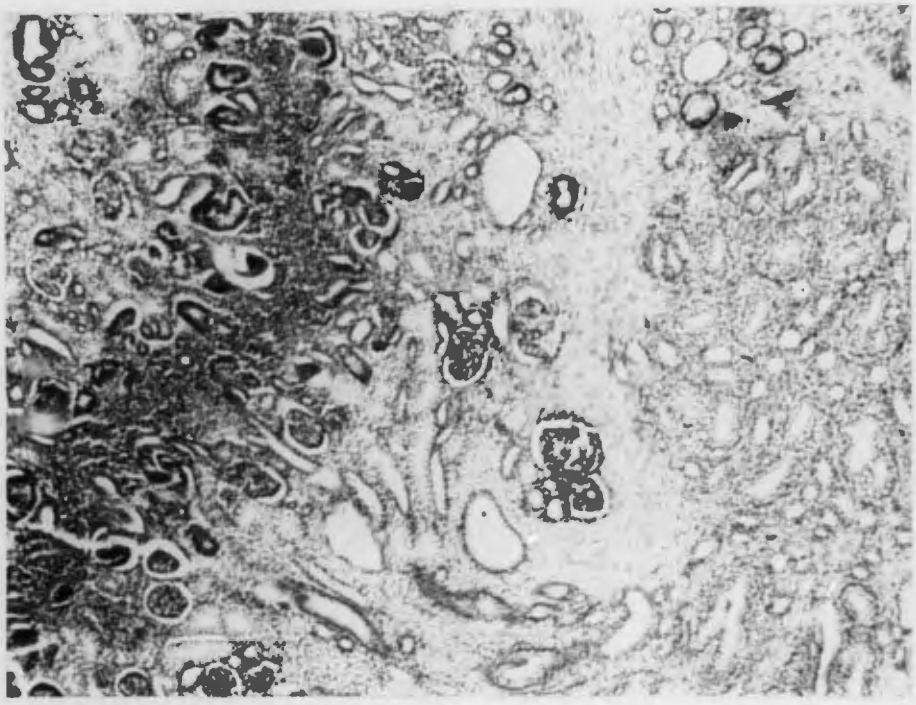

FIGURE VII

EXPERIMENTAL WORK ON POLYCYSTIC KIDNEYS

Petterson (1903) and Tollens (1904) independently proved that obliteration of the papilla of the rabbit's kidney did not result in cyst formation but in atrophy of renal tissue thus dealing the final blow to the obstructive theory of the pathogenesis of polycystic kidneys.

Reconstructions of microscopic sections of the kidney have been done by various authors (Meader, 1907; Forssman, 1913; Norris et al, 1938; Roos, 1941; Lambert, 1947). Most of the work was done on kidneys of infants except some of the reconstructions done by Norris et al and Lambert.

Micro-dissection studies on the kidneys of a newborn infant have been carried out by Bialestock (1956).

One fact has emerged from all these various sources and that is that cysts may develop from any part of the nephron and more than one cyst may develop from a single nephron. Some cysts may lose their connection with the nephron and appear to be isolated.

Not in a single instance has non-union of renal elements been proved to be the cause of cyst-formation.

There is no support for a simple concept-like obstruction and distension proximal to that. Cyst-growth can only occur as a combination of increased cellular growth and increase in

/cyst.....

cyst contents (Bialestock, 1956).

The best description of the various types of cysts found, is that of Lambert (1947). This author also differentiated the adult type of polycystic kidney from the congenital type on the basis of histological reconstruction. Tubular cysts communicate with the excretory ducts and pelvis in the adult but in the infant only closed and isolated cysts are found. Bialestock (1956) in one case studied, could not substantiate this.

Injection of the vascular system of polycystic kidneys of adults with radio-opaque material and then taking stereoscopic radiographs has been carried out to determine the nature of the vascular tree in this disease (Hinman et al, 1924 and Ritter et al, 1929). Compression and elongation of the peripheral branches of the renal artery, more marked in the interlobular arteries, were found by both groups of investigators.

The close association of the stretched arteries to the cyst walls were held to be the cause of haemorrhage into cysts and haematurea (Ritter et al, 1929).

The same authors also stated that the degenerative changes in polycystic kidneys are not merely due to mechanical pressure, but that vascular insufficiency secondary to cyst pressure may play a very important rôle. They found the vascular tree in

/this.....

this disease to simulate that found in chronic nephritis.

The influence of vascular occlusion on the development of hydronephrosis and its possible significance in the genetics of renal cysts was investigated by Hepler (1930) who indicated that vascular insufficiency may increase the rate and degree of cyst formation.

Herrick (1921) showed by perfusion of polycystic kidneys, removed at autopsy, that cyst pressure had a marked influence on the renal circulation.

PATHOLOGICAL PHYSIOLOGY OF POLYCYSTIC KIDNEYS

It has generally been accepted that symptoms are produced in patients with polycystic kidneys on account of a gradual replacement of functional renal tissue by an inert cystic mass.

In the early stages of the disease there would be a pure reduction in the number of functioning nephrons with those remaining being normal and active. In the later stages of the disease, with the development of secondary infection, fibrosis and vascular changes, even the remaining nephrons are no longer normal. Hydronephrosis due to cysts pressing on the pelvis and calyceal system may hasten this destruction (Lowsley et al, 1924).

Ward (1927) believed that the concentrations of various substances in cyst fluid passively followed the concentrations of the same substances in the plasma.

The possibility that cysts may not be a functionally inactive tissue was first investigated by le Clercq-Dandoy (1938) and later by Lambert (1947).

Inulin was injected intraperitoneally in two moribund patients and cyst fluid examined after death, showed that glomerular function is retained, at least in part, in some of the cystic nephrons (Lambert, 1947).

/An.....

An indication of tubular function was found in the fact that water reabsorbtion had taken place from cysts and back-diffusion of urea occurred as in normal tubules. Lambert was convinced that the cystic nephrons retain to a great extent their normal functional ability and that this may explain why patients with polycystic kidneys only develop renal failure at such a late stage of the disease, when very few normal nephrons are left.

Similar studies were carried out by Bricker et al (1954, 1955) on 6 patients with polycystic kidneys (5 adults and 1 child) and 5 patients with simple renal cysts coming to operation. They confirmed the work of Lambert (1947) and showed that functional ability was a property of cysts in polycystic disease but not of simple cysts and cysts at various depths were found to behave differently probably due to connection with different parts of the nephron.

Comment

The fact that the epithelial lining of the cysts retain some of the functional ability of the original tissue from which it is derived, or is in direct contact with functioning nephrons cannot be denied. That this activity is not effective function is proved by the gradual but steady decrease in total renal function in patients with this disease.

/Classification.....

Classification of cysts of the kidney

It is probably the best, if not pressed to the point of absurdity, to keep the various types of cystic kidneys in different groups, until such time as the questions of aetiology and pathogenesis have been settled. Lack of exact knowledge about the last two factors makes satisfactory classification difficult.

The following scheme was prepared after consultation of the works of a number of authors (Davis, 1925; Wells, 1936; Geisinger, 1935; Dakin, 1940; Braasch et al, 1944; Ochsner, 1951; Powel et al, 1951 and Frazier, 1951):

I True polycystic disease of the kidney

(1) Congenital type
- (a) Unilateral (?)
- (b) Bilateral (various forms)

(2) Adult type
- (a) Unilateral (?)
- (b) Bilateral

II Hypoplastic cystic kidneys
- (a) Unilateral
- (b) Bilateral

III Multicystic kidney

IV Simple serous cysts
- (1) Large solitary cysts
- (2) Multiple serous cysts

V Pyelogenic cysts

/VI.....

VI Parapelvic cysts (Peripelvic)

VII Haemorrhagic cysts

(1) Spontaneous
(2) Traumatic
(3) Associated with malignant disease

VIII Multilocular cyst

IX Dermoid cyst

X Endometrial cyst

XI Cysts secondary to pathological conditions in the kidney

(1) Cysts associated with chronic sclerosing renal disease - chronic nephritis, chronic pyelonephritis, arteriosclerosis

(2) Cysts secondary to

(a) Haematoma
(b) Calculus
(c) Tuberculosis
(d) Neoplasm

(3) Echinococcus cysts

XII Cysts in the kidney associated with

(1) von Hippel-Lindau disease
(2) Tuberous sclerosis

The last group, cysts associated with von Hippel-Lindau disease and tuberous sclerosis, has been added as this has not been found in any classification of renal cysts.

As no proof has yet been found of the congenital nature of the adult form of polycystic kidneys, the term "congenital" is applied only to the disease in infants.

As we believe that ample proof is available to justify such a division, polycystic kidneys of adults and infants are

/classified.....

classified as two distinct entities.

Hypoplastic polycystic disease is described as a separate entity by Bell (1950).

Multicystic kidney

This disease has been well defined by Baumann (1931) as a conglomerate of cysts loosely slung together by connective tissue. It has no renal shape, merely lies at the site where a kidney is normally found, posesses a rudimentary "renal artery" and has a degenerated ureter attached to it. It is not an aplastic process as small islands of normal renal tissue can be found in the septa between cysts.

Multilocular cysts

This probably best defined by Braasch et al (1933) as cysts within a cyst. These authors also believe in the essential unity of simple serous cysts and multilocular cysts on the basis of their similarity of situation in the kidney, unilaterality and similarity of wall structure. This condition has been adequately reviewed by Burrell, (1940); Frazier, (1951); and Powell et al, (1951).

Simple cysts

These cysts are also spoken of as single cysts but they are very rarely single. They are frequent in occurrence and cause

/clinical.....

clinical disturbance only if very large. Good descriptions of this condition has been given by Hepler (1930), Braasch et al (1944), Bell (1950) and Glaser (1952).

Multiple serous cysts

In this condition one has difficulty in differentiation, both clinically and pathologically, from polycystic disease of the kidney in an early phase. Around this differentiation great confusion has arisen in the past as either term has been loosely applied to one or the other of the two conditions. It is easy to visualize that a polycystic kidney in the course of its development may pass through a phase in which it resembles a kidney with multiple serous cyst.

To distinguish between these two conditions may be very difficult at such a stage (Henthorne et al, 1934; Braasch et al, 1944; Kutzmann et al, 1950).

Multiple cystic disease is not such a definite entity as true polycystic kidneys and does not cause the same disturbance in function and is not a hereditary disease. The cysts are separated by large areas of normal kidney, the disease is frequently unilateral (Braasch et al, 1944, 1951).

Multiple cystic kidney may occur as part of von Hippel-Lindau's syndrome and as such may be familial in occurrence.

/Cystic.....

Cystic disease of the kidney in association with von Hippel-Lindau syndrome

Various kidney lesions have been reported with this syndrome: hypernephromata, adenomata, medullary fibroma and cysts (Lindau, 1952) and haemangioblastoma (Sladden, 1930). The cysts are usually serous and multiple. The presence of true polycystic kidneys in this syndrome has never been described.

Two cases, those of Fraenkel (1921) and Donat (1935) are quoted by Dalgaard (1957) as evidence that polycystic disease does occur with von Hippel-Lindau disease.

The case of Fraenkel (1921) is not described as a case of polycystic kidney but merely as a patient with multiple cysts in the kidney. The same description is found in the report of Donat (1935) who found large areas of normal renal tissue between the cysts in his patient.

Cysts of the kidney have been described as the most constant visceral affection in von Hippel-Lindau syndrome (Donat, 1935).

The association of cysts of the kidney with cystic cerebellar tumour was first noted by Pye-Smith (1884) and has been reported by a great number of authors, among others Koch (1913), Lindau (1926), Knodel (1931), Craig et al (1941), Brain et al (1943), Tonning et al (1952).

/Only.....

Only one family with von Hippel-Lindau syndrome has been described in South Africa (Bird et al, 1953). No renal cysts were found in the one patient coming to autopsy.

Only very rarely does the renal lesion in patients with this syndrome, cause any clinical disturbance (Lindau, 1952) but has been described (Donat, 1935; Davison et al, 1936). Moller's (1952) patient, a boy of 12 years, who presented with intermittent haematurea, had his kidney removed and this was found to have multiple serous cysts. This boy belonged to a family in which several members had von Hippel-Lindau's disease, but he did not show any evidence of haemangiomatosis.

Cystic renal lesions in tuberous sclerosis

The fact that renal cysts occurring in tuberous sclerosis, von Hippel-Lindau syndrome and polycystic kidneys may frequently be associated with a lesion in the brain or vascular system of the brain, has lead many authors to speculate about the possible similarity in nature of these conditions (Donat, 1935; Moolten, 1943; Madonick et al, 1946).

No cases of the adult type of polycystic kidneys have been described in patients with tuberous sclerosis.

Only in two cases described by Eliakis (1937) and Inglis (1954) were true congenital polycystic kidneys found in infants

/with.....

with tuberous sclerosis. The type of cystic lesion usually described is either multiple cysts or simple cysts (Stewart, 1939; Potter, 1952).

## CYSTIC DISEASE OF THE KIDNEY IN ANIMALS

Kidney cysts have been found in a wide variety of animals.

The disease has been described in pigs (Ritchie, 1892; Osler, 1903; Davis, 1928), a newborn lion, two apes and a hen (Christeller, 1927) and a monitor lizard (Varanus) (Scott, 1925).

Horses, sheep, cattle, goats and cats have also been found to have this disease (Keizer et al, 1950). Graflin (1937) found cystic kidneys in fish and Schlumberger (1950) in a colony of goldfish with associated neurofibromata.

This finding in fish is of interest as it shows that cystic disease may also occur in a mesonephric kidney.

Meyer (1924) reported cystic liver and kidneys in two guineapig litter mates.

Cysts of the kidney in association with other visceral abnormalities have been described in the descendants of x-irradiated mice (Bagg, 1925).

Polycystic kidneys were found in a miscellaneous colony of albino mice being inbred by brother and sister matings for mammary gland lesions (Rupple, 1955).

## THEORIES ABOUT THE AETIOLOGY, PATHOGENESIS AND NATURE OF POLYCYSTIC KIDNEYS

A full discussion of this subject would really entail a review of almost everything that has been written about polycystic kidneys. Numerous theories have been put forward to explain the development of this disease, especially in the previous century. Many of these theories have become obsolete and are of historical interest only.

As knowledge about this disease accumulated, it became obvious that a hereditary tendency played a very important part in the aetiology of this disease. Today it is generally accepted that most, if not all, cases of polycystic kidney disease have a genetic background.

The pathogenesis of this disease has also been the subject of a vast number of communications and theories are almost as numerous as authors. The main theories of pathogenesis can be classified under the headings of retention, neoplasm, malformation and theories combining various of these aspects.

### Retention theories

These theories are based on a concept that obstruction to urinary outflow will lead to cyst formation due to distention of the proximal parts of the obstructed tubules.

/The.....

The first author to mention this as a possible cause of polycystic kidneys was probably Laurentius Heisters (1753). The chief protagonist of this theory was Virchow (1855) who believed that obstruction of the collecting tubules followed on the deposition of uric acid and calcium salts in the renal papillae. Later (1892) he modified his view and said that the obstruction of the collecting tubules was caused by connective tissue proliferation following on a foetal papillitis.

Prominent among the supporters of this theory were Singer (1894), von Mutach (1895) and Stieda (1901).

This theory gradually fell into disrepute. Most observers failed to find evidence of obstruction of the collecting tubules as described by Virchow.

The final blow was dealt to this theory by the work of Petterson (1903) and Tollens (1904) who showed independently that obstruction of the renal papillae in infants leads to renal atrophy and not to cyst formation.

Neoplastic theory

Beckmann (1856) believed that this disease was due to a primary connective tissue overgrowth with secondary mucoid degeneration.

That the disease was more in the nature of a cystadenoma due to tubular epithelial proliferation was proposed by Brigidi

/et.....

et al (1880), Phillipson (1888), Nauwerck et al (1892).

This theory, on its own, was never accepted by a wide group of investigators as the clinical behaviour of the disease was never that of a true neoplasm and the histological evidence for a neoplastic process was very scanty indeed. More recently Moolten (1943) stated that polycystic disease is a hamartomatous disease. This will be discussed later.

Malformation theories

This was first suggested as probably being the true nature of the disease by Hanau (1895) (quoted by Blatt, 1927) who suggested that an atresia of the papillae was the cause of obstruction of the collecting tubules.

Due to the association of polycystic kidneys with other malformations, cysts in other organs and its familial occurrence, the idea that this disease may be a malformation, came more and more into prominence. Kupffer (1865) described the kidney as developing from two distinct precursours: the metanephric blastema and the ureteric outgrowth of the distal end of the mesonephric duct.

For a long time a dispute raged about the exact mode of development of the kidney but eventually the work of Kupffer was substantiated and the dualistic theory of kidney formation

/became.....

became generally accepted.

Hildebrand (1894) was the first to suggest that the formation of polycystic kidneys was the result of non-union of the two formative elements. This theory has had such a logical appeal that, up till the present, it has remained one of the popular theories to explain the development of this disease.

Another malformation theory which was received with enthusiasm was that of Kampmeyer (1919, 1923). According to his work on normal foetal kidneys, earlier generations of nephrons atrophy and disappear and only the later generations persist in the adult kidney. In the process of atrophy these nephrons of the earlier generations, pass through a cystic stage. He explained the formation of polycystic kidneys on the basis of persistence of these cysts and growth at a later stage. Norris et al (1941) believed that this theory would also explain the occurrence of cysts in other organs.

Many objections have been raised against this theory, most important of these, probably, that one would expect to find cysts more in the vicinity of the pelvis than in the cortex of the kidney, if the theory were true. In polycystic kidney disease this is not so, as the cysts are usually widely scattered throughout the entire kidney substance and, if scanty in number, are more frequently cortical in situation.

Other malformation theories such as the persistence of

/mesonephric.....

mesonephric elements (Allbrittain et al, 1939) have never received great support.

Combination theories

Some authors tried to reconcile the divergent theories of pathogenesis into single concepts which would explain all the features of the disease. Not one of these are really worthy of consideration.

Discussion

The two most popular theories to explain the pathogenesis of polycystic kidneys are:

(a) The theory of non-union of the metanephric element with the ureteric outgrowth.

(b) The theory of persistent primitive nephrons which have failed to atrophy and have undergone cystic degeneration and increase in size.

One objection to the second theory was already mentioned above. Kampmeyer's statement that the early generations of nephrons undergo cystic degeneration has not been confirmed (Potter, 1952; Willis, 1958).

As stated previously, no definite case of non-union between the different formative elements of the kidney has been described in all the histological work that has been done on this subject.

/One.....

One fact does emerge from this work and that is that cysts may form from any part of the nephron and collecting tubules. Cyst formation is not a mere passive dilatation but an active increase in size of the cyst due to cell proliferation and increase in cyst contents (Bialestock, 1956).

The non-union theory does not provide any explanation for the occurrence of cysts in other organs.

The number of glomeruli and uniferous tubules is dependent on the number of branches arising from the collecting tubules, and if part or all of the collecting tubules are absent, glomeruli and uniniferous tubules fail to develop (Potter, 1952).

It is therefore doubtful whether proximal tubules and glomeruli will develop if union should not take place (Goldman, 1952).

Moolten (1943) was the first to introduce the concept of defective organizer activity in this disease. He stated that at a certain stage the organizer activity may fail or be inhibited in a certain tissue, and a corresponding failure or inhibition of differentiation may occur simultaneously. The intrinsic growth ability of such tissues are not lost, although they have lost the property of being controlled by organizers, which normally govern growth and differentiation, so that a great increase in size may occur.

/This.....

This theory is acceptable in that it explains not only the pathogenesis of polycystic kidneys and cystic disease of other organs but can also be reconciled with the concepts of genetic mechanisms.

"It is not unlikely that with further refinements in biochemical and biological techniques, many genetic anomalies will ultimately prove to have a metabolic basis, and that the structural defects by which they are now recognised will be seen as secondary features" (Sorsby, 1953).

One must agree with Potter (1952) that it is unlikely that a single theory will explain the development of all types of polycystic kidneys, especially the various types found in infants.

The nature of polycystic disease

Moolten (1943) believed that this disease should be classified with von Hippel-Lindau disease, multiple neurofibromatosis and tuberous sclerosis as a disseminated hamartiosis due to a defective organizer action.

Bialestock (1956) also believed that a defective organizer activity may be the cause of this disease and that the number of tissues affected and the severity of the disease depends on the time at which such an "organizer" acts.

It is of some interest that Herrick (1921) already stated

/that.....

that patients developing polycystic kidneys in adulthood do so entirely independently of any factor present at birth but are the result of a hereditary tendency which only comes to expression in middle life.

Author's view on the nature of polycystic disease of the kidneys

In the adult form of this disease we are probably dealing with an example of an abiotrophy.

The most important implication of this concept is probably that a genetically determined disease becomes manifest in a tissue, which has shown no abnormality of structure or function prior to the onset of the disease.

Of the four features usually described as characteristic of abiotrophies, familial stamp, symmetry of the lesion in bilateral organs, a characteristic reaction and anticipation only the second is prominently present in polycystic kidney disease.

The concept of anticipation is probably a fallacious one and to determine the similarity between different members of a family with a progressive disease may be difficult (Sorsby, 1953).

This concept of polycystic kidneys was reached independently of that of Dalgaard (1957) but is in agreement with his work. He also produced evidence that a significant intra-family correlation may occur.

In the congenital form of the disease it is more than likely

/that.....

that we are not dealing with one disease entity and different processes are probably at work in the pathogenesis of these lesions.

## THE INCIDENCE OF POLYCYSTIC DISEASE OF THE KIDNEYS IN ADULTS

### Clinical incidence

Numerous reports on this subject have appeared in the literature as indicated in table I.

It is important that these figures should be examined critically before any conclusions are drawn from them.

The authors who found this disease with greatest frequency reported their series from urological clinics (Melicow et al, 1940; Arrigoni et al, 1954).

The older reports suffer from the drawback that, before the use of pyelography became a standard procedure, the clinical diagnosis of polycystic disease was not made as frequently as at present when the disease can be detected in an early phase, (Hantschmann, 1933). With improvement in standard of living and resultant greater hospitalization and with an increased consciousness of the disease it is also observed more frequently although its incidence may not be greatly altered.

### Present investigation

In the 18 years (1940-1957 incl.) 22 patients with the adult form of polycystic kidney disease were admitted to Groote Schuur Hospital, Cape Town.

In the 8 years (1950-1957 incl.) a total of 168,986 patients were admitted to Groote Schuur Hospital and of these

/12.....

T A B L E  I

CLINICAL INCIDENCE OF POLYCYSTIC KIDNEY DISEASE IN ADULTS AS REPORTED IN LITERATURE

| AUTHOR | YEAR | CLINIC | TOTAL OF CASES | TOTAL OF ADMISSIONS | RATIO |
|---|---|---|---|---|---|
| Cairns | 1925 | London Hospital | Not stated | Not stated | 1:4800 |
| Braasch and Schacht | 1932 | Mayo Clinic | 193 | 680,000 | 1:3523 |
| Oppenheimer | 1934 | Mt. Sinai Hospital, N.Y. | 60 | 220,000 | 1:3500 |
| Oppenheimer | 1934 | Yewish Hospital | 22 | 143,322 | 1:6515 |
| Albrittain and Cornbrooks | 1939 | Univ. Hosp. Maryland | 17 | 99,054 | 1:5827 |
| Hausman | 1940 | Harlem Hospital | 5 | 67,000 | 1:3400 |
| Melicow and Gile | 1940 | Bentley Squirer Urol. Clinic, N.Y. | 77 | 14,155 | 1:184 |
| Mayers | 1948 | Los Angeles | Not stated | 1,300,000 | 1:4000 |
| Fergusson | 1949 | Central Middlesex Hospital | 29 | 100,000 | 1:3448 |
| Higgins | 1952 | Cleveland Clinic | 94 | Not stated | 1:4000 |
| Arrigoni, Cresseri and Lovati | 1954 | Instituto di Urologia, Milan | 24 | 8,211 | 1:342 |
| Simon and Thompson | 1955 | Mayo Clinic | 366 | Not stated | 1:2438 |

12 had the adult form of polycystic kidneys.

This gives a relative frequency of 0.000071 with 95% significance levels of 0.000031 and 0.000111.

These figures are too low, not only for reasons to be given below, but also because many patients with polycystic kidneys are diagnosed as out-patients and are not admitted to hospital. The figures given above are only for patients admitted to hospital.

It is significant that not less than 5 of these 12 patients belonged to the family with this disease with which this investigation was commenced.

Incidence in autopsy material

Table II is a summary of the autopsy incidence of polycystic kidneys as found by various authors. These figures are probably more reliable as an indication of the frequency of polycystic kidneys, but should also be corrected before any conclusions can be drawn from them.

It is not always clear what conditions have been included by different authors under the diagnosis of polycystic kidneys; whether they are all truly polycystic kidneys and whether other cystic conditions of the kidney are included as well, must remain unanswered.

As Bell (1935) pointed out the incidence is greatly altered

/by.....

TABLE II

AUTOPSY INCIDENCE OF POLYCYSTIC DISEASE OF THE KIDNEY IN ADULTS AS FOUND IN REPORTS BY VARIOUS AUTHORS

| AUTHOR | YEAR | CLINIC | NO. OF CASES | NO. OF AUTOPSIES | RATIO | COMMENT |
|---|---|---|---|---|---|---|
| Naumann | 1897 | Kiel | 16 | 10,177 | 1:636 | |
| Preitz | 1905 | Kiel | 8 | 3,500 | 1:438 | |
| Garceau | 1909 | Boston City Hospital | 10 | 2,439 | 1:244 | Quoted by Crawford 1923 |
| Barnett | 1917 | Collected Series | 41 | 10,761 | 1:262 | |
| Lowsley, Kingery and Clarke | 1924 | Brady Foundation, New York | 6 | 4,215 | 1:703 | |
| Davis | 1925 | Collected Series | 67 | 23,900 | 1:356 | |
| Ward | 1927 | Philadelphia General Hospital | 40 | 14,000 | 1:350 | Includes foetuses and newborn |
| Grüber | 1927 | Jena | 8 | 3,500 | 1:438 | |
| Ssokoloff | 1928 | Leningrad | 192 | 50,198 | 1:261 | Quoted by Hantschmann |
| Braasch and Schacht | 1933 | Mayo Clinic | 9 | 9,171 | 1:1019 | |
| Roscher | 1933 | Oslo | 7 | 3,995 | 1:571 | |
| Oppenheimer | 1934 | Mt. Sinai Hospital | 14 | 6,000 | 1:428 | Includes infants and children |
| | | Yewish Hospital | 13 | 2,060 | 1:158 | |
| Pabst | 1935 | Göttingen | 38 | 8,423 | 1:222 | Includes infants |
| Albrittain and Cornbrooks | 1939 | University Hospital, Maryland | 17 | 99,054 | 1:5827 | |
| Hausman | 1940 | Harlem Hospital | 5 | 67,000 | 1:13400 | |
| Melicow and Gile | 1940 | New York | 77 | 14,155 | 1:184 | |
| Rathbun | 1943 | Brooklyn Hospital, New York | 9 | 1,593 | 1:177 | Six infants included |
| Bell | 1947 | Minnesota | 77 | 32,360 | 1:420 | |
| Mayers | 1948 | Los Angeles | Not stated | 87,000 | 1:400 | |
| Ferguson | 1949 | Central Middlesex Hospital | 29 | 100,000 | 1:3500 | Includes infants and children |
| Nieuwhuyze | 1950 | Rijks Univ., Utrecht | 2 | 550 | 1:275 | Quoted by Van Schoonhoven |
| Robbins | 1952 | Boston | 22 | 15,000 | 1:681 | No children under 1 year |
| Bigelow | 1953 | Albany Hospital | 18 | 8,882 | 1:493 | Four infants in this group |
| Dalgaard | 1954 | Copenhagen | 143 | 98,000 | 1:773 | |
| Simon and Thompson | 1955 | Mayo Clinic | 35 | Not stated | 1:323 | |
| Uys | 1956 | Johannesburg, South Africa | 3 | 3,707 | 1:1236 | Only Bantu autopsies |

by the inclusion of stillbirths and young infants in a post-mortem series.

The inclusion or exclusion of unilateral cases of polycystic kidneys are also important.

Present investigation

The post mortem records of the department of pathology of the University of Cape Town Medical School for the years 1926-1957 (incl.) were searched for cases of polycystic kidneys. In the 32 years the total number of autopsies performed was 10,067 and polycystic kidneys in adults were found in 12 cases. This gives a relative frequency of 0.001192 with 95% significance levels of 0.000518 and 0.001866.

A better indication can probably be obtained for the years 1951-1957 (incl.).

Total number of autopsies performed on adults (21-100 years) - 2169. Number of cases of adults with polycystic kidney disease - 6.

This gives a relative frequency of 0.002766 with 95% significant levels of 0.000556 and 0.004976.

Comparison between the frequency of incidence in clinical and autopsy material

It can be observed at a glance that the disease is found far more frequently at autopsy than in clinical practice.

/This.....

This observation has lead to the statistical error that only one case in ten is diagnosed before death (Fergusson, 1949) or that only one case in ten produces symptoms (Fraser, 1954; Reed, 1955). Dalgaard (1957) pointed out that these figures are not comparable as they are derived in different ways and express different findings.

One has to admit, however, that in many instances polycystic disease of the kidney is a chance finding at autopsy and was not suspected to be present clinically. This may be due to the fact that the disease is still in a latent phase or else a complication of the disease, such as infection or uraemia, may dominate the clinical picture to such an extent, that the primary disease is not recognised. A dramatic complication such as rupture of an associated intracranial aneurysm may withdraw the attention from possible associated polycystic kidneys.

Present series

Of the 13 adults coming to autopsy who were shown to have polycystic kidneys only 5 were diagnosed as such clinically. The others had congestive cardiac failure, uraemia, subarachnoid haemorrhage and various other conditions dominating the clinical picture.

Frequency of polycystic kidneys in the living population

As this disease usually becomes manifest at a fairly

/advanced.....

advanced age and many people may harbour the disease and yet be asymptomatic, an estimation of its presence in the living population is no easy matter (Thiele, 1952).

This question, with the associated problem of morbid risk, is admirably discussed and figures calculated for Denmark by Dalgaard (1957). Besides the diagnostic problems mentioned above, the statistical material available at present, do not allow such a calculation for a South African population to be made.

Racial incidence of polycystic kidneys

Ward (1927) found relatively few cases in coloured people and thought that they were less susceptible to this disease.

Albrittain et al (1939) found the racial incidence in the white and non-white to be about equal.

Uys (1950) found 3 cases in 3,707 consecutive autopsies on Bantus. No comparable figures for europeans are available.

Present series

Of the total number of patients coming to autopsy (1926-1957) polycystic kidneys were found in 7 europeans and 5 coloureds.

In the years (1951-1957) the number of autopsies on european adults were 1039 and 2 cases of polycystic kidneys were found giving an incidence of 1/519.

/In.....

In the same period polycystic kidneys were found in 4 coloured patients out of a total of 772 autopsies on adults. Giving an incidence figure of 1/193. Polycystic kidneys were not found in 250 autopsies performed on Bantus in the same period.

The total number of cases do not allow a comparison to be made between the incidence in europeans and coloureds though it appears to be more common in the second group.

## THE INCIDENCE OF POLYCYSTIC KIDNEYS IN INFANTS

The incidence of this condition in pathological material as described by different authors in the literature is summarised in table III.

Campbell (1951) stated that one child in 250 is born with polycystic kidneys.

Bøøk (1951) found a frequency of 0.7 per 10,000 births.

Olow (1955) found only 48 cases of this disease among infants who died neonatal deaths (1944-1953) in Sweden.

### Present series

During the period (1926-1957),13 cases of congenital polycystic kidneys in stillbirths and infants were found in a total number of 10,067 autopsies. As this total include persons of all ages the figures for the years (1951-1957) may serve as a better guide to the evaluation of the incidence of this condition.

During this period 1097, autopsies were performed on stillbirths and infants up to 1 month of age and 7 of these had congenital polycystic kidneys. This gives a relative frequency of 0.006381 with 95% significance levels of 0.001669 and 0.011093. The small total number of cases make adequate comparison of the racial incidence impossible, but 5 coloureds and 2 europeans were found and this does not indicate a

/statistically.....

TABLE III

AUTOPSY INCIDENCE OF POLYCYSTIC DISEASE OF THE KIDNEY IN INFANTS AS FOUND IN REPORTS BY VARIOUS AUTHORS

| AUTHOR | YEAR | CLINIC | TOTAL NO. OF CASES | TOTAL NO. AUTOPSIES | RATIO | COMMENT |
|---|---|---|---|---|---|---|
| Bugbee and Wollstein | 1924 | New York | 15 | 4,903 | 1:327 | |
| Young | 1924 | Belgrave Hospital | 2 | 2,110 | 1:1055 | 20 Years |
| Wakeley | 1930 | Glasgow | 1 | 1,411 | 1:1411 | 16 Years |
| Bardram | 1930 | Copenhagen | 12 (Bilat.)<br>2 (Unilat.) | 4,435 | 1:370 | Autopsies on foetuses and children |
| Roscher | 1933 | Norwegian Path. Anat. Inst. | 7 (Bilat.)<br>4 (Unilat.) | 1,532 | 1:219 | Autopsies on stillborn and neonatal deaths |
| Murphy | 1947 | | 2 | 130,132 | 1:65066 | Quoted by Dalgaard |
| Bell | 1950 | Minnesota | 14 | 4,512 | 1:322 | |
| Campbell | 1951 | New York | 70 | 15,919 | 1:227 | |
| Potter | 1952 | New York | 50 | 16,000 | 1:320 | From a total of 50,000 deaths |
| Dalgaard | 1954 | Copenhagen | 24 | 10,734 | 1:447 | From a total of 147,046 births |

statistically significant difference in the racial incidence.

Comment

When the incidence in adults and infants ~~are~~ is compared for the years 1951-1957 to statistically significant difference can be detected.

# S E C T I O N  I I

## CLINICAL FEATURES AND COMPLICATIONS OF POLYCYSTIC DISEASE OF THE KIDNEYS IN ADULTS

## THE CLINICAL FEATURES OF POLYCYSTIC DISEASE OF THE KIDNEY

Polycystic kidneys have been the subject of a great many single case reports and of comprehensive studies on large series of patients. The literature which has accumulated on this subject during the latter half of the previous century and the first half of the present is so massive that a complete review is impossible.

Individual case reports frequently deal with rarities but series of patients described in great detail have done much to clarify our concept of this disease.

If we consider only those contributions which were made during the present century the work of Sieber (1905) on a collected series of 212 patients deserves mention as a first large scale evaluation of polycystic kidney disease.

The work done at the Mayo clinic on this subject since the first publication of Braasch (1916) have probably standardised our knowledge far more than any other contribution. Of special importance are the publications of Braasch et al (1932), Rall et al (1949) and Simon et al (1955), on the clinical aspects of this condition.

The monumental work of Dalgaard (1957) will probably become the standard of reference for all those interested in this subject. It is an excellent attempt of statistical analysis of

/various.....

various clinical aspects of the disease. Evaluation of prognosis, surgical treatment and genetic aspects are all carried out with irreproachable statistical methods.-

It would be impossible to add new information to the bulk of accumulated knowledge on the clinical features, especially as such a comparatively small group of patients are discussed. We did, however, attempt to provide a review of our knowledge of this disease and to bring together in one work, the features often described by various authors with specialised interests in a wide variety of publications.

Our material does show a certain degree of selection as those patients belonging to family I form the majority of this series. This feature provided us with a group of patients with the disease in a very early stage, frequently with no subjective disturbance due to its presence. The chief interest on our part was to attempt to find a method of early diagnosis. All the various clinical findings are therefore evaluated with the aim of early diagnosis in mind.

In those patients who were not examined personally, it was often difficult to know whether a feature was not present, or had not been looked for, when it was found to be absent in a clinical record. Only indisputable evidence to prove or to disprove a feature has been included in this analysis.

The clinical material used in this series have been set

/out.....

out in tables IV and VII.

In the following discussion the clinical features of the disease in adults will be considered and not in infants and young children as the material and information is too scanty for any valid information to be gained from it.

Table VII indicates the chief findings in the one infant and 4 children found in the clinical records of the Groote Schuur Hospital.

The clinical material for this analysis is composed of

(a) The thirty members of family I of whom 27 were personally examined by the author (see table IV).

(b) 14 Cases from the records of the Groote Schuur Hospital (see table V).

(c) Those cases coming to autopsy of whom adequate clinical notes are available (see table VI).

Sex ratio

In large series of cases of polycystic kidney disease in adults the sex distribution was almost always found to be equal (Braasch et al, 1932; Rall et al, 1949; Bell, 1950).

An unexplained difference in the sex incidence has been found by various authors.

Males were more commonly affected than females in the series reported by Pabst (1935), Frankson (1955) and Simon et al (1955).

/Sieber.....

TABLE IV

CLINICAL DATA ON PATIENTS BELONGING TO FAMILY I

| NO. | NAME | GENEALOGICAL NUMBER | GROOTE SCHUUR HOSPITAL NUMBER | SEX | AGE AT ONSET OF SYMPTOMS | AGE AT TIME OF DIAGNOSIS | AGE AT DEATH | DURATION OF DISEASE (TILL DEATH OR LAST FOLLOW-UP EXAMINATION) | METHOD OF DIAGNOSIS | ENLARGED KIDNEY | HAEMATUREA | ALBUMINUREA | BLOOD PRESSURE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H.C.B. | III 8 | - | F | - | 82 | - | 2 years | Pyel. | - | - | +++ | 240/130 |
| 2 | D.M.G. | IV 16 | 78811 | F | 54 | 54 | 63 | 9 years | Pyel. | Bilateral | + | ++ | 160/90 |
| 3 | P.A.M. | IV 18 | 145333 | M | 56 | 53 | 56 | less than 1 yr. | Pyel. | Bilateral | + | + | 200/130 |
| 4 | D.M.L. | V 4 | 182010 | F | ±42 | 44 | 45 | ±3 years | Pyel. | Bilateral | + | + | 180/100 |
| 5 | J.N.R. | V 5 | 153162 | M | ±39 | 39 | 39 | ±2 weeks | - | Right | + | ++ | ? |
| 6 | M.C.P.R. | V 6 | 148952 | F | 32 | 36 | - | 10 years | Pyel. | Bilateral | + | ++ | 170/100 |
| 7 | M.P.J.R. | V 7 | - | M | 27 | 27 | - | 12 years | Pyel.+Op. | - | - | Trace | 130/85 |
| 8 | E.D.G. | V 9 | 131358 | F | 47 | 47 | 49 | 2 years | Pyel. | Left | - | ++ | "High" |
| 9 | M.J.G. | V 10 | 53/0317 | F | ±40 | 48 | 49 | 9 years | - | Bilateral | - | ++ | 220/120 |
| 10 | M.J.G. | V 11 | 97793 | M | ±21 | 32 | - | 28 years | Pyel. | Bilateral | + | + | 200/110 |
| 11 | M.C.G. | V 12 | 57/67480 | F | ±43 | 43 | - | 3 years | Pyel. | Bilateral | - | ++ | 220/120 |
| 12 | J.H.D. | V 13 | - | M | ± | 31 | - | 2 years | Pyel. | - | - | + | 135/90 |
| 13 | E.D.C. | V 14 | 158991 | F | - | 29 | - | 3 years | Pyel. | - | - | - | 120/70 |
| 14 | E.J.v.R. | V 27 | - | F | - | 43 | - | 3 years | Pyel. | - | - | - | Normal |
| 15 | H.P.M. | V 28 | - | M | - | 41 | - | 3 years | Pyel. | - | - | Trace | 130/95 |
| 16 | M.J.B. | V 32 | - | F | - | 32 | - | - | Pyel. | - | - | ? | 135/85 |
| 17 | C.G.P. | V 34 | - | F | 33 | 33 | - | 3 years | Pyel. | Right | - | Intermittent | 180/100 |
| 18 | C.E.C. | V 36 | - | F | 44 | 44 | - | 3 years | Pyel. | Bilateral | - | + | 150/95 |
| 19 | H.P.C. | V 37 | - | F | - | 40 | - | 3 years | Pyel. | Bilateral | - | ++ | 180/110 |
| 20 | E.S. | V 38 | 55/09284 | F | 33 | 33 | - | 3 years | Pyel. | Bilateral | - | - | 170/100 |
| 21 | F.S. | V 39 | 55/06341 | F | - | 28 | - | 3 years | Pyel. | - | - | Trace | 150/80 |
| 22 | C.v.d.V. | V 43 | - | F | 36 | 38 | - | 5 years | Pyel.+Op. | Bilateral | - | + | 160/100 |
| 23 | D.M.du T. | V 45 | 55/12533 | F | - | 29 | - | 5 years | Pyel. | Bilateral | - | + | 175/110 |
| 24 | H.P.M. | V 48 | - | M | - | 33 | - | - | Pyel. | - | - | ? | ? |
| 25 | C.E.B. | VI 13 | - | F | - | 24 | - | 3 years | Pyel. | Bilateral | - | ++ | 130/80 |
| 26 | C.R. | VI 23 | - | F | - | 16 | - | 6 months | - | Right | - | + | 120/70 |
| 27 | M.C.P.G. | VI 29 | - | F | - | 16 | - | 3 years | Pyel. | - | - | + | 150/90 |
| 28 | N.C.G. | VI 30 | - | M | - | 15 | - | 3 years | Pyel. | - | - | - | 150/90 |
| 29 | C.S. | VI 56 | - | F | - | 16 | - | 4 years | Pyel. | - | - | + | 130/90 |
| 30 | E.D.C. | VI 65 | - | F | - | 18 | - | 4 years | Pyel. | Bilateral | - | + | 145/90 |

TABLE V

CLINICAL DATA ON CASES FROM THE RECORDS AT GROOTE SCHUUR HOSPITAL

| NO | NAME | RACE | GROOTE SCHUUR HOSPITAL NUMBER | SEX | AGE AT ONSET OF SYMPTOMS | AGE AT TIME OF DIAGNOSIS | AGE AT DEATH | DURATION OF DISEASE (TILL DEATH OR LAST FOLLOW-UP EXAMINATION) | METHOD OF DIAGNOSIS | ENLARGED KIDNEY | HAEMATUREA | ALBUMINUREA | BLOOD PRESSURE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 31 | H.V. | European | 28129 | F | ? | 24 | - | 21 years | Pyel.+Op. | Left | - | + | 165/100 |
| 32 | G.M.I. | European | 44222 | F | 34 | 34 | - | ? | Pyel. | Left | - | Trace | 125/70 |
| 33 | A.M.S. | European | 59931 | F | 68 | 68 | - | ? | Operation | Right | - | - | 200/110 |
| 34 | M.E.B. | European | 51977 | F | 41 | 41 | - | ? | Pyel. | Bilateral | - | Trace | 166/86 |
| 35 | G.J.T. | European | 42037 | M | 26 | 26 | - | 4 years | Pyel. | - | + | + | 125/75 |
| 36 | M.J.le R. | European | 78736 | F | 11? | 22 | - | ? | Pyel. | - | - | ? | 160/90 |
| 37 | J.E.G. | European | 122882 | M | 67 | 67 | - | ? | Operation | Left | - | - | 160/105 |
| 38 | H.T.B. | European | 137464 | F | ±35 | 42 | 44 | 9 years | Pyel. | Bilateral | + | - | 140/105 |
| 39 | D.T. | European | 142840 | F | 36 | 36 | ? | ? | Pyel. | Bilateral | - | + | 145/95 |
| 40 | C.D. | European | 179248 | F | 55 | 55 | - | ? | Pyel. | Left | - | Trace | 170/100 |
| 41 | J.B. | Coloured | 30223/55 | F | 30 | 30 | - | ? | Pyel. | Right | ? | - | 140/90 |
| 42 | L.C. | Coloured | 48331 | F | 25 | 25 | - | ? | Pyel. | Bilateral | ? | ++ | 220/160 |
| 43 | C.S. | Coloured | 52547 | F | 35 | 35 | - | ? | Pyel.+Op. | Left | - | - | 130/75 |
| 44 | E.D. | Coloured | 57304 | F | 39 | 40 | - | 3 years | Pyel. | Bilateral | - | + | ? |

TABLE VI

DATA OBTAINED FROM ADULT CASES IN WHOM POLYCYSTIC DISEASE OF THE KIDNEY WAS FOUND AT AUTOPSY

| NO | NAME | AGE | RACE | SEX | P.M. NO. | CLINICALLY DIAGNOSED | CLINICAL FINDINGS | | | | AUTOPSY FINDINGS | | | CAUSE OF DEATH |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CLINICALLY ENLARGED KIDNEYS | HAEMATUREA | ALBUMINUREA | BLOOD PRESSURE | ASSOCIATED ANOMALIES | CARDIOMEGALY | KIDNEYS | |
| 45 | G.M.S. | 47 | Eur. | M | 47/1926 | Yes | Bilateral | - | + | 240/? | Cystic liver | + | Bilat. L. | Uraemia |
| 46 | E.F. | 18 | Eur. | F | 40/1930 | No | No | - | +++ | 170/? | - | - | Bilat. L. | Puerperal eclampsia |
| 47 | Z.H.S. | 46 | Eur. | M | 137/1931 | No | No | - | ? | ? | Cystic liver | - | Bilat. L. | Peritonitis |
| 48 | A.G.S. | 68 | Eur. | M | 163/1940 | No | No | - | ++ | 170/100 | - | + | Bilat. L. | Dissecting aneurysms |
| 49 | J.A. | 48 | Col. | M | 32/1944 | No | No | - | Trace | 130/85 | Microcephaly | - | Bilat. L. + T.B. | ?Uraemia. Miliary T.B. |
| 50 | W.G.B. | 42 | Eur. | F | 14/1950 | No | No | + | +++ | 190/110 | - | + | Bilat. L. | Uraemia |
| 51 | G.H.M. | 63 | Eur. | F | 162/1950 | Yes | Right | - | ++ | 170/80 | Cystic liver Meckels Dis. | | Bilat. L. | Uraemia |
| 52 | R.H. | 55 | Col. | M | 545/1951 | Yes | Bilateral | - | ? | 155/100 | Cystic liver | - | Bilat. L. | Uraemia |
| 53 | J.K. | 56 | Col. | M | 39/1952 | Yes | Bilateral | - | ? | 245/145 | - | + | Bilat. L. | Bronchial Ca., Cerebro-vascular acc. |
| 54 | K.H. | 46 | Col. | F | 212/1954 | No | No | - | ? | 140/95 | Broad lig. cyst | + | Bilat. L. | Congestive cardiac failure |
| 55 | J.B. | 51 | Col. | M | 442/1956 | No | No | - | - | 140/110 | Cystic liver | + | Bilat. L. | Congestive cardiac failure |
| 56 | C.S. | 59 | Eur. | F | 481/1956 | No | No | - | ++ | 180/100 | Cystic liver | | Bilat. L. | Intracranial haemorr-hage |

TABLE VII

CLINICAL DATA OF INFANTS AND CHILDREN WITH CONGENITAL POLYCYSTIC KIDNEYS ADMITTED TO GROOTE SCHUUR HOSPITAL

| NO. | NAME | GROOTE SCHUUR HOSP. NO. | RACE | SEX | AGE | DURATION OF SYMPTOMS | METHOD OF DIAGNOSIS | ENLARGEMENT OF KIDNEYS | HAEMATUREA | ALBUMINUREA | COMMENT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 57 | Baby v.Z. | 160603 | European | M | 6 Weeks | 6 Weeks | I.V.P.+Clin. | Bilateral | ? | + | Died. No autopsy |
| 58 | J.C. | 21696 | Coloured | F | 3½ Years | 2½ Years | Clinical | Bilateral | Microscopic | ++ | Generalised oedema. Systolic. Blood pressure 160/?. Blood urea 63 mg.% |
| 59 | I.C. | 55377 | Coloured | M | 4 Years | 1 Month | I.V.P. | Bilateral | ? | ? | |
| 60 | D.G.K. | 10536/56 | European | M | 6 Months | 1 Month | Clinical | Bilateral | ? | ? | Hydrocephalic. Bilateral inguinal hernia and umbilical hernia |
| 61 | C.C. | 13051/57 | Coloured | M | 17 Months | 3 Months | Operation | Bilateral | No | No | |

Sieber (1906) and Higgins (1952) found the disease more frequently in females.

Infants

Campbell (1952) found a ratio of 46 males to 24 females which agreed with the ratio of the number of autopsies performed on each sex so that the sex incidence was equal.

Present series

(a) Adults: 39 Females and 17 males were found.

(b) Infants: In one the sex was not stated but 5 females and 7 males were affected.

(c) Children: 1 Female and 3 males were found.

Comment

The difference in the two sexes in our own material can probably be explained by the relatively small number of patients. It may be that factors which may not be obvious have caused a selection of material in favour of females.

The difference in the sex ratio may be explained, in part at least, by the fact that the male/female ratio in family I is 64/85.

Age distribution

(a) Age of onset of symptoms: From the earliest descriptions of this disease till the present time, attention has been

/drawn.....

drawn to the fact that this disease has two distinct peaks of incidence - one in the neonatal period and the other in late middle life.

At present we will limit our discussion to the disease in adults.

Most authors are agreed that the disease causes symptoms with the greatest frequency in the 4th, 5th and 6th decades (Sieber, 1905; Braasch et al, 1932; Fergusson, 1949 and Newman, 1950).

In the age-period 10-12 years this disease is indeed a rarity and even in the 20-30 year period few patients present with symptoms (Braasch et al, 1932). Davis (1925) reported a patient 98 years old and patients over 70 have repeatedly been encountered.

It must be clearly understood that the age of onset of symptoms does not denote the time of onset of the disease as the disease may be present for a long time without producing symptoms. This feature is especially well demonstrated in familial studies on polycystic disease. Patients may be examined because they belong to a family in which the disease has been found and they may be proved to have the disease long before they experience symptoms (Bell, 1935).

Present series

(See tables IV and V). Of the patients belonging to family I, 16 are asymptomatic. It is not unlikely that a number of

/them .....

them will remain so for a number of years. Of these 16 patients 5 were not 20 years of age at the time of diagnosis.

In family I the average age of onset of symptoms is 39 years.

If all the patients, of whom sufficient data are available, are considered then the average age of onset of symptoms is 38 years.

The distribution of the age of onset of symptoms:

| Age group: | 1-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |
|---|---|---|---|---|---|---|---|---|
| No. of patients: | 0 | 1 | 4 | 11 | 6 | 3 | 2 | 0 |

The greatest number of patients (74%) thus fell in the age group 30-39 years.

This is in agreement with the findings of most authors (Eisendrath, 1919; Fergusson, 1949; Rall et al, 1949; Frankson, 1955 and Simon et al, 1955). The average age at death of those patients who were not suspected to have polycystic kidneys clinically, but in whom the disease was discovered at autopsy, was 47 years.

From table IV the duration of symptoms can be found. The column labelled "Duration of disease" is merely an approximation as the duration of the disease could only be calculated if the exact time of onset could be established and neither time of diagnosis or of onset of symptoms provide this evidence.

It is clear that a patient may be a symptomatic carrier of

/the.....

the disease for a period of less than 1 year to more than 28 years.

Table VI shows that many patients never have any symptoms of their underlying disease at all.

POLYCYSTIC KIDNEYS IN CHILDREN AND YOUNG ADULTS

Among the older authors there were many who followed Virchow in his belief that polycystic kidney disease did not occur in the age-group 5-20 years. They believed that polycystic kidneys occurring in infants and adults were two distinct disease entities with different aetiology never showing their presence in children or young adults.

Against this view was the evidence provided by Albarran et al (1903), Dunger (1904) and Sieber (1905). These authors collected reports of cases from the literature to prove that the disease did manifest itself in the first and second decades, not including the neonatal period. Sieber (1905) found 32 such cases. Further case reports were added by Olesen (1954). From earliest times cases in this age period have probably received more attention than they deserved, in the sense that they were regarded as a bridge between the infantile and adult forms of the disease and their occurrence used as proof of the essential unity of the two disease entities (Cumming, 1928; Halbertsma, 1931; Oppenheimer, 1934; Bell, 1950).

On closer examination of the cases reported in this age-group one is struck by the fact that they are very frequently case reports probably considered noteworthy on account of their rarity.

If large series of reported cases are examined one finds that the disease, in this age period, is distinctly rare.

/Simon.....

Simon et al (1955) found 3.6% in the age-group 1-9 years out of a total of 366 patients and only 1.1% in the age group 10-19 years. Oppenheimer (1934) found no cases in the age group 0-20 years out of a total of 59 patients.

Thiele (1952) found only one patient out of a total of 25 with this disease before the age of 20 years.

It is a valid observation made by Wells (1936) that post-mortem examinations are not carried out frequently on patients in this age period and thus many of the patients with latent disease are not detected.

Bell (1950) is at a loss to account for the poverty in numbers of patients in the age group 1-20 years as he believes the infantile and adult forms of the disease to be identical and expresses the problem as follows: "We cannot construct clearly the structure of a cystic kidney which permits its possessor to survive into adult life and then die of uraemia. No infant kidney has been described which is open to that interpretation but it is clear that those who survive must have much more normal parenchyma than is found in the infant kidneys that I have studied". The rarity of polycystic kidneys in childhood has been used by some authors as evidence that the adult form of polycystic kidneys cannot be congenital in origin as one would expect more cases of polycystic kidney disease in children coming to light

/in.....

in that period when infectious diseases and nephritis are common. One would also expect a peak of deaths in early infancy which gradually declines during childhood as those with adequate renal reserve can exist longer, but this is not the case (David et al, 1900; Herrick, 1921).

Present series

In family I the diagnosis was made in 5 patients under the age of 20 years, 1 male and 4 females. They were all asymptomatic at the time of diagnosis and were still asymptomatic, 3 years later. Their ages at the time of diagnosis were 18, 16, 15, 16 and 16 years respectively. Of the cases considered to be potential sufferers from polycystic kidneys, 6 are under the age of 20 years. Four children between the ages of 6 months and 4 years were found in the records of Groote Schuur Hospital (see table VI).

Comment

It is our impression that the disease in children may be an indication of one of three possibilities:

(a) Some cases, especially those under 10 years of age are, in reality, examples of the neonatal form of the disease which have enough functional renal tissue to carry them into early childhood.

/(b).....

(b) Those cases occurring in adolescence are probably examples of the adult form of the disease coming to an early clinical expression.

In this respect, our cases from family I have to be disregarded as they were detected on special investigation, and not because the patients were symptomatic.

(c) In rare instances, a case may be found where the disease has followed a protracted course from infancy into adulthood such as described by Willan (1928).

This question will be further considered in the section on the heredity of polycystic kidneys.

PAIN IN POLYCYSTIC KIDNEY DISEASE

Abdominal pain has been found to be the symptom with which the majority of patients present by various authors (Braasch et al, 1932; Cannon, 1947; Rall et al, 1949; Newman, 1950; Higgins, 1952; Dalgaard, 1957). Pain, as an initial symptom, was found in 71% of 233 patients by Simon et al (1955).

The pain is most often described as being of a dull aching nature or a dragging sensation in the loin. Pain may be of a short duration or almost constantly present.

It may vary in intensity from mere discomfort to severe incapacitating pain. Backache may be associated with both types of pain or may be present apart from it.

This type of pain is assumed to be due to the large kidneys pressing on neighbouring structures, torsion of the renal pedicle and increased intrarenal or intracystic tension (Reaves, 1942; Simon et al, 1955). Pain may, however, be of a more severe and acute nature and may have the features of typical renal colic. This type of pain is usually associated with haematurea and passage of blood clot down the ureter. It may also occur when calculi are passed or may be associated with renal infection.

It is likely that this type of pain is always due to obstruction of the urinary passages (Shapiro, 1929; Wells, 1936).

Braasch et al (1932) noted that patients may get relief from

/the.....

the dull aching pain by lying down or on supporting the abdomen.

Present series

Pain as a symptom occurring during the course of this disease was found in 22 patients (68.7%) of a total of 32 of whom adequate clinical notes were available. (Of these 17 were females and 5 were males). In the vast majority the pain was of a dull aching nature and only rarely severe and of the acute variety.

Two of the female patients complained that tight clothing aggravated their pain; both had very large kidneys.

One patient had acute pain associated with massive haematurea following on severe exertion. Another patient had severe pain associated with feverishness and tenderness over the enlarged left kidney. She was assumed to have had an infected cyst.

Comment

We found the same significant greater frequency of this symptom in females as noted by Dalgaard (1957) but can offer no explanation for it except that it may be influenced, in some way, by pregnancy. Pain was not noted to occur in young patients unless they have haematurea.

Pain may be the first symptom and as such may bring the patient to the doctor. The pain may similate some other renal condition to such a degree that the basic pathology is not recognised.

/Haematurea.....

Haematurea

This is one of the prominent symptoms of polycystic kidney disease and should in reality be included as a complication of it. As it occurs so frequently it has become customary to group it with the symptoms and signs of this disease.

It may be slight in amount or be so severe as to be exanguinating, demanding transfusion. Usually it is intermittent and does not last very long. Haematurea may last a long time and cause a severe degree of anaemia.

Painless haematurea is probably the rule, but acute pain may be associated with the bleeding and, as stated, is assumed to be due to the passage of clots down the ureter.

Retention of urine may complicate a bout of haematurea but is usually of short duration and is often followed by the passage of a large amount of blood-stained urine. The most likely explanation for this is haemorrhage into a cyst with temporary compression of the ureter (Balfour, 1911).

Haematurea is frequently the earliest symptom of polycystic kidneys and even, if it is only found on microscopical examination of the urine, it is more liable to be treated with suspicion than a trace of albumin in the urine. Such a patient is then more likely to be subjected to a full urological examination (Newman, 1950).

/Bleeding.....

Bleeding may occur spontaneously or follow on an injury, often slight in nature, to the abdomen or may be precipitated by over-exertion.

It is generally accepted that haematurea is due to rupture of a bloodvessel into a cyst and secondary rupture of the blood-filled cyst into the calyceal system. Yden (1954) demonstrated this very well by means of pyelography carried out shortly after an episode of haematurea and with the patient X-rayed in various positions. Ritter et al (1929) showed that bloodvessels are closely associated with the walls of cysts and often lie within the cysts, covered only by a fold of epithelium. Such vessels could easily be torn and cause haematurea if the cyst ruptured into the pelvis. This also explains why haematurea may occur in young patients and is not necessarily associated with hypertension.

The frequency with which this symptom occurs, has been reported to vary between wide limits. Halbertsma (1931) found it in one-fifth of his patients while Shapiro (1929) found it to be present almost invariably.

Simon et al (1955) found macroscopic haematurea at one time or other, during the disease in 50% of their 233 patients. Albrittain et al (1939) in 64% of their patients. Of 109 patients with microscopic haematurea, 39 had never had

/macroscopic.....

macroscopic haematurea (Simon et al, 1955).

Difference in frequency in the two sexes have not been found by most workers although Braasch et al (1932) believed it to be more common in men. They suggested that this symptom may go unnoticed in females in the early phases.

Present series

Both macroscopic and microscopic haematurea are grouped together under the heading of haematurea.

Of 26 patients who were symptomatic and who had adequate notes, this feature was present in 8 (30%) which is in agreement with the findings of other authors. Of these patients 1 had microscopic haematurea only. Two presented with haematurea as the chief complaint. The youngest age at which a patient experienced haematurea was 21 years. One patient had severe haematurea after over-exerting himself.

Comment

Haematurea may be the first symptom of this disease but is an unusual finding in the age-group 10-20 years.

Lee et al (1953) analysed 1000 consecutive cases of haematurea investigated urologically. 152 Patients had the source of bleeding in the kidney, 85 had essential haematurea and 6 had polycystic kidneys.

/It.....

It would be interesting to follow up patients with essential haematurea to see how many later prove to be suffering from polycystic kidneys.

When the cause of haematurea is considered to be the rupture of a bloodvessel into a cyst as outlined above, it is clear why this symptom does not occur in the early phases of the disease, when cysts are small and isolated.

The warning uttered by Walters et al (1934) should perhaps be re-iterated at this stage. A patient with known polycystic kidneys may still have another cause of haematurea in his urinary tract, such as a neoplasm.

Palpable renal tumours

This is the third feature of the triad which is so frequently described in polycystic kidneys: pain, haematurea and enlarged kidneys. Patients do not present with a lump, which they have felt, as often as they do with the other two features. An enlarged kidney may be present for a long time without causing any symptoms and may be found accidentally by the patient or may be a chance finding during a routine examination.

It is not always clear whether renal enlargement was found early or late in the course of the disease by authors who

/described.....

described this feature.

Simon et al (1955) found initial enlargement of both kidneys in 51.1% and of one kidney only in 26.8% of their patients. Of 24 who did not have large kidneys initially, 12 later developed palpably enlarged kidneys. Bell (1950) stated that 90% of patients develop large kidneys if the disease is advanced, but that it may be absent in the early stages.

Enlarged kidneys were not found in the early stages by Lowsley et al (1945).

Dalgaard (1957) found it a very common feature of the disease, occurring halfway through the course of the disease and with significantly greater frequency in females. This greater frequency in females is explained on the basis that abdominal palpation is often easier in women.

Present series

Bilateral enlargement of the kidneys occurred in 22 patients (44%) and unilateral enlargement in 12 patients (21%) out of a total of 56 patients.

Three patients belonging to family I did not have enlarged kidneys at the first examination but developed this feature later.

The sign was present far more often in females than in males.

/In.....

In family I (table IV) there are 5 patients with renal enlargement but with no symptoms of renal disease. These patients have been observed for a period varying from 6 months - 4 years and not one of them have developed symptoms during that period.

The oldest of these 5 patients is 40 years and the youngest 16 years and all are females.

11 Patients with polycystic kidneys who are asymptomatic also have no renal enlargement.

Comment

Palpably enlarged kidneys may be a very early finding in patients with polycystic kidneys. Careful examination should be carried out to determine if this sign is present as it is a very important aid to diagnosis if it can be elicited.

Most patients with polycystic kidneys will, however, develop palpably enlarged kidneys if other factors, which make examination of the abdomen difficult, are not present.

Bilateral large irregular masses with all the features of renal tumours are virtually pathognomonic of polycystic kidney disease, but unilateral renal enlargement may cause considerable difficulty as a diagnostic problem.

We would like to draw attention to a clinical sign which has been described by Veil (1914) and Osler (1915) and which

/is.....

is due to the presence of bilateral large kidneys.

The abdomen assumes a characteristic shape, with bulging flanks, so that the upper abdomen is wider than the thorax and also flattened.

This sign was observed in 4 patients who all had large kidneys.

## CARDIOVASCULAR DISTURBANCES IN PATIENTS WITH POLYCYSTIC KIDNEYS

It is generally accepted today that polycystic kidneys are frequently associated with an elevated blood pressure.

"Among the most unequivocal examples of hypertension and cardiac hypertrophy due to primary renal lesions is that presented by polycystic disease of the kidneys" (Fishberg, 1954).

This association was probably first clearly stated by Braasch (1916).

The fact that the blood pressure may be raised in polycystic kidneys was not accepted without opposition. Many authors contested this statement and believed that the blood pressure was either not raised or only slightly so and only in the exceptional case; then being due to associated nephritis or coincident essential hypertension (Rosenberg et al, 1924; Willan, 1928; Shapiro, 1929; Bell et al, 1928; Rosenberg, 1932). Bell (1935) altered his view on this subject and accepted hypertension as a feature of this disease.

Zemitsch (1939) showed that there was no correlation between the age of the patients with polycystic kidneys and their blood pressure but that hypertension also occurred in younger individuals thus ruling out the possibility that the raised blood pressure in polycystic kidney disease is due to coincident

/essential.....

essential hypertension.

The frequency with which a raised blood pressure has been reported in this disease, varies between statements that it occurs only rarely (Shapiro, 1929), to a statement that it always occurs if other factors which tend to lower the blood pressure (cardiac infarction, fever, anemia and uraemia) are absent (Oppenheimer, 1934; Thiele, 1952).

In different series reported by Schacht (1931), Rall et al (1949), Higgins (1952) and Simon et al (1955) hypertension was found to be present in more than 70% of their patients during the course of the disease (All taking 140-145/90 as upper limit of normal blood pressure).

The cause of the hypertension is thought to be the gradual reduction in functional renal tissue. That a mechanism similar to the Goldblatt kidney may be at work here has been speculated about by a number of authors (Hollo et al, 1940) and others. The work of Ritter et al (1929) on the vascular supply of polycystic kidneys to some extent supported the view that gradual vascular occlusion due to cyst compression may cause renal ischaemia.

It does not, however, satisfactorily explain the matter as these vascular changes do not occur in all patients (Fishberg, 1954). There is also no adequate explanation why approximately 30-40% of sufferers from polycystic renal disease do not develop

/hypertension....

hypertension despite advanced renal insufficiency (Goldman, 1952).

The degree of renal insufficiency becomes no direct relationship to the development of hypertension (Hollo et al, 1940; Rall et al, 1949).

Hypertension and the symptoms produced by it, may bring the patient to the physician (Higgins, 1952; Frankson, 1955). Both these authors found that the correct diagnosis may not be made for a considerable time if patients present with hypertension. Only a full urological examination may bring the underlying condition to light. In general, it is not an early sign but comes as a fairly constant one in the later stages of the disease (Albrittain et al, 1939). Malignant hypertension in a patient with polycystic kidneys has been described by Heptinstall (1952).

Present series

Blood pressure was determined by the auscultatory method and in those patients who were personally examined, repeated readings were taken with the patient at rest.

If a value of 150/90 is adopted as an upper limit to the normal range of blood pressure then, in this group, the blood pressure was found to be raised in 27 patients of a total of 52 on whom it was recorded. One patient had his blood pressure annotated as "high" but no actual figures was given.

/Two.....

Two had systolic pressures of 240 and 170 respectively but diastolic pressures were not given.

Two patients, in congestive cardiac failure, had raised diastolic pressures and low systolic pressures. Four patients had elevated diastolic pressures and low or normal systolic pressures but were otherwise normal. One patient with a low blood pressure was admitted in a state of collapse and died shortly afterwards but the heart was not found to be enlarged at autopsy.

If we include the five probable cases of hypertension we find that 32 of these patients are hypertensive (61%).

A raised blood pressure may occur at a very early phase in polycystic kidney disease, as is shown in table I, patients nos. 27 and 28. These two children are asymptomatic and yet at the ages of 15 and 16 respectively they have blood pressures of 150/90. These readings were confirmed by repeated measurement at long intervals.

Of those patients personally examined 3 were not initially hypertensive but developed moderate hypertension in a period of 3-5 years (Patients No. 2 (IV 16); No. 17 (V 16); No. 22 (V 22); Table I).

Two of the patients regarded as potential sufferers from polycystic kidney disease are hypertensive (Patients No. V 2 and V 45).

/Case.....

Case V 45 is of interest as she has a blood pressure of 190/110 at the age of 31 years, and has no definite excretory pyelographic signs of polycystic kidneys. Her twin sister has polycystic kidneys.

Of those patients regarded as probably having suffered from polycystic kidneys case IV 22 is of interest.

> A male aged 53 years, died in uraemia with the diagnosis of malignant hypertension due to chronic nephritis. Pyelography was never carried out and an autopsy was not performed. His blood pressure ranged from 195/140-210/150 and he had large amounts of albumin as well as granular casts in the urine.

Of the hypertensive patients, only 5 had symptoms which could be attributed directly to their hypertension.

Comment

Elevation of the blood pressure may be an early sign of polycystic kidney but it is not commonly so.

What is important though; is that a patient may present clinically as suffering from essential hypertension and may have no other clinical evidence of polycystic disease. The correct diagnosis may not be made, until the patient develops additional signs of polycystic kidney disease or is subjected to pyelographic examination.

/Retinal.....

Retinal changes

Bell (1950) stated that retinitis is uncommon and that about 50% of patients with polycystic kidneys have retinal changes, in the form of arterial narrowing, while haemorrhages and exudates are distinctly rare. The rarity of true retinitis in this condition has also been accentuated by Zemitsch (1939), Köhler (1947). Braasch et al (1932) found retinal changes in 57% of their 193 patients. Higgins (1952) found retinal sclerosis in 68% of his patients.

Rall et al (1949) found evidence of raised blood pressure by means of retinal examination in 71.5% of 105 patients with polycystic kidneys. They could not correlate these changes with the degree of severity of hypertension or renal dysfunction.

In the present series, adequate notes on the retinal findings were only available in those patients belonging to family I. Of these 30 patients, only 4 had retinal changes. The patients were all hypertensive and the degree of retinal change was equivalent to a grade II retinopathy (Keith et al, 1939) in 3. A grade III retinopathy was found in one patient.

Cardiac decompensation

Very few authors have discussed this complication of polycystic kidney disease but, those who did, found it only

/very.....

very infrequently in their series, and then usually as a terminal event (Braasch, 1916; Braasch et al, 1932; Bell, 1950).

Present series

Cardiac failure occurred in 3 of the adults with polycystic kidneys. In all of these it was a typical hypertensive cardiac failure.

4 Patients complained of dyspnoea on effort and of these only 1 was not hypertensive.

Oedema and effusion into body cavities

This feature has been reported occasionally but all authors are agreed that it is an unusual finding in polycystic kidney disease (Atonna et al, 1926; Shapiro, 1929; Bell, 1950).

The cause of oedema in this disease is unknown. It may be due to cardiac decompensation or loss of serum proteins or both (Bell, 1935).

Present series

Oedema unassociated with cardiac failure was found in 4 patients out of a total of 56 patients.

Pleural effusion and ascites, similarly, are very rare findings in patients with polycystic kidneys. One patient in the present series had a pleural effusion associated with

/congestive.....

congestive cardiac failure.

Ascites may be found in patients who also have gross liver destruction due to coincident polycystic disease of the liver, but it is also a rare finding.

Vascular accidents

Sieber (1905) found 10 cases of cerebral haemorrhage in his collected series of 212 patients. Vascular accidents are not more common in patients with this disease than in another group of hypertensive patients (Braasch et al, 1932; Bell, 1950). It must be remembered, however, that these patients may have associated aneurysms of the intracranial vessels and these may rupture, even at a stage when they are not hypertensive.

In the present series of 56 adults only 3 cases of intracranial vascular accident could be found.

URINARY FINDINGS IN POLYCYSTIC KIDNEY DISEASE

From the earliest investigations up to the present, examination of the urine has received a great deal of attention as a diagnostic method.

Sieber (1905) postulated that the urine will remain free from abnormal elements, notably albumin, as long as there is enough normal renal tissue left to cope with the functional needs of the body. This is probably wrong as albuminurea may be present before there is any appreciable loss of functional renal tissue.

Balfour (1911) already pointed out that a characteristic urinary finding, which is specific for polycystic kidney disease, does not exist and that the urinary changes closely simulated those found in chronic interstitial nephritis. This similarity is only lost if blood is found in the urine in polycystic disease.

Cases have been described where the urine has remained normal throughout the course of the disease with only terminal albuminurea, but this is distinctly uncommon (Mohr, 1911; Maier, 1924; Niecke, 1930; Lambert, 1947).

Bell (1950) found albumin in the majority of his patients and it varied in quantity from a trace to large amounts.

He is of the opinion that the albuminurea is due to cysts interfering with the blood supply of the glomeruli by stretching

/or.....

or compression of the arteries and veins. No disease of the glomeruli is present in the early stages.

The fact that albuminurea may be present intermittently was probably first described by Beck (1901). This feature was confirmed by Love et al (1902), Sieber (1905), Hitzrot (1912) and Maier (1924).

The significance of a trace of albumin in the urine as an early diagnostic sign was stressed by Newman (1950) and Goldstein (1951).

Various authors who reported on large series of cases of noted albuminurea of varying degree in a large percentage of their patients. Fuller (1929) found it in all his patients with polycystic kidney disease belonging to one family.

Braasch et al (1932) found it in 95% of cases, Oppenheimer (1934) in 71% of cases, Rall et al (1949) in 78% of cases. Several authors merely state that it is usually present (Thiele, 1952) or that it is present in the majority (Simon et al, 1955).

Albuminurea

In those cases personally examined by the author, albumin was tested for by either the sulphonsalicylic acid method or the boiling test described by Zwarenstein (1950).

Only definite observations were recorded as positive.

In most of the patients personally examined by the author

/the.....

the urinary examination was repeated on several occasions.

Quantitative estimations of albumin in the urine were not carried out.

Present series

Of a total of 49 patients of whom the information was available, albuminurea was found in 39 patients (79.5%).

It is of great significance that, of the 11 patients who are regarded as potential sufferers from polycystic kidney disease, albuminurea was present intermittently.

Intermittent albuminurea has also been found in one of the proved cases of polycystic kidneys belonging to family I (see table IV, patient No. 17 (V 34)).

The amount of albuminurea varied from a trace to +++ in quantity.

In 5 patients it was the only abnormality found, except for pyelographic signs of polycystic kidneys on which the diagnosis was based.

Comment

Albuminurea was by far the most common abnormality found in this series.

It is possible that the marked tendency to albuminurea may be a characteristic of the disease in this family.

/All.....

All the young patients and those regarded as potential sufferers from the disease, were tested for orthostatic albuminurea but it did not alter the findings.

No reference could be found to this finding as such a prominent early feature of the disease.

As proved by the "potential sufferers" albuminurea may be present before the presence of polycystic kidneys can be detected by other means.

Newman (1950) made the significant observation that a trace of albumin is frequently ignored by the doctor who first examines the patient. If, however, pus or red cells were found the patient was referred to a urologist at a much earlier stage of the disease.

Albuminurea may be the earliest sign of polycystic kidneys and may be the only sign for a considerable time. When all methods fail to bring the cause of the albuminurea to light, an intensive family history may raise a suspicion of the nature of the underlying condition.

Casts

There is a wide variation in the frequency with which various authors describe the presence of casts. Those authors who have found casts to be present, described these as hyaline or granular.

/Braasch.....

Braasch (1916) found casts in 12% of patients, Oppenheimer (1934) in 17% of patients, Braasch and Schacht (1932) in 11% . Goldstein (1951) thought it to be an unusual finding and so did Herrick (1921).

On the other hand, other authors state that formed elements are frequently found (Thiele, 1952). Reaves (1942) found casts in one third of his series.

Present series

Of a total of 40 patients of whom information is available about microscopical examination of the urine, casts were found only in 3 instances (7.5%). Only one patient belonging to family I had a few granular casts (Patient No. 5 (V 5), table IV).

The great variability in this finding probably depends on the type of patient described.

In the present series, in which young patients predominate, secondary changes in the kidneys are not common and this may account for the absence of casts.

Haematurea

The presence of red blood cells in the urine on microscopic examination has been discussed under the heading of haematurea.

Pyurea

This finding will be discussed under the heading of infection

/as.....

as a complication of polycystic kidneys.

Specific gravity

This relatively simple test is one of the earliest to indicate impaired renal function in polycystic disease (Davis, 1925; Goldstein, 1951) and is also of great help as a prognostic aid (Geisinger, 1935).

As one would expect, in a condition in which there is a gradual reduction in the quantity of functional renal tissue, as in polycystic kidneys, the specific gravity falls and the urine increases in quantity (Braasch, 1916; Maier, 1924; Bell, 1950).

Polyurea may occur in polycystic disease (Veil, 1914; Shapiro, 1929; Götzl, 1933; Hantschmann, 1933). The specific gravity may be low and the kidney unable to concentrate even in the presence of normal blood N.P.N. values (Frankson, 1955).

Determination of the specific gravity of individual specimens of urine obtained by ureteral catheterization can help to identify the affected or more affected kidney by its lower specific gravity (Fullerton, 1924).

A normal specific gravity does not however, rule out the presence of polycystic disease of the kidneys (Braasch, 1916).

Present series

The available information in this particular instance

/is.....

is so scanty in the clinical and post-mortem cases that only those patients belonging to family I will be considered.

A fixed low specific gravity was found in only 3 patients. The one of the patient had a high blood urea and died shortly after examination.

Both the others are alive and show only moderate impairment of renal function.

## RENAL FUNCTION IN POLYCYSTIC KIDNEY DISEASE

The test for renal function which is employed most commonly is the blood urea level. Most authors are in agreement that in the advanced stages of the disease, the blood urea is raised in the majority of these patients.

A blood urea level of 40 mg.% or more was found in 67% of 117 patients examined for it by Braasch et al (1932). Higgins (1952) found a raised blood urea in 70% of his patients.

33% Of the patients of Oppenheimer (1934) had an elevated blood urea at some time or other during the course of the disease.

The remarkable degree to which patients can tolerate a high blood urea level, has been noted frequently (Braasch et al, 1932).

### Present series

Blood urea estimations were carried out on 27 of the adult patients.

Values exceeding 40 mg.% were present in 18 of these patients (66%).

Blood urea values exceeding 100 mg.% were found in 10 patients. Blood urea values between 40 mg.% - 100 mg. % were found in 8 patients.

Of the 10 patients with the blood urea levels over 100 mg.%,

/8.....

8 are dead. All died within a year of the estimation of this value. Of 2 no further information is available.

One patient (10) VII has had a blood urea level varying between 50-100 mg.% with which he has been able to carry on fairly satisfactorily for about 10 years.

Another patient (8) IV 16 had a blood urea level exceeding 45 mg.% for at least 9 years. Thus if the blood urea level exceeds 100 mg.% the outlook is poor (Frankson, 1955).

Other renal function tests could not be carried out as only the minority of these patients were admitted to hospital for investigation.

Comment

A raised blood urea is a late event in this disease and thus not an early diagnostic sign. If it is markedly raised it has a grave prognostic significance.

From the reports of other authors, who investigated large series of patients it would seem that there is no functional test which is specific for the early diagnosis of polycystic kidneys.

It would seem that in the early stages of the disease the excretory tests (e.g. Indigo-Carmine and P.S.P.-excretion) may be impaired while the blood urea and N.P.N. levels are still normal or only slightly raised (Braasch et al, 1932; Walters, 1934).

/Uraemia.....

Uraemia

This is the final state to which all patients with polycystic kidneys are, insidiously - but steadily, progressing. As described earlier, there is a gradual loss of functional renal tissue in this disease and eventually the remaining fraction of functionally able parenchyma cannot cope with the needs of the body and uraemia develops.

A uraemic death is the common mode of exitus for sufferers from this disease. Many observers have been astounded at the remarkable way in which patients with polycystic kidneys can live for a long time with a fair degree of comfort despite the presence of a marked degree of nitrogen retention (Köhler, 1947; Higgins, 1952).

Numerous reasons have been put forward to explain this tolerance:

The parenchyma which remains between the cysts is normal (Blatt, 1927).

The kidney has a great functional reserve (Oppenheimer, 1934).

The slow development of the disease, makes adaptation possible (Higgins, 1952).

Cysts are not functionally inert but retain at least a part of their activity (Lambert, 1947).

/Uraemia.....

Uraemia may be slow in onset and progress or may run a rapid course. It has been said, however, that a patient with polycystic kidneys does not die rapidly in uraemia unless he has had uraemic symptoms previously (Shapiro, 1929).

Patients may experience attacks of uraemia from which they may recover (Blatt, 1927).

The symptoms usually attributed to uraemia are: loss of appetite, nausea, vomiting, constipation or diarrhoea, weakness, general failing health and weight loss.

Present series

On account of the difficulties encountered in determining the frequency of uraemic symptoms in patients not personally examined only patients belonging to family I will be considered here.

Of 30 members affected by this disease, 6 are reported dead. They all died in uraemic coma. Of these 6 patients, 3 had uraemic symptoms before death but these 3 patients all died within 1-2 years of the onset of their uraemic symptoms.

Two of these patients presented with uraemic symptoms.

One patient who is alive has had her symptoms for about a year and has deteriorated steadily during that period.

Rapidly advancing uraemia occurred in 3 patients but only

/one.....

one did not have previous renal complaints.

Comment

The onset of uraemic symptoms is a grave prognostic omen in patients with polycystic kidneys.

Anemia

As in other forms of chronic renal insufficiency, anemia also occurs in polycystic kidneys.

Moderate to severe anemia was found in 28.7% of their patients (Simon et al, 1955). Higgins (1952) found 23% of patients with a haemoglobin below 75% (11.5 G.). Braasch et al (1932) found 56 of patients with a haemoglobin of 70% or less.

The degree of anemia is proportional to the degree of renal inefficiency (Oppenheimer, 1934; Simon et al, 1955).

The cause of the anemia may be due to chronic blood loss, marrow depression or circulating haemolytic bodies (Goldman, 1952).

Present series

Of 22 patients in whom the haemoglobin was estimated, there was a haemoglobin level below 11 G. present in 8 patients (36%). Of these 8 patients, 5 had a blood urea above 100 mg.% and only 2 had normal blood urea levels and no haematurea.

/Not.....

Not one of the patients with a haemoglobin level above 11 G. had a blood urea level of more than 85 mg.%.

The lowest haemoglobin value found was 6 G. This patient did not have haematurea.

Comment

In our limited experience, we may thus agree with other authors that anemia is a fairly common finding in polycystic kidneys and that there is a certain degree of correlation with the severity of renal dysfunction.

PIGMENTATION OF THE SKIN IN POLYCYSTIC KIDNEY DISEASE

This is an uncommon physical finding which has been described sporadically at long intervals but has never been evaluated in a large series of patients. Mitchell (1930) drew attention to this sign in children with chronic interstitial nephritis.

The first author who described it was probably Tändler (1894), who stated that bronzing of the skin may occur and Sieber (1905), confirmed this.

Apparently Osler (1909) observed two patients with skin pigmentation and states that Garceau had also described it.

Büttner (1936) described a patchy brownish pigmentation of the abdominal skin in a patient with bilateral polycystic kidney disease. He drew attention to the rarity of the condition and wrongly quotes Clairmont as having described it before.

Formijne et al (1938) described a female patient with almost universal pigmentation but more on the trunk than on the limbs and a male with a patchy brown pigmentation of the shins. Melicow et al (1940) found it in an elderly male who had polycystic kidneys with associated hypernephroma. The pigmentation resembled that following on deep X-ray therapy and was localised to the abdomen.

/Thiele.....

Thiele (1952) described this finding in an adult male who presented it like a case of bronze diabetes. He had renal insufficiency, bilateral large kidneys, intense grey-brown discolouration of the skin and glycosurea. At autopsy bilateral polycystic kidneys, cystic liver and cystic pancreas were found.

The patient described by van der Schoot (1955) belonged to a family with polycystic kidneys and at autopsy was found to have associated cirrhosis of the liver.

Present series

(1) European female, H.V. (Patient No. 31, table V) aged 43 years. This patient had bilateral polycystic kidneys for many years and associated hydatid cysts of the liver. Areas of pigment were present on the body but a detailed description of this is not given. No glycosurea was present. Blood pressure was 165/100.

(2) European female, C.D. (Patient No. 40, table V) aged 55 years. She presented with abdominal masses which, on pyelography, proved to be polycystic kidneys. The liver was also enlarged. The skin had a yellowish-orange appearance, described as coffee bronze.

There is no record of her blood pressure. There was no glycosurea. Blood urea level was 62 mg.%. Liver biopsy did not show evidence of haemochromatosis. Skin biopsy showed increased melanin deposit in the basal layers of the skin.

(3) European female, G.H.M. (Patient No. 51, table VI)

/aged.....

aged 63 years. She had a family history of polycystic kidneys in her 2 sisters and a daughter had renal symptoms. Deep pigmentation of the exposed parts was present. Blood pressure was 170/80. No glycosurea was present. Kidneys were enlarged. Blood urea was 650 mg.%. At autopsy the adrenals were normal.

The first two patients did not come to autopsy.

Comment

Various theories have been proposed to explain this phenomenon.

The enlarging kidney causes pressure atrophy of the adrenal gland (Shapiro, 1929). Lefevre (1932) (quoted by Formijne et al (1938) stated that associated adrenal cysts caused adrenal insufficiency. Pigmentation has, however, never been described in the mouth in this condition.

Renal insufficiency causes retention of a melanogenic substance in the blood with resultant pigmentation (Formijne et al, 1938).

Not one of these theories are really satisfactory. It is of some interest that Mitchell (1930) collected 30 cases of chronic interstitial nephritis in children in whom skin pigmentation occurred. This description of the pigmentation agrees with that found in polycystic kidney disease, but the basic cause of the phenomenon is not known and the reason for

/its.....

its rarity remains unexplained.

## COMPLICATIONS OF POLYCYSTIC DISEASE OF THE KIDNEYS IN ADULTS

It would be reasonable to expect that a kidney, so markedly deformed and functionally disturbed, would be prone to other complicating pathological conditions. Despite the fact that this state of affairs is admitted, it is inclined to be overlooked, after a diagnosis of polycystic kidneys has been made (Bobbitt, 1943).

It is usual to classify these complicating conditions as infective and non-infective, but the overlap is so great that they had probably better be discussed individually.

The inclusion of some factors under clinical features of the disease and others under complications, is somewhat arbitrary. Haematurea is, in the strict sense of the word, a complication but it is such a constant feature of the disease that it has become customary to list it as one of the chief clinical features.

It is almost the same with uraemia, as a complication or feature of the disease.

### Complications due to the size of the kidneys

When the remarkable size which these deformed organs obtain, is called to mind, it is difficult to explain why they do not cause greater disturbance due to pressure on, or deformity of neighbouring structures.

/Intestinal.....

Intestinal obstruction, due to a large kidney, which was relieved by nephrectomy was described by Rischbieth et al (1913). Obstruction of the descending colon was found by Young (1924) who also states that Rolando (1922) found a similar case. Lichtheim (1892) had to do a gastro-enterostomy for duodenal compression. Ptosis of the kidney with torsion of the ureter and resultant hydronephrosis may occur (Albrittain et al, 1939; Mathé, 1949).

Torsion of the renal pedicle due to the large size and mobility of the kidney may cause renal vein thrombosis and resultant gangrene of parts of the kidney (Watson, 1915).

Rupture of a polycystic kidney due to injury, often trivial in nature, has been described several times (Johnson, 1910; Paus, 1914; Braasch, 1916; Oppenheimer, 1934; Weidner, 1938; Schwartz, 1944).

Cyst rupture

Rupture of a cyst into the perirenal tissue can cause severe pain and lumbar swelling due to perirenal haematoma formation (Collis et al, 1905; Ritter et al, 1929; Rolnick, 1942).

Cyst rupture into a pelvis or calyx has been described under haematurea.

/Infection.....

Infection

This is probably the commonest complicating factor of polycystic kidneys.

Lazarus (1937, 1944) thought that this susceptibility to infection is due to interference with drainage resulting from pressure of cysts on intrarenal and extrarenal tubular system.

Bobbitt (1943) thought that frank suppuration is not as common in polycystic kidneys as in normal kidneys.

Suppuration was the most feared complication in pre-antibiotic days and can still, in this deformed and functionally impaired organ, cause a destruction of the last remains of functionally able tissue and thus becomes grave threat to the life of the patient. In the last century when the suppuration could not be controlled unusual complications resulted such as renal abscesses rupturing into the stomach and intestine (Sieber, 1905).

Oppenheimer (1934) classified infections in this condition as:

(a) Pyelitis, pyelonephritis or infected hydronephrosis, any of which may be secondary to moderate obstruction of the pelvi-ureteral junction due to pressure of cysts.

(b) Purulent infection of isolated cysts secondary to blood-stream infection.

/(c).....

(c) Diffuse infection of urinary parenchyma and cysts with occasional spread to surrounding tissues and perinephric abscess formation.

Perinephric abscesses have been described as occurring, either secondary to renal abscess or diffuse spreading infection (Morissey, 1924; Twinem, 1936; Rolnick, 1942). In the case of Twinem it was a complication occurring bilaterally.

Infection found at autopsy in 29 out of 173 cases by Dalgaard. Of these patients 20 had pyelonephritis, pyelitis or infected hydronephrosis and 4 had purulent infection localised to individual cysts. Perinephric infection following on extension of diffuse renal infection or renal abscess was found in 5 cases.

Remote effects of renal suppuration have been described in the form of bacterial endocarditis in association with infected polycystic kidney disease (Robertson, 1947).

Clinical evidence of infection

Symptoms of infection were found in 21% of 233 patients (Simon et al, 1955). These symptoms were predominantly frequency of micturition, burning, chills and fever. Pyurea was present (10 pus cells or more per h.p.f.) in 43.2% of whom about $^{3}/_{5}$ had never had symptoms of infection. Higgins (1952)

/and.....

and Rall et al (1949) found infection as evidenced by pus cells in the urine in more than 60% of their patients.

Symptoms of infection may be the presenting feature of polycystic kidneys.

Present series

Adequate examination of the urine was carried out in 41 patients. Of these pyurea (more than 10 pus cells per h.p.f.) was present in 13. One patient, (No. 20 (V 38)) had an episode of acute abdominal pain, fever and tenderness over the enlarged right kidney with no pus in the urine. All her symptoms rapidly disappeared on the administration of antibiotics and she was thought to have had an infected cyst. These were her first symptoms of renal disease.

Of the 13 patients with pyurea 5 never had any symptoms of urinary infection.

Of the 13 patients with pyurea 7 had the presence of organisms in the urinary tract proved by means of bacteriological culture.

Three of the 12 patients who were diagnosed at autopsy had evidence of suppuration.

Comment

It seems as if infection is as constant a finding in this

/disease.....

disease as haematurea. For some reason or other, probably because it is usually more dramatic, haematurea is given far more prominence as a feature of this disease.

Infection usually occurs when the disease is fairly advanced and is therefore only rarely an early indication of the presence of polycystic kidneys. It may, however, be the presenting feature of polycystic kidneys as described in the case above.

If the presence of a few pus cells in the urine should be treated with the same concern as a few red blood corpuscles, one would probably detect more "silent" cases of polycystic kidneys.

Tuberculosis in Polycystic kidneys

This is a very rare complication in comparison with the frequency of suppuration. It is remarkable how frequently it has been reported on by French authors (Uteau, 1927; Chauvin et al, 1927; Roubier et al, 1935).

Hihman et al (1924) had one case in their series used for injection experiments. Woolley (1918) also reported 1 case. A good description and review of the literature up to that time is given by Roubier et al (1935).

/Present.....

Present series

A microcephalic, mentally defective coloured male, J.A. (Patient No. 49, table VI) aged 48 years was admitted in a state of collapse and died 3 days later without a diagnosis being made.

At autopsy, bilateral polycystic kidneys with superadded chronic renal tuberculosis were found. Tuberculous epididymitis and haematogenous miliary tuberculosis of liver, lungs and spleen were also present.

No primary tuberculous lesion could be detected.

Comment

Tuberculous infection of a polycystic kidney will probably cause great difficulties in diagnosis, especially if the diagnosis of polycystic kidney has been established. The added symptoms and signs of tuberculous infection may be interpreted as being due to the underlying condition as they are so similar.

Only the constant consideration of the fact that complications of any nature may occur in this disease will prevent such an error.

Renal calculi in polycystic kidneys

The marked deformity of the renal calyceal system in polycystic kidney disease would on theoretical grounds, favour the formation of calculi due to inadequate drainage, stasis and infection. In actual fact, the occurrence of renal

/calculi.....

calculi as a complicating factor is uncommon, although several authors found a considerable percentage of their patients to have this complication.

Shapiro (1929) thought it to be a rare complication but Oppenheimer (1934) found it in 23% of his patients and Rall et al (1949) and Simon et al (1955) in 14% of their series.

In general the pathological incidence of renal calculi is greater than the clinical incidence. It is difficult to evaluate this feature, as a history of renal colic is not very useful seeing that painful haematurea is a fairly common feature of polycystic kidney disease.

On the other hand, if a patient does present with clinical evidence of calculi and the patient is not fully investigated the underlying condition may not be diagnosed.

Lazarus (1944) stated that calculus formation is a hazardous occurrence for the patient due to a further interference with drainage and hastening of renal destruction due to pressure atrophy and increased susceptibility to infection.

The types of calculi vary but usually multiple small calculi are present.

Large staghorn calculi in polycystic kidneys have been described (Greene, 1928; Thomas, 1928; Lazarus, 1934).

/We.....

We found only 1 instance where a patient had definitely passed a urinary calculus and one doubtful instance.

Comment

It would seem as if calculi are uncommon in polycystic kidneys especially if one keeps in mind that there is marked urinary stasis due to deformity of the calyceal system and that superadded infection also occurs frequently.

One explanation may be, that the kidney, in the phase that it shows maximal deformity and greatest liability to infection, secretes urine of a low concentration in large volumes. These last factors may counteract the other tendencies to calculus-formation.

It is important that the diagnosis of renal calculus in association with polycystic kidneys should be made at an early stage as this complication is an added risk in a kidney which is already diseased.

Neoplasm occurring as a complication of polycystic disease of the kidney in adults

This is a very rare complication. It was not found in the present series.

It is not unlikely that this association may be found more frequently if all patients with polycystic disease of the

/kidneys.....

kidneys should come to autopsy. The associated malignant disease is usually not diagnosed as there are no signs or symptoms on which a differentiation can be made between these two conditions at an early stage. In most instances the neoplasm was a chance finding at operation or autopsy or neoplasm was diagnosed and the polycystic condition of the kidney was an unexpected finding.

Oppenheimer (1934) could not find any record in the literature of such a complication of polycystic renal disease. All the cases of this association were reported since that time. Walters et al (1934) found three cases in a series of 85 patients suffering from polycystic kidneys. Only one was described in detail and that was a male aged 67 years with an adenocarcinoma, grade III.

Lynch et al (1935) described hypernephroma occurring in two brothers both suffering from polycystic kidneys, and added a third case in which hypernephroma was a chance finding at operation on a patient with polycystic disease of the kidney. Clemmesen (1942) also reported hypernephroma occurring in two members of a family in which polycystic kidney disease also occurred. Only one patient with hypernephroma had associated polycystic kidney disease. The one case is also included in Dalgaard's (1957) material. Other case reports of hyper-

/nephroma.....

nephroma in polycystic disease of the kidney are those of Tomoff (1937), Melicow et al (1940), Bobbitt (1943), Hayward (1946) and Newman (1950). Carcinoma complicating polycystic disease was also found by Baurys (1945), Baurys et al (1950), Johnson (1953) and Borski et al (1954).

The case described by the last two authors is of interest as bilateral carcinoma occurred in this patient with polycystic kidneys.

An intracystic papilloma was found by Wells (1936).

A case of angio-myosarcoma and a case of fibrosarcoma were described by Lowsley et al (1945). Hildebrand (1894) described a child of two years with sarcoma complicating bilateral polycystic kidneys.

For the sake of completeness may be added the finding of fat sequestra in the renal pelvis (Bobbitt, 1943) and cholesteatoma (Mathé, 1954).

Comment

It is fortunate that this complication is such a rare event, as we do not posess the means of differentiating these two conditions at an early stage.

If these patients are known to be suffering from polycystic kidney disease the diagnosis of neoplasm will probably not be made (Baurys, 1945).

## METABOLIC COMPLICATIONS OCCURRING IN PATIENTS WITH POLYCYSTIC KIDNEYS

### Uraemia

This has already been described under the clinical features.

### Renal osteodystrophy

The main features of this condition are failure to grow, bony deformities, difficulty in walking, increasing weakness, polyurea, polydipsia and uraemia (Bass et al, 1938).

The syndrome of renal osteodystrophy may be caused by a wide variety of pathological conditions in the kidney and lower urinary tract, provided they are present for a long time (Kretschmer, 1948).

The age incidence varies but usually falls within the first or second decade and shows its greatest frequency just before puberty, (Bass et al, 1938).

From the previous discussion on the incidence of polycystic kidneys, it became clear that, this age period, is the one in which polycystic kidneys are rarely found.

Polycystic kidneys are a very rare cause of renal osteodystrophy (Sheldon, 1935). Those who survive through infancy may develop renal rickets or dwarfism (Hausmann, 1940).

A number of case reports of "rickets" in association with

/cystic.....

cystic kidneys are not quite acceptable as the renal lesion is not that of true polycystic kidneys (Cameron, 1918; Patterson, 1919; Greene, 1922; Mitchell, 1952).

In a number of instances the presence of true polycystic kidneys, as the underlying renal lesion, in this condition was proved (Brockman, 1926; Sheldon, 1935; Bass et al, 1938; Mazzeo, 1938; Kretschmer, 1948; Keizer et al, 1950; Jackson et al, 1950).

A family history of polycystic kidneys was not present in any of these patients.

The case of Kretschmer (1948) is interesting in this respect as a family history of Bright's disease, hypertension and albuminurea was obtained.

The patient described by Brockman (1926) is so young (13 months) that it is possible that this child had coincident true rickets and congenital polycystic kidneys.

The case of Jackson et al (1950) is noteworthy as this patient was 25 years old, had true diabetes mellitus and at autopsy was 25 years old, had true diabetes mellitus and at autopsy was found to have bilateral hypoplastic kidneys and cystic pancreas.

An unusual case was described by Burkholder et al (1947). A female of 47 years who was known to have polycystic kidneys developed massive calcinosis and showed no skeletal changes.

/The.....

The cause of the renal osteodystrophy in polycystic kidneys is probably not the cystic change as such, but the associated interstitial nephritis.

"The clinical findings are determined by the functional and not the morphological alterations of the kidney" (Greene, 1922).

Personal observations

No evidence of renal osteodystrophy could be found in any of the patients observed by us under the age of 20.

Comment

From the cases reported in the literature it appears as if most of these children had the disease at a very early age and are probably examples of late survivors of the congenital form of the disease.

We could find no description of a case, which could be described as an adult type of polycystic kidney coming to early expression, in which renal osteodystrophy occurred.

Gout

Patients with chronic renal disease and a raised serum uric acid level, only rarely develop gout (Daughaday, 1952).

Only three cases of gout occurring in patients with polycystic kidneys could be found in the literature.

/Quincke.....

Quincke (1904) described a male aged 55 years who had been troubled with gout for the last few years of this life and at autopsy was found to have heavy uric acid deposits in the bones of the knee and great toe joints. Sieber (1905) collected 2 cases (both males) from the literature. Goldman (1952) commented on the rarity with which gout occurs in patients with polycystic kidneys and a raised serum uric acid.

Present series

European male, M.J.G. (Patient No. 10 (VII), table IV) aged 49 years. This patient was the first member of family I to be examined by the author. His first symptom of renal disease occurred at the age of 21 when he had an episode of haematurea. He has had recurrent bouts of haematurea ever since. The diagnosis of polycystic disease of the kidneys was made at the age of 32 years on retrograde pyelography. At the age of 44 he experienced the first symptoms of gout - an attack of severe pain and swelling of the right first metatarso-phalangeal joint, subsiding and recurring in the left foot.

His joint symptoms have returned intermittently since that time and he experiences dramatic relief from the use of colchicine. Renal function is poor and both kidneys are massively enlarged and irregular. Blood pressure was 190/100. Albuminurea ++. Excretory pyelography shows poor excretion of the dye. Blood urea 68.5 mg.%. Blood uric acid 8.1 mg.%.

/Saltlosing.....

"Saltlosing nephritis" in patients with polycystic kidneys

The syndrome of saltlosing nephritis was first described by Thorn (1944) in a male aged 21 who died 4 years later and was found to have bilateral polycystic kidneys (of normal size) at autopsy.

Borst (1949) described a similar disturbance of water- and salt metabolism in a male aged 42 with bilateral polycystic kidneys and chronic renal insufficiency.

These two patients never had any abnormal elements in the urine except an occasional trace of albumin in the second instance and in both the blood pressures were low or normal. Blood urea and N.P.N. were raised and sodium chloride low. Both improved remarkably on the administration of NaCl.
"It is our belief that the clinical syndrome that has been described, is probably not associated with a typical pathological lesion, but rather occurs late in the course of insidious, slow but progressive renal disease" (Thorn, 1944).

Present series

One patient, who probably had this condition, was found.

European female, M.J.G. (Patient No. 10 (V), table IV) aged 48 years. She was first seen in November 1954 for a complaint of fatigue and weakness. She knew that she

/was.....

was hypertensive and that her kidneys were large.

She had the very characteristic facial expression found in so many of the females belonging to this family: a pale puffy face with loss of outer $^{1}/_{3}$ of the eyebrows, looking very much like myxoedematous patients.

Both kidneys were enlarged and irregular. Blood pressure 220/120.

Fundi: Grade III retinopathy.

Urine had an S.G. of 1008 and contained albumin ++. She was admitted to the Groote Schuur Hospital on the 19th March, 1955 for same complaints as before: weakness, fatigue and pain in the loin. Her blood pressure was 150/85 and the urinary and physical findings were otherwise unchanged. She had an epileptiform convulsion on the night of admission.

She was put on a diet containing 20 g. proteins per day and restricted salt.

The chemical analysis of the blood on admission showed:

Blood urea - 162 mg.%
Serum Potassium - 3.6 meq./L
Serum Sodium - 139 meq./L
Serum Chloride - 96 meq./L
$CO_2$ Combining power - 58 vols.%
Calcium - 5.8 mg.%
Phosphorus - 5.5 mg.%

On the salt restricted diet for 11 days the serum electrolytes showed the following:

/Serum.....

Serum Potassium - 4.3 meq./L
Serum Sodium - 115 meq./L
Serum Chloride - 75 meq./L
$CO_2$ combining power - 57 vols.%
Calcium - 6.2 mg.%
Phosphorus - 5.0 mg.%

The salt restriction was stopped and amphojel and calcium lactate given. After 10 days on this regime the following was found:

Blood urea - 103 mg.%
Serum Potassium - 5.2 meq./L
Serum Sodium - 122 meq./L
Serum Chloride - 102 meq./L
$CO_2$ combining power - 57 vols.%
Calcium - 8.5 mg.%

The patient was discharged with instructions to take a low protein diet with unrestricted salt intake. She was much improved after her discharge from hospital but neglected her diet, gradually deteriorated and died in coma 6 months later.

Comment

This case is certainly not as striking as the two cases quoted previously but clearly illustrates the disastrous results which may follow if a patient with the salt-losing tendency is put on a routine low protein/salt diet.

## PREGNANCY AS A COMPLICATION OF POLYCYSTIC KIDNEY DISEASE

Relatively few reports on this subject have been published in comparison with the great frequency with which polycystic kidneys has been the subject of study. The importance of this association was first indicated by Sieber (1905) and, since that time, the subject has been discussed from various points of view by Heinsius (1913), Crabtree (1942), Findley (1947), Brugsch et al (1948), Bell (1950).

The physiological increase in work imposed on the kidney during pregnancy may disturb the precarious ballance of renal function which may exist in a patient with polycystic kidneys (Maier, 1924). This increased load on a diseased kidney may bring to light new symptoms or, aggravate symptoms already present (Sieber, 1905; Heinsius, 1913; Bell, 1950).

The objective evaluation of the influence of pregnancy on the course of polycystic kidney disease is difficult, if not impossible. From reports in the literature no information is available about the renal function before and after pregnancy and it is difficult to find a suitable group of patients for comparison with the pregnant females.

It is easy to understand why such widely divergent opinions have been expressed about the influence of pregnancy on the

/natural.....

natural course of polycystic kidneys.

Many authors believe that pregnancy acts like a traumatic influence on this disease (Sieber, 1905; Heinsius, 1913; Maier, 1924).

Findley (1947) states that no evidence is available to prove that pregnancy accelerates the development of the renal cysts.

Numerous instances have been reported in which the patients date their symptoms from a pregnancy (Heinsius, 1913; Blatt, 1927; Henninger, 1938).

Frequently the first physical finding indicating renal disease is found shortly after delivery - an abdominal lump (Cairns, 1925; Shapiro, 1929; Rathbun, 1943). This is probably explained by the fact that a lump, which would otherwise be detected with difficulty, becomes easily palpable through the lax abdominal wall in the puerperium.

The difficulty of finding an adequate control group is again encountered when an attempt is made to establish the incidence of toxaemia of pregnancy in patients with this disease.

A considerable number of case reports of pre-eclamptic toxaemia or eclampsia occurring in these patients have been

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published (Dijckerhoff, 1919; Rosenberg et al, 1924; Blatt, 1927; Burns, 1933; Bell, 1935; Reaves, 1942; Young, 1946; Dörr, 1948; Giannico, 1954). Another complication which has been described frequently in patients with polycystic kidneys is pyelitis of pregnancy (Henninger, 1938; Crabtree, cit; Brugsch et al, 1948). Crabtree found it in 10 out of 11 pregnant females with polycystic kidneys.

There is no evidence that polycystic kidney predisposes the sufferer from it, to abortions and premature labour (Dalgaard, 1947).

From these case reports the outlook seems to be poor if a female with polycystic kidneys should become pregnant. When the literature is searched for the number of children a woman may bear with safety when she has this disease, one finds quite a different result.

There are authors who believe that patients with this disease are exceptionally fertile (Brugsch et al, 1948).

Cases have been reported where a female, who eventually died of polycystic kidneys, had passed through 17 pregnancies (13 children and 4 abortions) (Podgurski, 1930); 15 pregnancies (12 children and 3 abortions) (Wagner, 1881) and 14 pregnancies (Bell, 1950) but these are exceptions. Higgins (1952) found 1-9 pregnancies in 42 out of 51 females and no increased

/complication.....

complication rate.

The contradiction becomes even more perplexing when reports are encountered of patients who had nephrectomies for one reason or other and yet passed through one or more pregnancies with one polycystic kidney and lived for many years after (Krönlein, 1899; Branham, 1947).

Present series

Of 19 females belonging to family I who are definitely suffering from this disease and are married, information is lacking in one and two had no children. One of these two is sterile, but the cause is unknown, and the other does not want to have children. Of the remaining 16 the number of children vary from 1 to 10 per patient. The oldest patient (84 years) has had 7 live children and 3 abortions.

There is no significant difference between the number of children which affected and non-affected members of the family produced. Abortions occurred very infrequently in this family.

European female, C.G.P. (Patient No. 17 (V 34), table IV), aged 33 years. She was quite asymptomatic and no abnormality could be detected on physical examination. At the age of 33, when she was pregnant for the 8th time (6 live children and 1 abortion) she developed

/a.....

a pyelitis one month before the birth of the child. She has had a albuminurea which has been intermittently present ever since. Directly after delivery the right kidney was easily palpable but later became difficult to feel as she is rather obese. Her blood pressure has also increased in the 3 years that she has been under observation. I.V.P. grossly abnormal.

European female, C. v.d. V. (Patient No. 22 (V 43), table IV), aged 38 years. She was quite well with first pregnancy at age of 23 but with the second she was troubled with severe nausea. At 3 months her blood pressure was 150/95 and the urine contained a large quantity of albumin.

Her blood pressure increased, albuminurea increased and she developed ankle oedema. Conservative treatment failed and the pregnancy was terminated by hysterotomy in the 4th month and she was sterilized. Kidney cysts were noted at operation. At present her blood pressure is 150/90 and albumin + is present in the urine. I.V.P. grossly abnormal.

Two other patients dater their symptoms from the time of their last pregnancy (H.T.B. No. 38, table V) and (J.B. No. 55, table VI). Further information is lacking about these two patients except that the first patient had severe toxaemia with each of her 4 pregnancies, which all ended in abortions.

/European.....

European female, E.F. (Patient No. 46, table VI), aged 18 years, died in eclampsia. At autopsy polycystic kidneys and an ilio-caecal intussusception were found.

Comment

The wide variations in response to pregnancy are remarkable even within one family.

One patient, H.B. (Patient No. 1 (III 8), table IV) passed through 10 pregnancies and reached the age of 84 years without symptoms of renal disturbance.

Another patient, C. v.d. V. (Patient No. 22 (V 43), table IV) had to have her second pregnancy terminated at 4 months for rapidly deteriorating toxaemia of pregnancy.

No correlation could be found between the number of pregnancies and the severity of the disease in the mother.

There are authors who advise against pregnancy so that the mother's kidney function should not deteriorate, and on account of the risk that the child may be burdened with the disease (Higgins, 1952). Other authors believe that if pregnancy should occur it must be terminated and the patient sterilized for the same reasons (Maier, 1924).

A hard and fast rule for all patients cannot be laid down. Bell (1935) probably summarised the whole matter when he stated

/that.....

that, in an advanced case with low renal reserve, typical nephritic toxaemia will probably occur, but no disturbance is likely to appear in the patient with adequate renal reserve.

The line of action to be followed in a patient with polycystic kidneys who becomes pregnant has clearly been indicated by Brugsch et al (1948).

(a) Pregnancy should be discouraged for the reasons mentioned above. (They also mention that labour may be difficult due to large abdomen of child with congenital polycystic kidneys and regards this as a contra-indication to pregnancy. It is important to note, however, that congenital polycystic kidneys does not occur in the offspring of adults with polycystic kidneys).

(b) If the disease is in the latent stage, pregnancy may be complicated by pyelitis or haematurea. The patient must then be managed with care till a stage is reached when pregnancy can be terminated with safety for the child.

(c) Pregnancy has to be interrupted if renal function deteriorates. It seems logical that if a female has had toxaemia with one pregnancy she will probably have trouble again with succeeding pregnancies so that sterilization may be considered.

# S E C T I O N  I I I

## THE RADIOLOGICAL FEATURES OF POLYCYSTIC DISEASE OF THE KIDNEYS

## THE RADIOLOGICAL FEATURES OF POLYCYSTIC KIDNEY DISEASE IN ADUTLS

Retrograde pyelography was introduced by Voelcker et al (1906) using collargol as a contrast agent. With this method Adrian et al (1913) first described the pyelographic diagnosis of polycystic kidneys.

Intravenous urography became an accepted method of examination with the introduction of Sodium Iodide as a contrast medium by Osborne et al (1923). It was only in the late 1920's however, that intravenous urography was accepted as a safe method of examination with the introduction of the pyridin-iodine compounds as contrast media.

It is of some importance to keep these facts in mind if one should consult older statistics on the clinical incidence of polycystic kidneys, as this method of examination completely altered the position of polycystic kidneys as a clinical entity.

Where polycystic kidneys had previously only been diagnosed clinically in rare instances, or had been a chance finding at operation or post mortem, it became a condition, which could be diagnosed with a fair degree of confidence. As one would expect, in the years following on the introduction of pyelography, there was an apparent increase in the clinical incidence of polycystic kidneys.

/On.....

On account of the safety and relative ease with which either method of pyelography can be carried out, and the highly characteristic radiological findings, in a typical case of polycystic kidneys, other methods of radiological examination never became widely used in this condition.

As pyelography is the most widely used aid to diagnosis, and the only one used in the present series, it will be discussed first and at the end of this section, the other methods of radiological investigation will be mentioned.

A vast literature has accumulated upon this subject but outstanding among the works published on this subject are those of Grauhan (1926), Hennig (1929), Henninger et al (1939), Barquin et al (1947), Hickel et al (1949), Ochsner (1951) and Braasch et al (1951). The first systematic analysis of the radiological signs in this disease was done by Billing (1953).

The radiological picture of polycystic kidneys is a reflection of the pathological changes in the kidneys which in turn is influenced to a great extent by two factors (Billing, 1954):

(a) The type of renal pelvis, which varies between two extremes:

  (i) a large ampulla with only minor calyces originating from it.

  (ii) A small ampulla with very long major calyces.

(b) The size and situation of the cysts. If cysts are small

/and.....

and evenly distributed throughout the entire kidney, the picture will be one of uniform enlargement and not of pelvic or calyceal deformity. Also, if fairly large cysts are not in relationship to calyces or pelvis, no deformity will be produced (Heninger et al, 1939). One may add to this that polycystic kidney disease is a progressive condition in which the radiological signs may even change in the same kidney.

If attention is paid to these variable factors, it is obvious that one cannot expect one characteristic radiological picture in this disease and that it would almost be impossible for one universally valid diagnostic sign to be present.

Present series

The material is divided into two groups:

(a) Patients belonging to family I (table IV) whose radiographs were, in the majority of cases, personally seen by the author.

(b) Patients on whom information was obtained from the clinical records of the Groote Schuur Hospital (table V). As old radiographs are usually destroyed, most of the information had to be obtained from the reports of radiologists.

In the discussion only the material of group (a) will be

/used.....

used i.e. those radiographs which were personally seen by the author.

Group (a) - Initial intravenous pyelograms were obtained on 56 patients belonging to family I. Of these patients, 27 were proved, by means of pyelography, to have the disease.

In 18 patients the initial intravenous pyelogram left no doubt about the diagnosis.

In 14 patients the intravenous pyelogram was suggestive of polycystic kidney disease and in 3 cases no diagnosis could be made. One of these 14 patients, developed such a typical clinical picture that repeated examination was not necessary. 2 Patients had repeated intravenous pyelograms done and these were diagnostic. 3 Patients had retrograde pyelography done with conclusive results.

The remaining 8 patients, of whom 2 were re-examined by intravenous pyelography, have changes which are only suggestive although kidney function was normal and the excretion of contrast medium adequate.

These suggestive changes, with associated other clinical findings such as hypertension or albuminurea, bring these patients into the group of potential sufferers from polycystic kidneys.

Retrograde pyelography carried out on the 3 patients, in

/whom.....

whom no diagnosis could be made on intravenous pyelography, led to a definite diagnosis.

In conclusion, we thus found that, out of 27 patients with polycystic kidneys, intravenous pyelography led to a diagnosis in the first instance in 18, and on repeated examination in 20 patients. No diagnosis could be made by this method in 3 patients and retrograde pyelography gave the answer, as it also did, in 3 of the cases with suspicious changes.

Group (b) - In the clinical group of patients of whom 16 did not belong to family I, intravenous pyelography was carried out on 11 patients. These pyelograms were diagnostic in 4 cases, suspicious in 3 cases and normal in one case. Retrograde pyelography was done on 8 patients. It was a failure in 1 instance. It was the method of diagnosis without preliminary intravenous pyelography in 2 cases. In one case it was suggestive. In 5 cases it was diagnostic where the intravenous pyelography had failed.

The high rate of satisfactory results found in this group of patients belonging to family I who were examined by means of intravenous pyelography is probably due to the fact that most of them were asymptomatic, had good renal function and could excrete the contrast agent sufficiently to give an adequate radiological picture.

/The.....

The radiological features of polycystic kidneys, as described by various authors, will now be described under different headings. The nature of these individual features and the diagnostic value attached to them and our experience with them will then be discussed. There may be objections to an analysis of signs into rather artificial compartments and it certainly does appear absurd in the outspoken form of the disease. Such a division of the pyelographic findings was done solely in search of the characteristic features of the disease in the earliest phase of their evolution.

Only the pyelograms (50 in all) of the members of family I were personally examined and among these, there were 22 cases with definite polycystic kidneys and 8 with suspicious changes. Only these 22 definite radiographs will be used in the following discussion. As most of these patients had polycystic kidney disease in an early phase, this material is not representative of the usual radiographic findings in clinical practice. Our chief aim, again, was the detection of early radiological signs of this disease.

Plain radiograph of the abdomen

Unilateral or bilateral enlargement of the kidneys may be observed. It is rarely a sufficient method of examination but

/may.....

may be useful in providing a clue to the diagnosis (Köhler, 1947; Newman, 1950; Ochsner, 1951; Frankson, 1955).

In addition to enlargement, irregularity of the outline of the kidney may be observed. Presence of calculi may be detected (Oppenheimer, 1934). Associated bony abnormalities may be noted e.g. spina bifida occulta (Keizer et al, 1950).

Present series

Enlargement was found in 7 instances, always in advanced stages of the disease.

Irregularity of outline was seen in 2 instances. No calculi were observed. Spina bifida occulta was observed in 7 patients with, and 16 patients without polycystic kidneys. (See the section on associated malformations and linkage for further details).

Pyelographic changes found in polycystic kidneys

Under this heading, signs of both intravenous- and retrograde pyelography are discussed. The first two signs to be described can usually be found on intravenous pyelography only.

(a) Enlargement of outline of the kidney

The outlines may be difficult to trace in instances where the kidneys are very large probably due to the loss of perirenal fat (Billing, 1954). The medial margin of the kidney may

/encroach.....

encroach on the psoas lines (Hennig, 1929). The enlargement is mostly in a longitudinal direction (Barquin et al, 1947).

Although the kidneys may be enlarged for other reasons and polycystic kidneys may be relatively small, Billing (1954) found all polycystic kidneys to have a length exceeding 14 cm. (plate focus distance 100 cm.).

Present series

Accurate measurements could not be made as one could not be certain of a standard focal distance being used in the radiographic technique.

Definite enlargement was found in 14 out of a total of 22 cases. In two other patients the enlargement was doubtful.

(b) Irregularity of the renal outline

This sign is caused by cysts of fairly large size under the capsule of the kidney causing bulges on the surface.

This sign will only be observed if a major part of the kidney outline is observed and this is uncommon if the kidney is large (Billing, 1954). Such an irregular outline must be differentiated from scarring and foetal lobulation. In the last named condition the kidney is normal in size, the bulges are large and not as numerous as in polycystic kidneys (Barquin et al., 1947).

/This.....

This is a very suggestive sign when it is marked.

Present series

This sign was observed in 5 patients. There was an associated increase in size in all of them (see fig. VIII). If the conditions mentioned above are excluded, this may sometimes be a fairly early sign.

Changes in the contrast filled pelvis and calyceal systems

(a) Increased parenchymal thickness

Billing (1954) held this for a pathognomonic sign of polycystic kidneys, if it is not due to a locally expanding process. It is measured between the nearest laterally directed minor calyx and the surface outline. Normally it is 2-7 cm. and Billing found it to exceed 3 cm. only once in a normal kidney. In all but two cases of polycystic kidneys, did it exceed 3 cm. Other authors have not described this sign.

Present series

As far as measurements could be depended upon a parenchymal thickening of over 3 cm. was found in 2 patients. In both these patients there was marked renal enlargement. In our material this sign did not appear to be as useful as in Billing's experience.

/133.....

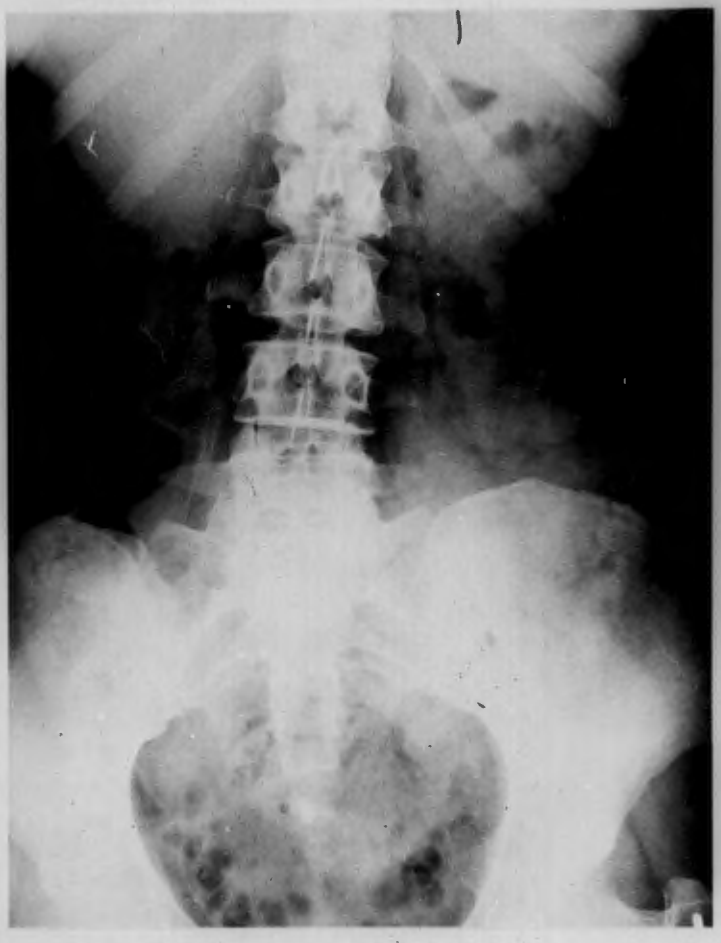


FIGURE VIII

Patient No. II (V 12) M.C.G. Poor renal function and no contrast medium in the calyceal system. Massive enlargement of the left kidney visible with well marked irregularity of the renal outline at the lower pole.

(b) Alterations in position of the contrast-filled pelvis

(i) Lateral displacement - This sign is probably due to enlargement of the parenchyma medial to the pelvis and can only be considered to be present if the distance between the medial margin of the pelvis and the lateral border of the vertebral column is greater than the width of a vertebral body (Billing, 1954).

It has been observed by many authors including Braasch (1916), Eisendrath (1919), Braasch et al (1932), Köhler (1947). Lateral displacement of the lower pole only has been observed by Ochsner (1951). It is an inconstant finding in polycystic kidneys and frequently present in normal kidneys (Billing, 1954).

Present series

This sign was indisputably present in only one patient.

(ii) Medial displacement of the upper pole - This sign is described by Fort (1941), Barquin et al (1947) and Hickel et al (1949). These authors do not clearly define what is meant by this sign. It was not found in the present series.

(iii) Downward displacement of the pelvis - It is to be expected that, with such a marked increase in size, as is often the case in polycystic kidneys, these organs will be

/situated.....

situated at a lower leven than normal. It has been described very frequently. It is best detected with the patient in the erect position (Hickel et al, 1949).

Present series

This sign was present in 7 patients of whom all, but one, had enlarged kidneys. Most of these patients were not X-rayed in the erect position so that this may invalidate our findings. There is no indication that this appears only in the disease, although one of the early cases and 2 of the potential cases have a marked degree of renal ptosis.

(iv) Alteration in the axis of the kidney - The long axis of the kidney becomes vertical and thus parallel to the vertebral column instead of being parallel to the psoas lines (Braasch, 1916; Morissey et al, 1924; Henninger et al, 1939; Köhler, 1947). It is due to enlargement of the kidney, difficult to define and not pathognomonic of polycystic disease of the kidney (Billing, 1954).

Present series

This sign was present in 9 patients and only in 2 patients were the kidneys not markedly enlarged.

Note on alteration in position

The apparently contradictory statements as to the direction

/of.....

of displacement of the kidney can probably be explained by relative increase in size on one part of a kidney due to local cyst growth causing various types of displacement. If this is the case, it is also clear that not one of these signs could be expected to be present early in the disease.

(c) Alterations in the size and shape of the pelvis

The indentations of the pelvis and calyces caused by cysts are smooth, rounded and clearly defined and these features serve as points of differentiation from other forms of renal pathology (Morissey et al, 1924; Grauhan, 1926; Barquin et al, 1947). The pelvis of the kidney is less often affected than the calyceal system (Braasch et al, 1951).

(i) Compression of the pelvis - This may occur due to pressure of neighbouring cysts causing indentations or flattening of the pelvis (Newman, 1950).

Present series

This sign was found in 12 patients, all with other evidence of polycystic kidneys as well. The pelvic compression is usually a part of a generalised distortion of the pelvi-calyceal system.

(ii) Enlargement of the pelvis - This is usually an elongation with very little increase in width, (Adrian et al,

/(1913).....

1913; Atonna et al, 1926; Ochsner, 1951; Goldstein, 1951). This elongation of the pelvis is usually asymmetrical and the pelvis is distorted (Barquin et al, 1947).

Present series

This feature was found in 5 patients. All had large kidneys radiologically or clinically.

(iii) Horn-shaped ampulla - This was first described by Henninger et al (1934), who thought it was due to increase in parenchyma cranial and caudal to the pelvis compressing it.

Köhler (1947) states that the pelvis becomes progressively more intrarenal.

This sign, as indicated by Henninger et al (1934) is probably the same sign as described by Blatt (1927) as absence of the pelvis and by Morissey et al (1926) as loss of definitions of the pelvis. It may be present when a normal kidney is in an abnormally low position and is of little diagnostic value (Billing, 1958). It was not observed in the present series.

(d) Alterations in calyceal system

(i) Increase in size of the calyceal system - The distance between the most superior and the most inferior minor calyces are increased to more than 9 cm. (Billing, 1954). The

/elongated.....

elongated, widened calyceal system eventually exceeds the pelvis in size (Fort, 1941; Barquin et al, 1947).

Present series

In 16 cases this was definitely present. In 4 other cases it was at the upper limit of normal.

(ii) Calyceal elongation - This sign is the earliest one described as characteristic of polycystic disease (Adrian et al, 1913). This and the previous sign is held to be due to increase in size of the kidneys with resultant stretching of the calyces (Bell, 1950). Grauhan (1926) thought it to be an intrinsic feature of these kidneys, whether large or small. It is probably the most frequently described pyelographic feature of polycystic kidneys (Shapiro, 1929; Spencer, 1937; Braasch et al, 1951).

As a diagnostic sign it only has value if several calyces are involved (Köhler, 1947).

Lengthening of the calyces can be produced by any increase in size of the kidney, no matter what the cause may be, it may even be found in compensatory hypertrophy (Henninger et al, 1939). It may be difficult to assess and the variations of the normal are great but it is characteristic of polycystic kidneys if it occurs to a marked degree (Billing, 1954).

/present.....

Present series

This was the most common sign and was present in 20 of the patients. In the earliest stages this may occur without obvious increase in size of the kidneys.

(iii) Alteration of the angles of calyces - The alteration of the angles and directions of calyces were thought to be very important signs by Hickel et al (1949) and was present in 80% of their cases. This is probably one of the earliest signs of the disease but can only be determined with some difficulty due to the great variations in the normal orientation of calyces on the pyelogram.

The upper and lower major calyces may project at right angles from the pelvis so that they lie in a straight line (Henninger et al, 1939).

Fort (1941) described a similar sign to which his name has been attached: the upper and lower major calyces form an angle of more than $180^{\circ}$ with the pelvis. This was also found by Barquin et al (1947) and Hickel et al (1949).

Present series

Alterations of the angle of calyces were present in 20 of our cases. In some of the earliest cases this sign proved

/of.....

of great help when a follow-up excretory pyelogram was done after a few years (see figs. IX and X).

Upper and lower major calyces in a straight line were seen in 3 instances and upper and lower major calyces forming an angle greater than 180° in 3 instances. These two signs can, obviously, only occur if there is great enlargement and deformity of the kidney.

(iv) Compression of calyces - This may affect a localised part of a calyx, in the form of a semicircular impression (Braasch, 1916; Hausmann, 1940; Fort, 1941; Barquin et al, 1947). Multiple indentations of an elongated calyx may impart a serpentine appearance to a calyx (Hennig, 1929; Hickel et al, 1949). If multiple indentations are present it is almost pathognomonic of polycystic kidneys (Billing, 1954).

More advanced degrees of calyceal compression may lead to complete obliteration of a calyx or so-called calyceal amputation, or, if it affects the peripheral part of a calyx, cause the appearance of a shortened calyx (Braasch et al, 1932; Newman, 1950). "Amputation" of multiple minor calyces may give the pelvis a square or oval appearance (Spencer, 1937; Hausmann, 1940).

Present series

This sign was present in 20 patients and shared with calyceal

/elongation.....

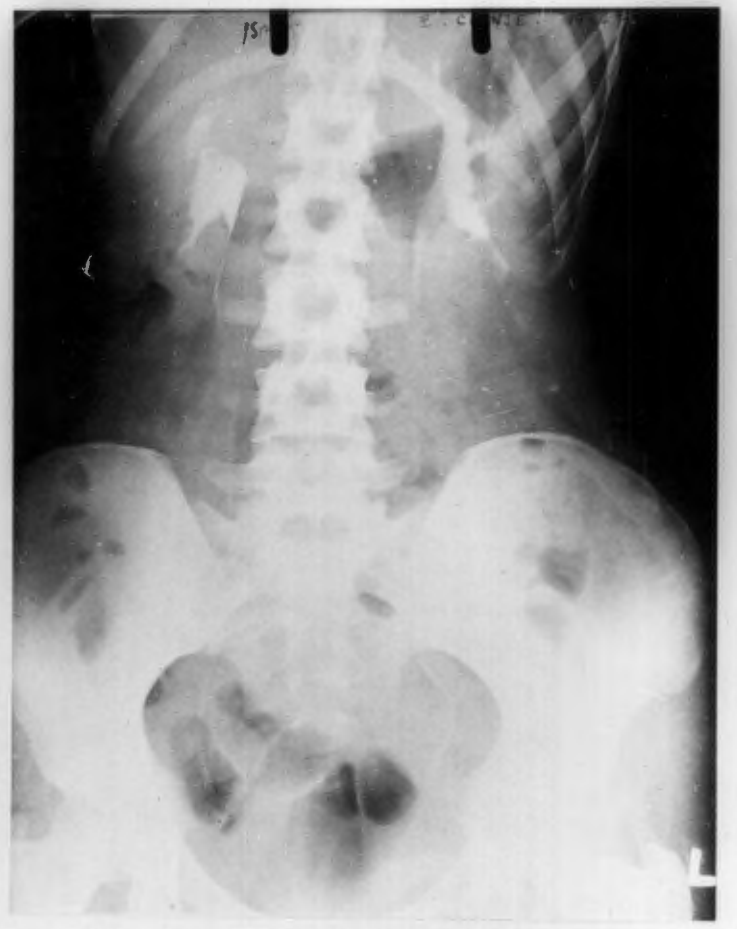


FIGURE IX

Patient No. 30 (VI 65). This excretory pyelogram was taken at the age of 18 years when the patient had a slightly enlarged left kidney. The left lower major calyx is laterally displaced and compressed. Four years later she had bilateral large irregular renal masses.

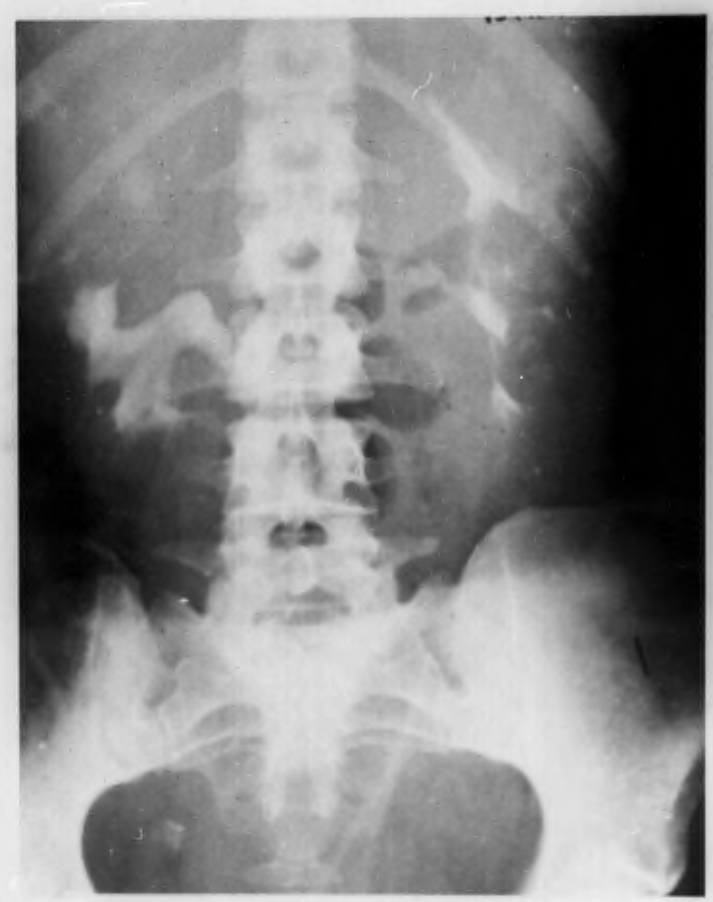


FIGURE X

Patient No. 22 (V 43) C.v.d.V. Female aged 36. On the left a long drawn-out calyceal system is seen with alterations in the angles of the calyces, calyceal compression and elongation. There is also an early degree of crescent formation in the left side in the region of the middle calyx.

elongation the first place as the most common signs. Multiple indentations were present in 16 patients. These two signs are probably the earliest findings on pyelographic examination.

(v) Widening of calyces - This usually involves the peripheral ends of major calyces and includes minor calyces (Braasch et al, 1932; Bell, 1935). Dilatation may be of a bizarre nature and also affect the pelvis (Newman, 1950). Bulbous enlargement of the peripheral end of a calyx was first described by Grauhan (1926) and Braasch et al (1951). This peripheral dilatation may be flattened or indented (Köhler, 1947). Henninger et al (1939) stated that this enlargement was probably due to a hydronephrotic effect following on obstruction of the neck of the calyx due to stretching.

Present series

It was found in 9 patients (see figs. XI and XII). We cannot agree with the statement of Ochsner (1951) that it is a more common sign than calyceal narrowing.

(vi) Crescent formation - This is probably due to cysts in the region of the renal papillae (Henninger et al, 1939; Braasch et al, 1951). These rounded papillae project into the dilated peripheral ends of calyces and produce this deformity.

It has been described very frequently among others by

/Hennig.....

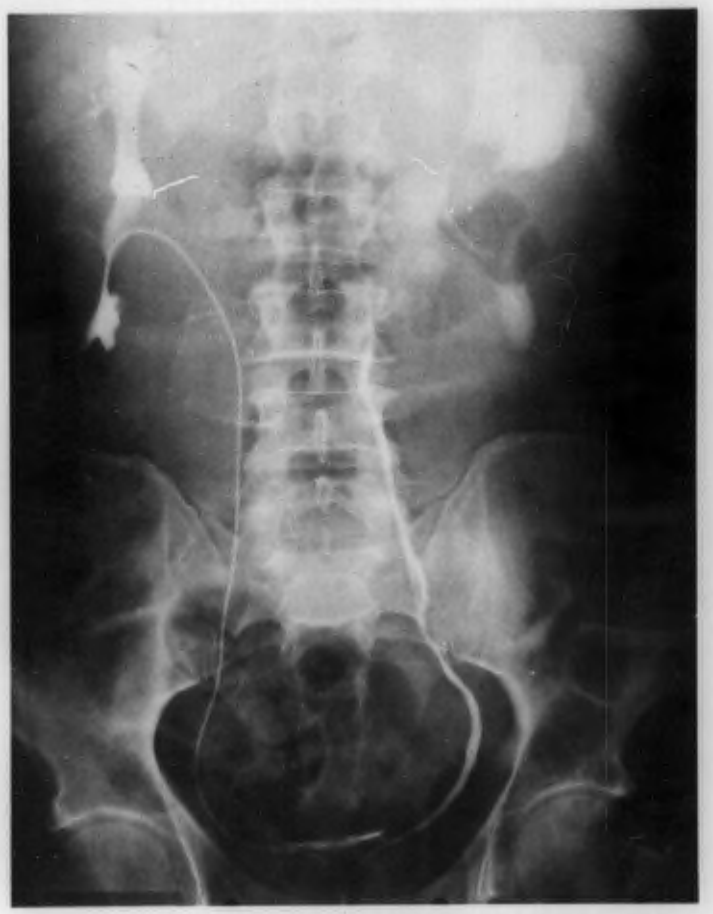


FIGURE XI

Patient No. 3 (IV 18) P.A.M. Male aged 56. Marked enlargement of the calyceal system. Upper and lower major calyces on the right in a straight line and parallel to the vertebral column. Marked peripheral dilatation of calyces on left.

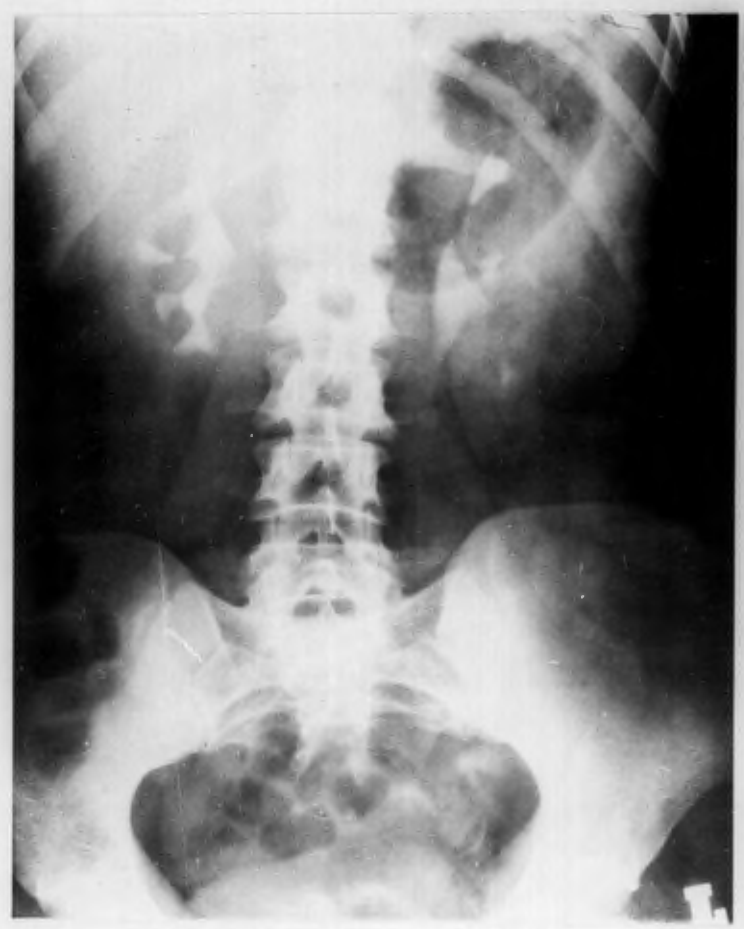


FIGURE XII

Patient No. 18 (V 36) C.E.C. Female aged 46 years. Enlargement of calyceal system present. Rounded impressions into the calyces causing narrowing of the calyceal necks. Widening and flattening of the peripheral ends of the calyces.

Hennig (1929), Braasch et al (1931) and Ochsner (1951).

Present series

Crescents were found on 17 occasions and thus ranks with one of the frequent signs in our series (see fig. XIII).

(vii) "Hyperramification" - This has frequently been described and some authors (Barquin et al, 1947) believe it to be a pathological feature of this disease, that the calyceal system subdivides. This is known not to be the case. The appearance is probably produced by numerous cysts projecting into the peripheral ends of dilated calyces producing thin lines like so many minor calyces (Henninger et al, 1939).

Present series

The "Hyperramification" appearance was found in 2 patients with advanced polycystic disease.

(viii) Confetti sign - Compression of major calyces and dilated minor calyces cause collections of radio-opaque material in small irregular pools apparently unconnected with the renal pelvis (Hickel et al, 1949). Also described by Barquin et al (1947).

Present series

It was observed in 3 patients. It is not a reliable sign on its own, but with other signs it may be helpful.

/(ix).....

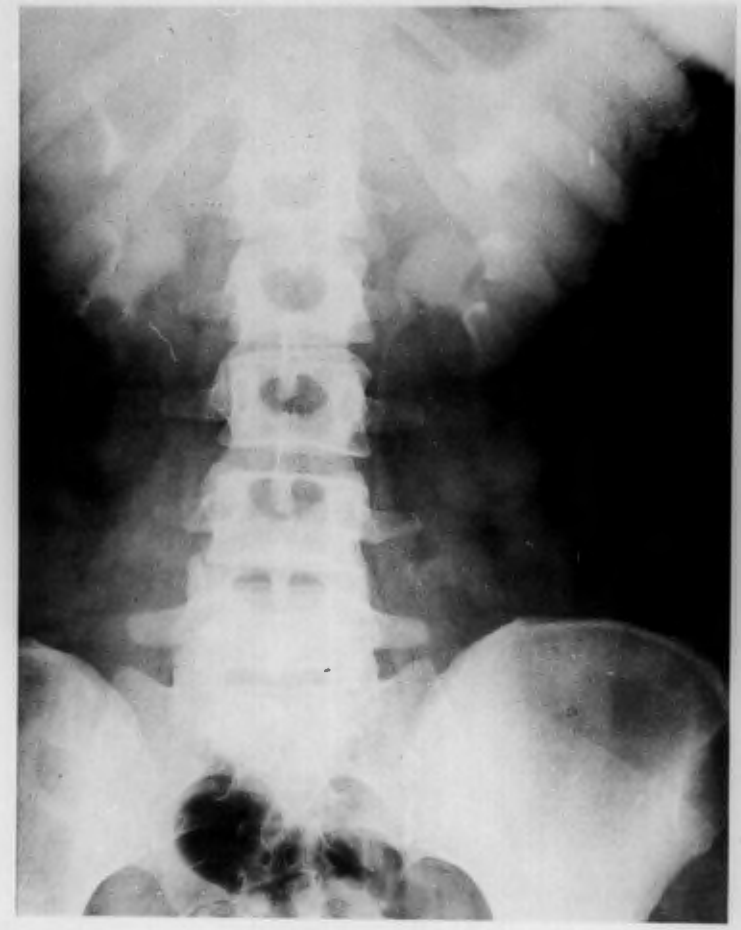


FIGURE XIII

Patient No. 25 (VI 13) C.E.B. Female aged 24 years. Bilateral renal enlargement not well shown on radiograph. Crescent formation illustrated.

(ix) Rosette sign - This sign was observed by Fort (1941), Barquin et al (1947) and Hickel et al (1949) and according to these authors, first described by Surraco (1939). It apparently occurs in the upper pole of the kidney and is produced by a group of minor calyces with their axis radiating like the spokes of a wheel.

This sign has not been observed in this series.

Bizarre Picture

If a number of the features already described under deformities of the pelvis and calyceal system occur in the same kidney, a bizarre picture is produced, which is not found in any other kidney lesion. If the calyceal system is compressed and widely separated into their irregular lines the so-called "spider" appearance is produced. Wide branching of the calyceal system with irregular thinning and dilatation produces the "Dragon" appearance (Reaves, 1942; Newman, 1950).

Present series

Bizarre appearance was present in 9 patients. This feature is pathognomonic of the advanced case of polycystic kidney disease (see fig. XIV).

/Communication.....

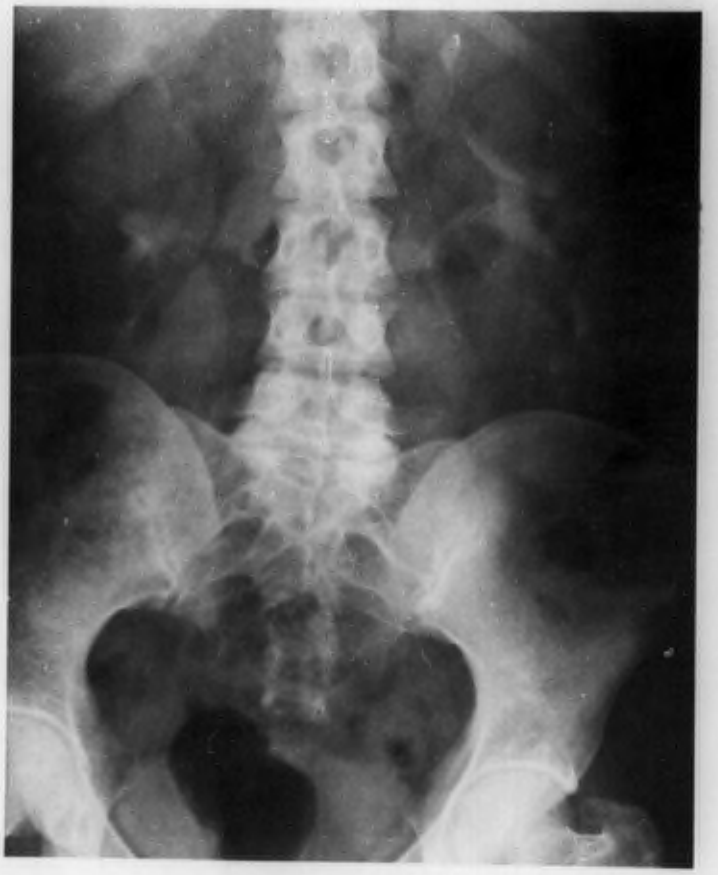


FIGURE XIV

Patient No. 19 (V 37) H.P.C. Female aged 40. Asymptomatic but has bilateral large, irregular renal masses. "Spidery" appearance demonstrated. Poor renal function.

Communication of cyst-cavities with the pelvis or calyceal system

Isolated reports of this finding have appeared from time to time (Grauhan, 1926; Hennig, 1929; Giannico, 1947; Duff, 1948; Thiele, 1952). Hillenbrand (1949) described a case in which it was the only diagnostic finding.

Deuticke (1942) found it in several cases but it is noteworthy that in all of them the pyelographic examination was carried out shortly after an episode of haematurea.

This condition may be more frequent than it is generally believed to be, provided the patient is radiologically examined shortly after the rupture of the cyst and is also X-rayed in the prone position to show up ventrally situated communicating cysts (Yden, 1954).

Present series

Cysts communicating with the pelvis or calyceal system were not observed but not one of these patients were examined shortly after an episode of haematurea.

Pyelographic abnormalities of the ureters

(a) Medial displacement of the ureter

This was described by Spencer (1937). This displacement chiefly affects the upper $^{1}/_{3}$ (Hennig, 1929; Spencer, 1937; Goldstein, 1951).

/Ureteral .....

Ureteral displacement is due to enlargement of the lower pole of the kidney (Fort, 1941).

Personal series

In 6 instances this was marked. All these patients had large kidneys (see fig. XV).

(b) Angulation of the ureter

This occurs at the pelvic-ureteral junction and has been described by Spencer (1937) and Goldstein (1951).

Present series

In both cases observed by us there was an associated ptosis of the kidney.

Bilaterality of lesions

This feature is probably one of the main differentiating features of polycystic disease of the kidneys (Spencer, 1937; Nolan, 1945; Goldstein, 1951).

Lesions may, however, only be observed on the one side, which may indicate that the disease is more advanced on that side, or that the appearance of polycystic disease is simulated by another lesion, or that the disease is truly unilateral. This last fact cannot be established on pyelographic examination alone (Thiele, 1952).

A very careful re-examination of the least affected side

/will.....

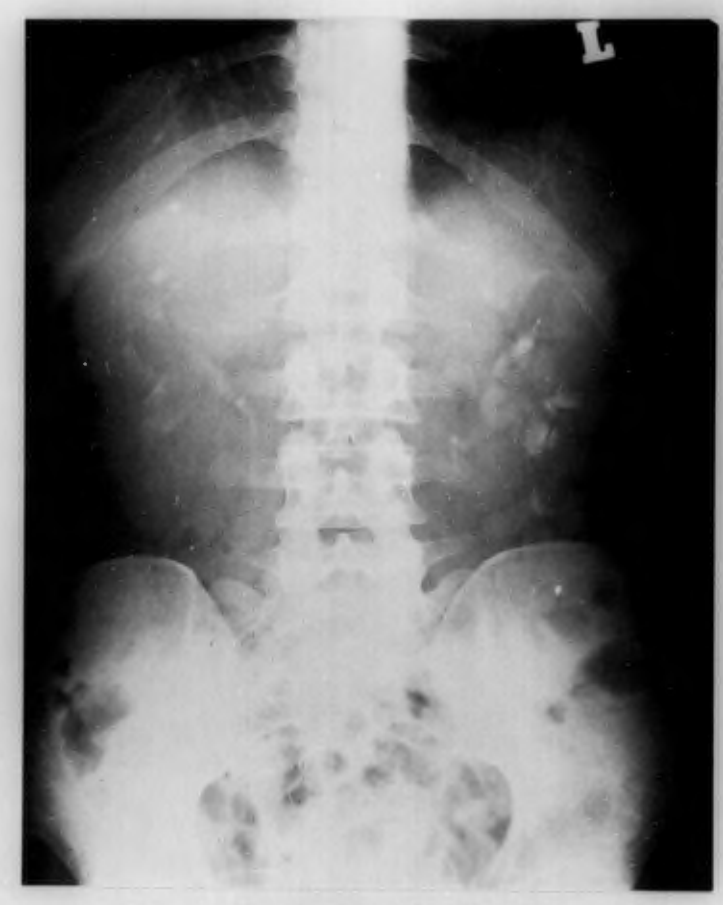



FIGURE XV

Patient No. 12 (V 13) J.H.D. Male aged 31 years. Asymptomatic. No clinical abnormality present except albuminurea. Radiological enlargement of both kidneys. Distorted calyceal system with "confetti" sign fairly well marked. Medial displacement of right ureter present.

will often show the earliest pyelographic signs of polycystic kidney disease. In such a case retrograde pyelography may have to be done, to get perfect images of the entire calyceal tree (Köhler, 1947).

Present series

Changes were observed in all the definite cases to be bilateral and in doubtful cases predominantly or apparently entirely unilateral.

The earliest pyelographic signs of polycystic kidney disease

Calyces are narrowed and hardly noticeably elongated (Reaves, 1942). Calyces are narrowed and parenchyma of kidney thickened to suggest a localised mass (Sussman, 1937).

Dilatation of the calyceal system is an important sign but no single sign is diagnostic for polycystic kidneys (Henninger et al, 1939). Before the diagnosis can be made, the lesions must be fairly well advanced and calyceal elongation is the earliest sign (Grauhan, 1926). Köhler (1947) finds the combination of a number of suggestive signs useful, to establish the diagnosis. Many of the signs described as early indications of polycystic kidneys also, occur in normal kidneys and no indisputable early sign exists (Tilk et al, 1941).

In our experience there is definitely no single sign which

/will.....

will establish the diagnosis but a number of signs in combination may lead to a fair amount of certainty about the underlying pathology.

Of these signs calyceal elongation and indentation, alteration of the normal angles of calyces, and crescent formation are the most important. These changes may only be of a minor degree, but widespread throughout both kidneys and are signs to be looke for with care. Repeated examinations may have to be carried out to establish the value of a sign which is considered to be an early indication of the presence of polycystic kidneys.

How long does a typical deformity take to develop sufficiently to be diagnosed on pyelography?

Sussmann (1937) found typical lesions to develop in a girl of 14 years over a period of 17 months. Initially she had only shown slight calyceal compression and increase in parenchymal thickness.

In a patient, who had a normal kidney on excretory pyelography and retrograde pyelography, whose other kidney was removed for polycystic disease (Lazarus, 1937), found a typical pyelographic picture to have to develop 3 weeks after the operation. Reaves (1942) states that a typical lesion may develop in a year's time.

In our experience with patients who were completely asymptomatic and yet showed suspicious changes in the excretory

/pyelogram.....

pyelogram these abnormal features were accentuated on repeated excretory pyelography 2-3 years later without an obvious clinical deterioration in the condition taking place.

What method of pyelographic examination should be followed?

Most authors find excretory urography unsatisfactory and state that retrograde pyelography is the method of choice in examining these patients (Albrittain et al, 1939; Henninger et al, 1939; Newman, 1950). This preference for retrograde pyelography is due to the poor function in many cases of polycystic kidneys with an inadequate excretion of contrast medium so that satisfactory radiographs are not obtained.

In the present series excretory pyelography was a highly successful method of examination. Out of a total of 27 patients with polycystic kidneys belonging to family I, excretory pyelography enabled a diagnosis to be made in 20 (74%).

In 6 patients with unsatisfactory or doubtful results the answer was obtained on retrograde pyelography.

These highly satisfactory results can probably be attributed to the fact that most of these patients were healthy and had good renal function so that they were examined at the optimum time for establishing a diagnosis.

In an investigation of a family such as carried out in this investigation, it would be extremely difficult to arrange

/for.....

for all members to have retrograde pyelography done. It is not unlikely that patients would submit to an instrumental procedure with the willingness which they showed to have intravenous pyelography performed. Many of those advised to have a retrograde pyelography done, refused it. Renal function was so good in most of these patients that only in a minority of instances better pyelographic pictures would have been obtained by retrograde pyelography.

The diagnostic value of pyelography

Higgins (1952) found that a pyelographic diagnosis could be made in the vast majority (78.8%) of patients and so did Simon et al (1955).

Both these authors sorted to retrograde pyelography if excretory pyelography failed.

One has to keep in mind that in the earliest stages of the disease not even a retrograde pyelogram may lead to a diagnosis. A patient may thus have a normal pyelogram and still be suffering from the disease (Thiele, 1952; Barquin et al, 1947). A very early polycystic kidney may be very difficult to differentiate from the variations in appearance of the normal pyelogram (Billing, 1954).

If the clinical evidence is in favour of a diagnosis of polycystic kidneys a negative pyelographic result does not

/exclude.....

exclude this condition (Reaves, 1942).

The statement by Wells (1936) that a normal pyelogram and a normal kidney at operation excludes polycystic kidney disease and by Braasch et al (1932) that this disease can be excluded if bilateral pyelograms are normal, cannot be accepted.

Fergusson's (1949) statement that a negative excretory pyelogram does not become positive and excludes the presence of polycystic disease must be rejected.

Present series

In 30 patients belonging to family I, a pyelographic diagnosis could be made in 27, who were examined radiographically. In the clinical group of patients 13 had pyelograms done of which 12 were diagnostic. Thus out of a total of 40 patients who had pyelograms done the diagnosis was made in 39.

In a patient whose abdomen can be palpated with ease, it is unlikely that an outspoken pyelographic appearance of polycystic kidneys will be found, if the kidneys are not enlarged on clinical examination. This is in agreement with the classification of Hickel et al (1949):

(a) Polycystic disease which can be diagnosed with ease. Kidneys are bilaterally enlarged and irregular and the pyelographic findings classical. The clinical diagnosis is made before the pyelographic diagnosis.

/Polycystic.....

(b) Polycystic disease diagnosed with difficulty. Kidneys are not palpable, laboratory investigations are inconclusive, the radiological abnormalities are not clear cut and liable to be normal or may appear to be unilateral.

(c) The diagnosis cannot be made with clinical, laboratory or radiological aid.

Other forms of radiological diagnosis

(a) Perirenal air insufflation

This has been found of some use in the diagnosis of polycystic kidneys by Nozkay (1932) and Hickel et al (1949) if other methods fail. Most authors do not use it on account of the danger of complications (Tilk et al, 1941). Perirenal adhesions preclude the use of perirenal air as useful form of examination (de Klerk, 1958).

(b) Pneumoperitoneum

This is of no use in the early stages of the disease (Grauhan, 1926). It may be a radical procedure in patients who already are very ill (Blatt, 1927; Tilk et al, 1941).

(c) Aortography

In large polycystic kidneys the arteries are stretched out but difficult to see in the early cases, and may occur in large

/kidneys.....

kidneys of any nature (Billing, 1954). He does not think that it ought to be necessary if careful pyelography is carried out. Frankson (1955) mentioned one case examined by this method but does not describe it.

It is doubtful whether this method will ever gain a prominent place in the early diagnosis of polycystic kidneys.

(d) Percutaneous cyst puncture and filling with contrast medium

Retrograde pyelography is done at the same time.

This was described by Lindblom (1952) and Frankson (1955) who found it a useful diagnostic aid in 6 cases.

This is also not a method for early diagnosis.

(e) Nephrotomography

A large quantity of contrast medium is rapidly injected intravenously and combined with renal tomography (Evans et al, 1954). They had no success with one case with polycystic kidneys but this method may in the future prove to be of value.

# S E C T I O N  I V

## DIAGNOSIS, DIFFERENTIAL DIAGNOSIS AND PROGNOSIS

THE DIAGNOSIS OF POLYCYSTIC KIDNEYS

In the fully developed case there can be little difficulty in establishing a diagnosis of polycystic kidney disease. A patient with abdominal pain, haematurea, bilateral large irregular renal masses and typical pyelographic findings presents a picture of a clear-cut and well defined clinical entity.

Should one wait for this clinical picture to develop, before a diagnosis is made, many early cases will not be detected.

Polycystic kidneys may produce symptoms and signs which simulate so many other conditions that it may truely be called the great immitator (Dooley, 1940).

When a renal lesion, which may produce symptoms and signs of a varied nature, is further complicated by such factors as calculus formation, infection or neoplasm, there is no end to the variety of ways in which it may present.

There is a progressive increase in size of the kidneys due to cyst growth and this is accompanied by a gradual destruction of the renal parenchyma. All clinical and radiological signs are produced by these two factors. The degree to which each has progressed will determine the clinical picture at that stage.

It cannot be accentuated strongly enough that a full and

/comprehensive.....

comprehensive family history is of inestimable value in detecting this disease. Once a family history of polycystic kidneys, or kidney disease has been obtained, signs, which otherwise would have caused no comment, may assume a new significance.

The bilateral renal enlargement, as outlined above is highly characteristic but unilateral enlargement may bring numerous other conditions into the differential diagnosis. In the early case the kidneys will probably not found to be enlarged and the diagnosis may be missed. On the other hand, renal enlargement may be the earliest and only sign for a long time.

If no renal enlargement is detected clinically, one will have to rely on a pyelogram (intravenous or retrograde) to provide the answer.

Such a patient, without renal enlargement but with hypertension and albuminurea may, on clinical and laboratory evidence, be considered to be suffering from chronic nephritis or pyelonephritis, unless pyelography is carried out.

Examination of the urine, blood chemistry estimations and renal function tests have no part in making an early diagnosis. These methods may merely indicate renal dysfunction which in turn may lead to pyelographic studies.

There is only one, fairly constant and reliable, diagnostic

/aid.....

aid and that is pyelographic examination and even this may fail to be positive in the earliest phases of the disease.

In the earliest phases of the disease, before symptoms or radiological signs are produced, the diagnosis may not be made except on direct inspection of the kidney at laparotomy (Frankson, 1955).

CLINICAL FORMS OF THE DISEASE

As an aid to diagnosis various authors have made an attempt to classify the disease into various clinical types.

Albarran et al (1903) divided the disease into three forms:

(a) Chronic nephritic type. Presenting like Bright's disease with cardiovascular symptoms and signs and lasting a long time.

(b) Surgical type with unilateral renal symptoms and signs progressing to uraemia.

(c) Uraemic type with vague symptoms but sudden, rapid downhill course to uraemia and death.

Braasch (1916) described three stages in this disease:

(a) Latent stage. Usually occurs in young adults. Polycystic kidneys a chance finding at operation or autopsy.

(b) Stage of renal enlargement and/or haematurea. These patients are usually seen in surgical clinics.

(c) Stage of Uraemia.

Maier (1924) found two forms of the disease:

(a) Patients with symptoms of a general nature suggesting uraemia.

(b) Patients with symptoms of renal disease, more of local than general nature.

/Oppenheimer.....

Oppenheimer (1934) described eight different ways in which patients with this disease may present.

Bell (1950) also described three stages:

(a) Early. Patients have palpable kidney enlargement but no symptoms. This is unusual as kidneys are not often palpable before onset of symptoms. An abnormal pyelogram may prove the presence of the disease (see table IV for evidence that kidneys may be palpable long before symptoms are produced).

(b) Surgical type. A palpable kidney with evidence of infection or haematurea.

(c) Medical type. Renal insufficiency dominates the whole picture and chronic nephritis is simulated. Uraemia develops slowly but may have a very sudden onset.

We have found it impossible to classify this disease into rigid compartments and agree fully with Dalgaard (1957) that there is such a degree of overlap between groups with different symptoms, and such a merging of one group into the other, that such a classification is not of much value.

From the work of other authors and from our own experience we think that a broad grouping into three stages, which must be

/seen .....

seen as rather artificial divisions of the course of a disease which is gradually but relentlessly progressive, may serve some purpose.

Stage I - The patients have no symptoms at all and the disease is discovered on routine clinical examination for other reasons, for example, life insurance (Frankson, 1955), or when a family is investigated. (In the present series 15 patients (50%) belonging to family I fall into this group). Such patients may also be discovered at operation or at autopsy.

Stage II - Patients in this group have symptoms of varying nature and intensity but more often of the "surgical" type. They may present with haematurea, abdominal mass or pain either singly or in various combinations or with hypertension and symptoms of renal insufficiency.

Stage III - Unless patients die of intercurrent disease or of vascular accidents they all progress at varying rates to the stage of uraemia which heralds the end for them.

In all these phases various complicating diseases may occur and the one phase may rapidly change into the other. This staging is in agreement with that of Braasch (1916) and Dalgaard (1957).

THE AIM OF EARLY DIAGNOSIS

The question may well be asked why such pains should be taken to diagnose, in its early stages, a condition for which so little can be done in the way of cure.

Birch-Jensen (1954) believed that these patients should be kept symptom-free as the asymptomatic ones have a better prognosis than those with symptoms. This could be done by early diagnosis, advising them to avoid strenuous work and by combating infection.

Young patients who have seen the effects of polycystic kidneys in other members of the family and are conscious of its hereditary nature are often anxious to know whether they have the disease or not. They know that they may transmit it to their offspring and want to know this when they intend to marry. If genetic-hygienic measures are to be instituted in patients with this disease, it is going to be of no value in the patient in the 4th or 5th decade but should be instituted in the early reproductive phase of the patient's life, if a correct diagnosis can be made at that stage. This subject will be further discussed under the genetic aspects of this disease.

Patients with intracranial aneurysms frequently suffer rupture of the aneurysm at a fairly early age before hypertension

/has.....

has developed. The presence of polycystic kidneys influences the prognosis, as such a marked tendency to develop hypertension at a relatively early age, exists in these patients.

As pointed out previously, patients may present with hypertension and yet have polycystic kidneys in a very early stage. A correct diagnosis here, is also of great value in prognosis.

DIFFERENTIAL DIAGNOSIS

As stated before, the presence of bilateral large irregular renal tumours leave very little doubt about the diagnosis of polycystic kidneys especially if associated symptoms and signs are also suggestive.

The most important other condition which may cause bilateral renal enlargement and has to be differentiated from polycystic kidneys is renal neoplasm.

Küster (1896-1902) found 13 bilateral cases in a total of 601 cases of renal neoplasm and Albarran et al (1903) reported 3 cases. Lubansch (1925) found 1 case of bilateral carcinoma in a group of 233 cases of carcinoma of the kidney and 1 case of bilateral sarcoma in a total of 110 cases of renal sarcoma.

Alnor (1952) reported a case of bilateral primary hypernephroma and one case of carcinoma with metastasis to the other kidney. Bilateral hypernephroma also described by Bailey et al,(1950)

Bilateral renal neoplasm is a rare finding and one can imagine that clinical differentiation may be very difficult.

Uraemia and hypertension in the presence of renal tumour or tumours favours a diagnosis of polycystic kidneys rather than renal neoplasm (Katz et al, 1924).

Bilateral hydronephrosis may also be the cause of bilateral renal masses being palpable. The differentiation can usually

/be.....

be made on pyelographic examination. Bilateral dilatation of the renal pelves does not occur in polycystic kidneys unless there is associated urethral or bilateral ureteral obstruction.

Bilateral pyonephrosis is another rare condition which has to be considered in the differential diagnosis. This has been well described by Goldstein et al (1939). This condition may occur in association with polycystic kidneys. The condition on its own can only be differentiated on the bases of retrograde pyelographic studies.

Polycystic disease may closely simulate chronic pyelonephritis. Chronic pyelonephritis does not cause renal enlargement.

Chronic glomerulonephritis may have to be differentiated from polycystic kidneys. Once again, the absence of renal enlargement in the first condition, serves as an aid. The added features of albuminurea, presence of casts in the urine and S.G. of the urine may be of help. Marked albuminurea is not common in polycystic kidneys. Both may pass urine with a low fixed S.G.

Pyelography is also of great use here if the polycystic disease is advanced to such a degree that a characteristic deformity is produced.

PROGNOSIS FOR ADULTS WITH POLYCYSTIC KIDNEY DISEASE

This is one of the most difficult aspects of this condition.

Polycystic kidney disease shows a great variation in mode of onset, course and rate of progression, from case to case. Patients with this disease are also prone to suffer numerous complications of a local or general nature. If all these variable factors are taken into consideration it is clear that the estimation of the outlook for each patient must be more or less an individual matter.

There are authors who believe that the prediction of the probable cause of the disease is impossible (Niecke, 1930).

Opinions about this subject differ widely and range between frank pessimism and guarded optimism. Low et al (1944) state that diagnosis of polycystic kidney disease is a mandatory sentence of death from uraemia and the only hope of escaping this is to die of an accident or intervenent disease. This is certainly true but the question still remains: "How long does it take?".

The fact remains that, once these patients develop symptoms, there is a slow but relentless downhill course to a uraemic death (Hantschmann, 1933).

This progression may not be a steady one but may show fluctuations, with periods of haematurea or nitrogen retention which may last a few weeks (Higgins, 1952).

/The.....

The rate of progression is extremely variable.

There are numerous case reports of patients who have lived for 20-30 years with symptoms of this disease (Braasch et al, 1932; Lazarus, 1937).

In contrast with this are the case reports of patients who are asymptomatic or only mildly symptomatic and then rapidly deteriorate and die within a few months in uraemia (Niecke, 1930; Bell, 1950).

The most puzzling of all, are those patients who lead an active and normal life and are found to have polycystic kidney disease at autopsy. It is not unlikely that these differences in opinion are due to differences in the type of material described.

Patients with this disease, who present with generalised symptoms of hypertension or renal failure, are admitted to medical wards. They have a very poor prognosis and figures based on such material is not representative of the disease in the general population.

Patients who present with "surgical" symptoms such as pain, haematurea or a lump usually do so at a younger age period and have a better outlook (Köhler, 1947; Frankson, 1955).

Cause of death

The majority of these patients die of uraemia. Uraemia

/as.....

as the cause of death was found in 50% of patients (Montgomery, 1948), 65% (Higgins, 1952) and 60% (Dalgaard, 1957).

Present series

Of 18 patients who were dead at the time of this report, 10 had died of uraemia (55%).

Age at death

The average age at which death occurred was found to be 50 years (Oppenheimer, 1934; Higgins, 1952). Rall et al (1949) found it to be 49.3 years and Dalgaard (1957) 51.5 years.

Present series

The average age at death, of those patients who were known to be suffering from polycystic kidneys, was found to be 52 years. The average age at death of these patients, in whom the disease was a chance finding at autopsy, was 47 years.

Duration of disease

This is very difficult to determine as the exact time of onset of the disease cannot be known with certainty. The time of onset of symptoms is usually used for this calculation but it must be kept in mind that the disease may be present without producing symptoms or may produce symptoms very late in the course of its development. Braasch et al (1932) found that from their group of deceased patients (74) it could be calculated

/that.....

that 30% died within 2 years of onset of symptoms while another 15% died within 2-4 years of onset of symptoms.

Rall et al (1949) found that the average duration of the disease from onset of symptoms till death was 9.3 years in their series.

Dalgaard (1957) found that where the disease started before the 50th year, 44% of the women and 33% of the men were alive after 12½ years (while in the normal population 94% of women and 95% of men were alive after this time).

In the group where the disease first appeared after the 50th year, 54% of the women and 14% of the men were alive 2½ years after the commencement of the disease, while in the normal population there were respectively 98% and 97% surviving after this time.

Present series

This group is too small and the information on the cases obtained from clinical records too incomplete to allow valid calculations to be made.

The 6 patients belonging to family I (table IV) who died had their disease for an average period of 4.8 years.

It should be pointed out that the average duration of the disease in the patients, who had symptoms and were examined at the last follow-up, is 8.3 years.

/Uraemia.....

Uraemia as a factor in prognosis

As pointed out previously, more than 50% of patients with this disease die in uraemia.

The onset of uraemic symptoms is usually considered to be of grave significance.

Willan (1928) found that 10 out of 13 patients died within 2 years of the onset of uraemic symptoms. Rall et al (1949) found the average duration of life after the onset of uraemia to be 2.2 years in 17 of their patients of whom only one survived 5½ years. Simon et al (1955) found that all patients with uraemic symptoms died within 3 years. Dalgaard (1957) found that more than 90% of patients with uraemic symptoms died within the 5 year period in which the uraemia started and the rest in the next 5 year period.

Information about this feature is not available in the present material.

Comment

The great variability in the clinical course of this disease and the liability to other complications make it an impossibility to predict what course the disease will follow in a particular patient.

There is no symptom or sign by which the potentially severe

/case.....

case can be recognised at an early stage.

Each case has to be discussed on its own merits and, besides the primary disease, the presence of other factors such as hypertension, infection, pregnancy and intercurrent disease have to be given due consideration.

# S E C T I O N  V

## MALFORMATIONS ASSOCIATED WITH POLYCYSTIC DISEASE OF THE KIDNEYS

ASSOCIATED MALFORMATIONS

The occurrence of other developmental defects in association with polycystic kidney disease, has strengthened the belief of its congenital nature.

From a relatively early stage in our knowledge of polycystic kidneys, various authors have accentuated the fact that associated malformations may be a diagnostic aid in differentiating this form from other forms of renal disease.

In many reported series, it is not quite clear whether one is dealing with the adult form or the congenital form of the disease. Conclusions are then drawn with regard to the association of other developmental anomalies with polycystic kidneys, which may be true for the congenital form of the disease but certainly not for the adult form.

The more frequent association of developmental anomalies with congenital polycystic kidneys than with the adult has been commented on by various authors (Ritchie, 1892; Sieber, 1905; Sears, 1926; Hausmann, 1940; Lambert, 1947).

Most of the material collected from the literature is in the form of case reports and with a few collected series. Of the last named, the most important are those of Bugbee et al, (1924); Campbell (1951) and Bigelow (1953).

As Dalgaard (1954) rightly points out, we lack information

/on.....

on the average frequency of occurrence of each malformation in the population. Before we know this, it is difficult to exclude the co-incidence of a malformation as being due to chance. The great frequency with which these associated malformations have been described certainly weighs heavily against the possibility that it is a chance occurrence.

The same author also warns against the selection of other members of a family with some associated malformation, without taking into consideration the frequency of this malformation in the entire family.

Malformations in association with the adult form of polycystic kidneys

The literature was searched for such malformations and special note taken whether such malformations occurred in other members of the patient's family.

The present material was then investigated to determine whether such an association could be confirmed or not.

(a) Cystic disease of the liver

This is the most constant associated defect found in association with polycystic kidney disease in the adult. The cysts may vary in number and size from a single cyst to a large number of cysts replacing almost the entire liver substance.

/Incidence.....

INCIDENCE OF CYSTIC LIVER IN PATIENTS

WITH POLYCYSTIC KIDNEY DISEASE

| AUTHOR | YEAR | TOTAL NO OF PATIENTS WITH POLYCYSTIC KIDNEYS | TOTAL NO OF PATIENTS WITH CYSTIC LIVERS | % |
|---|---|---|---|---|
| Lejars | 1888 | 14 | 4 | 28.0 |
| Ritchie | 1892 | 88 | 11 | 25.0 |
| Luzatto | 1901 | 90 | 5 | 5.5 |
| Küster | 1902 | 249 | 49 | 16.0 |
| Blatt | 1927 | 9 | 2 | 22.0 |
| Braasch et al | 1932 | 9 | 4 | 44.0 |
| Oppenheimer | 1934 | 14 | 4 | 28.5 |
| Rall and Odel | 1949 | 46 | 15 | 33.0 |
| Bell | 1950 | 87 | 35 | 40.0 |
| Thiele | 1952 | 4 | 2 | 50.0 |

From the accompanying table it can be seen that in the larger series of patients, cystic liver usually occurs in about 28% of cases.

Cystic disease of the liver on its own must be a rare disease, but exact figures for this are not availabde.

The occurrence of polycystic kidneys in patients with cystic disease of the liver has been described by various authors.

Moschowitz (1901) found polycystic kidneys in 19% of cases with cystic liver and Comfort et al (1952) in 54%. Melnick

/(1955).....

(1955) found 50% of cases with cystic liver to have polycystic kidneys and Davis (1925) found 60% of patients with cystic liver thus affected.

The occurrence of these two malformations can therefore assumed to be a fairly constant one and not a mere chance association.

The familial occurrence of polycystic kidneys and liver has been reported by Höhne (1896); Thompson (1903); Cairns (1925); Reason (1933); Steglich (1935). Werner (1940) also commented on its association with polycystic kidneys and its probable indication of a common genetic factor.

Clinical features of associated liver cysts

It is very rare for the liver lesion to produce symptoms (Walker, 1946).

When symptoms are produced it is usually due to hepatic failure but portal obstruction may cause ascites and splenomegaly (Waterson, 1946).

The most common finding, if the liver is also cystic, is apparently an irregular non-tender enlargement of the liver.

Present series

Of those patients coming to autopsy, cystic disease of the liver was found in 7 cases out of 14 with polycystic kidneys (50%).

/Only.....

Only one member of family I has come to autopsy and no liver cysts were found. Not one member of this family has clinical evidence of cystic liver but this does not exclude the possibility that it may be present.

Of the other 14 adults, of whom clinical notes are available, 3 had an enlarged, regular, non-tender liver. No symptoms due to the hepatic lesion were present in any of these patients.

(b) Cystic pancreas

This is a more unusual associated malformation with polycystic kidneys than cystic liver.

Braasch et al (1932) found it in one case associated with cystic liver and polycystic kidneys.

Thiele (1952) also described it with cystic liver and polycystic kidneys.

## THE ASSOCIATION OF ANEURYSMS OF THE INTRACRANIAL ARTERIES WITH POLYCYSTIC KIDNEYS

The simultaneous occurrence of these two conditions in one patient was first described by Borelius (1901) and was discussed in some detail by Dunger (1904), who also reported a case and also mentioned three similar cases seen by Schmorl. If these cases of Schmorl are considered to be valid, then this phenomenon had only been reported on 8 occasions up to 1939. Since then a large number of reports have appeared, either singly or the subject was mentioned in passing, usually in large series of patients coming to autopsy on account of intracranial haemorrhage.

A list is given of all the authors who have described the association of these two conditions, with the number of cases described by each, indicated in brackets. Only patients with indisputable evidence of polycystic kidneys are included and no cases with single or isolated renal cysts.

Borelius (1901) (1), Dunger (1904) (1), Fearnsides (1916) (1), Katz et al (1924) (1), Snapper et al (1939) (1), McDonald et al (1939) (1), O'crowley et al (1939) (3), Wilson et al (1940) (1), Forster et al (1943) (1), Sahs et al (1943) (2), Magee (1943) (1), Madonick et al (1946) (1), Suter (1949) (2), Sahs (1950) (2), Ask-Upmark et al (1950) (5), Brown (1951) (6), Hamby (1952) (3), Robbins (1952) (4), Bigelow (1953) (3), Steelman et al (1953) (1),

/Poutasse.....

Poutasse et al (1954) (3), Stehbens et al (1954) (2), Wilson et al (1954) (1), Juste (1955) (2), van der Schoot (1955) (1), Melnick (1955) (4), Uys (1956) (1), McCaughey (1956) (1), Walton (1956) (8), Holmes (1958) (1), Mitchell et al (1943) (1).

This gives a total of 65 cases of this association reported in the literature. The cases of Magee (1943), Ask-Upmark et al (1950) and Wilson et al (1956) are included, although these authors are not explicit whether, in their series of subarachnoid haemorrhage coming to autopsy, the polycystic kidneys were found in those patients with ruptured aneurysms.

To this list may be added the three cases of Schmorl mentioned by Dunger (1904) and the case mentioned to Kartagener et al (1947) in a personal communication by Uehlinger. The case of Forster et al (1943) deserves to be mentioned. This was a child of 17 months in whom an aneurysm of the basilar artery occurred in association with large bilateral polycystic kidneys. It is the only example of a aneurysm occurring in a child that has been described.

From those cases, on whom sufficient information could be obtained, it was found that the incidence was equal in both sexes.

In those in whom rupture of an aneurysm occurred the average age at which this occurred was 41 years. A definite

/family.....

family history of polycystic kidneys was present in 6 patients and a probably history in 2 more.

Associated cysts of the liver were reported in 14 instances but this is not a reliable figure as this information is not always supplied and probably liver cysts occur more frequently. Interesting as these case reports may be, it still is important to evaluate whether the simultaneous occurrence of two conditions, which are not particularly common, in the same individual, is not merely a chance association.

To answer this question help can only be obtained from large series of autopsy reports in which the incidence of both conditions independently and in combination has been determined. Suter (1949) in an autopsy series of 5960 cases found 27 cases of intracranial aneurysm and 5 cases of polycystic kidneys. In two instances were polycystic kidneys associated with ruptured intracranial aneurysms.

Brown (1951) in a series of 11245 autopsies found 148 intracranial aneurysms and 36 cases of polycystic kidneys. Simultaneous occurrence was found in 6 cases. Polycystic kidneys were thus found in 4% of patients with ruptured intracranial aneurysms, and 16.6% of patients with polycystic kidneys had an intracranial aneurysm.

In an autopsy series of 8882 cases Bigelow (1953) found 47

/intracranial.....

intracranial aneurysms of congenital nature and 18 cases of polycystic kidneys. Of the 14 adults in whom the skull was opened 3 had associated aneurysms. Thus of 18 patients 16.6 had intracranial aneurysms.

It is unfortunate that, in all patients coming to autopsy, the intracranial contents are not examined as the incidence of intracranial aneurysms, in patients with polycystic kidneys would then probably be much higher.

From these figures, however, it is obvious the occurrence of these two conditions together is far more frequent than would be expected on a basis of chance association.

Intracranial haemorrhage occurring in patients with polycystic kidneys

In a collected series of 212 patients with polycystic kidneys Sieber (1905) found that 10 had died of apoplexy. Coombes (1909) found 5 examples in 44 cases of polycystic kidneys. Bigelow (1953) in an analysis of 499 cases of polycystic kidneys (collected series) found that 47 had died of intracranial haemorrhage. Bell (1935) thought it unusual for a patient with polycystic kidneys to die of intracranial haemorrhage. Intracranial haemorrhage is due to hypertension, which is common in patients with polycystic kidneys (Braasch et al, 1933; Suter, 1949).

/As.....

As many authors have pointed out, the occurrence of subarachnoid haemorrhage in these patients with polycystic kidneys does not necessarily mean that a ruptured aneurysm is present (Bigelow, 1953).

A fair number of cases have been reported of subarachnoid haemorrhage occurring and at autopsy a ruptured blood vessel being found but no evidence of an aneurysm (Dunger, 1904; McKinley, 1920; McGregor, 1926; Sands et al, 1927; Oosting, 1944; Lambert, 1947). Some of these patients were hypertensive and had evidence of cerebral arteriosclerosis which could account for this complication. In some of the younger age groups it is not unlikely that an aneurysm had been present but was completely destroyed at the time of haemorrhage.

The presence of intracranial aneurysm in a patient with polycystic kidneys

From the figures of Suter, Brown and Bigelow quoted above, it is seen that in their series intracranial aneurysm occurred in 16.6%-40% of cases with polycystic kidneys. Robbins (1952) found 4 cases (18%) of intracranial aneurysm in 22 cases of polycystic kidney and Juste (1955) 2 cases (9%) in 23 cases of polycystic kidney. The figure of 40% of Suter is probably too high on account of the small number of cases in his series.

/Of.....

Of great clinical significance is the diagnosis of an intracranial aneurysm in patients with polycystic kidneys and vice versa. Patients known to suffer from polycystic kidneys, in whom an intracranial aneurysm was diagnosed and treated have only been recorded by Hamby (1952) (Case 20) and Poutasse et al (1954) (Case 3). Patients who had an episode of subarachnoid haemorrhage from which they recovered and who later developed symptoms and signs of polycystic kidneys have been recorded by Brown (1951) in a woman of 21 who developed clinical evidence of polycystic kidneys 12 years later. Sussman (1937) described a girl of 14 who developed sudden severe left sided headache and a right hemiplegia which cleared up completely and 2 years later developed typical radiological signs of polycystic kidneys. The presence of an aneurysm was not proved in this patient. The case of Steelman (1954) had an intracranial aneurysm ligated, at the age of 23, and showed evidence of polycystic kidneys 2 years later.

Patients known to have polycystic kidneys, who suffer a fatal subarachnoid haemorrhage and who are found to have a ruptured aneurysm at autopsy, have been described by Suter (1949), (Case 2); Brown (1951), Hamby (1952), Poutasse et al (1954), (Case 2); Juste (1955).

Patients with a history of renal disease but not of

/polycystic.....

polycystic kidneys, who develop a fatal subarachnoid haemorrhage and are found to have a ruptured aneurysm at autopsy have been described (Katz et al, 1924; Brown, 1951 (Case 3)).

Patients with polycystic disease of the kidneys who suffer an episode of subarachnoid haemorrhage at a relatively young age, with a low blood pressure at the time of the ictus and who recover without an angiogram having been done. This has been described by Snapper et al (1939) (Case 1), Madonick et al (1946) (Case 2).

Patients with polycystic kidneys in whom an unruptured aneurysm is found at post mortem is quite rare (Fearnsides, 1916; Bigelow, 1953). The aneurysm did not produce symptoms during life in these two patients.

Comment

If it is considered that the vast majority of cases of co-excisting intracranial aneurysm and polycystic kidney disease have been reported in series of cases of fatal sub-arachnoid haemorrhage, and that only in 3 instances an unruptured aneurysm was found, this combination of lesions is of grave significance to the individual in which it occurs.

The patient, with this combination, usually dies as a result of the ruptured intracranial aneurysm before his renal disease becomes clinically manifest (Poutasse et al, 1954).

/The.....

The degree of cystic change of the kidneys and the level of the blood pressure determines the outlook for these patients (Walton, 1956).

This author also believe that these patients are often considerably younger than most cases of bleeding aneurysm.

Present series

In the group of patients coming to post mortem intracranial haemorrhage occurred in one patient.

Coloured female, C.S. (Patient No. 43, table VI), aged 59. Patient was admitted to hospital in a stuperose condition with no history available. Blood pressure was 180/100 and marked albuminurea was present. Lumbar puncture revealed a heavily blood-stained C.S.F. Patient deteriorated rapidly and died.

At autopsy large bilateral polycystic kidneys were found and multiple cysts in the liver. A large haemorrhage had occurred in the left cerebral hemisphere and ruptured through into the lateral ventricle. No aneurysm was found.

European female, E.D.C. (Patient No. 13 (V 14), table IV). At the age of 26, when she was otherwise quite well, she developed a sudden severe frontal headache followed shortly afterwards by vomiting.

She was admitted to the City Hospital for infectious diseases, Cape Town, and was found to have a slight

/temperature.....

temperature, neck rigidity and signs of meningeal irritation.

Lumbar puncture revealed a blood-stained xanthochromic C.S.F. Patient was transferred to Groote Schuur Hospital. Examination showed in addition to the above findings a blood pressure of 110/70. A systolic murmur over the praecordium radiating into the neck. Palpable femoral pulses and no abnormality of the urinary tract. No abnormal signs were found on examination of the nervous system.

Carotid and vertebral angiography were carried out. The only abnormality detected was a small suspicious area at the right carotid siphon on the A.P. view. The films were considered to be normal.

She steadily improved and was discharged, apparently quite well. When family I was investigated for the presence of polycystic kidneys this patient was examined in 1956. No abnormality could be found except the praecordial systolic murmur already described. Blood pressure was 120/70. No urinary abnormalities was present.

Intravenous pyelography carried out at that stage revealed the early changes of polycystic kidneys.

In 1958 she was re-examined clinically and intravenous pyelography carried out again. Both kidneys were easily palpable but it was doubtful whether they were enlarged or not. Blood pressure was 130/75. No urinary abnormalities was present. Intravenous pyelography confirmed the changes seen in 1956 and showed progression of these changes.

/Comment.....

Comment

This patient belongs to those group of patients who suffer an episode of subarachnoid haemorrhage, recover, and are later found to have polycystic kidneys.

On account of her age, the low blood pressure at the time of the ictus and the suspicious changes on arteriography it is more than likely that she has an intracranial aneurysm. Failure of an aneurysm to be demonstrated on angiography does not of necessity exclude its presence (Hamby, 1952; Walton, 1956).

It is important, from the prognostic point of view, that polycystic kidneys should be detected early in a patient with a ruptured intracranial aneurysm. A patient presenting with subarachnoid haemorrhage, should be carefully examined for enlargement of the kidneys and if doubt, pyelography should be carried out.

Diverse Malformations described in association with polycystic kidney disease in adults

The following malformations have been described in single cases and only rarely in families. The malformations will be enumerated, followed by the authors describing them.

Horseshoe kidney (Glaser, 1918; Frankson, 1954; Simon et al, 1955).

/Bilateral.....

Bilateral congenital polycystic kidney duplex (Washburn, 1930; Braasch et al, 1951).

Polycystic disease in one kidney with agenesis of the other kidney (Jona, 1942).

Cirrhosis of the liver occurring in 3 sisters, of whom two also had polycystic kidney disease and one of these had an intracranial aneurysm and an aneurysm of the renal artery (van der Schoot, 1955).

Portal fibrosis (Parker, 1956).

Spina bifida occulta (Hünner, 1939; Thiele, 1952; Keizer et al, 1952). The last-named authors described it in a family. They think that spina bifida occulta will often be found in patients with polycystic disease of the kidney but that the converse is not of necessity true.

Naevus pigmentous or vasculosus (Paus, 1914). This was also observed in relatives of patients with polycystic kidneys but the information provided is inadequate (Eppinger, 1929).

Cystic spleen (Barnett, 1914; Cumming, 1928).

Cystic lung (O'Crowley et al, 1934).

Myopia (Cairns, 1925).

Coarctation of the aorta (Schamroth et al, 1955).

Coarctation of the aorta with patent ductus (Bigelow, 1953).

Polythelia in 4 members of a family with polycystic kidneys (White, 1929).

/Cysts.....

Cysts of the choroid plexus (Sieber, 1905).

Colloid cyst of the third ventricle (Wyn-Jones et al, 1934).

Acromegaly and deformity of the sternum and cystic liver (Cumming, 1928).

Low set deformed ears in father and son both with polycystic kidneys (Hilson, 1957).

Myopia, colour blindness, dystrophia myotonia and arachnodactyli (Booth et al, 1957).

Congenital absence of gall bladder (Zimmerman, 1948).

The split hand described in association with cystic kidneys by Lorenz (1955) occurred in a hypoplastic cystic kidney and not true polycystic disease.

DEVELOPMENTAL ANOMALIES ASSOCIATED WITH CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEYS

There is a vast literature on this subject commencing with that of Meckel (1822) which was swelled to great proportions in the 19th century. These are usually single case reports and as such have a curiosity value at most and are probably too selected to be of statistical use.

When, however, the case reports of polycystic kidneys of infants and adults are compared one is immediately struck by the greater frequency of congenital malformations, usually of a grave nature, occurring in the former group.

Whilst the malformations occurring in the adult form are commonly of a limited nature (cystic liver, pancreas and intra-cranial aneurysm) the associated anomalies in infants are of a more widespread nature and of greater danger at an early age to the patient.

Such associated malformations have been reported with varying frequency by different authors. Bell (1950) in 7 out of 28 patients (25%). Campbell (1951) found it in 39 out of a total of 70 patients.

A list of the malformations which have been described with polycystic kidneys is given here and, although it cannot

/claim.....

claim to be exhaustive, it can serve as an indication of the severity and nature of such anomalies.

Many of these defects occur singly but it is more frequent to find 2 or more in a patient.

Malformations of the urinary system

| | |
|---|---|
| Renal agenesis | Ureteral atresia |
| Renal duplication | Double ureter |
| Renal ectopia | Megaloureter |
| Horseshoe kidney | Ectopia vesicae |
| Atresia of pelvis and calyces | Agenesis of bladder |
| Urethral agenesis | Persistent cloaca |
| Urethral valves | Diverticuli of the bladder |
| Hypoplasia of adrenals | Persistent urachus |

Malformations of the genital system

| | |
|---|---|
| Pseudo hermaphroditism | Duplication of female genital tract of various degrees |
| Hypoplasia of penis | Vesico-vaginal fistula |
| Hypospadias | Absence of ovary |
| Undescended testis | Absence of fallopian tube |

Malformations of the cardiovascular system

| | |
|---|---|
| Patent ductus arteriosus | Interventricular septal defect |
| Patent foramen ovale | Stenosis of pulmonary artery |
| Absent ductus arteriosus | |

/Malformations.....

Malformations of the central nervous system

| | |
|---|---|
| Hydrocephalus | Meningo-encephalocoel |
| Anencephaly | Meningocoel |
| Gliosis | Malformations of the brain |

Malformations of the musculo-skeletal system

| | |
|---|---|
| Exomphalos | Club foot |
| Aspalosomia | Club hand |
| Celosomia | Polydactyli (hands and feet) |
| Congenital diaphragmatic hernia | Syndactyli (hands and feet) |
| Inguinal hernia | Cleft palate |
| Agenesis of skeletal muscle | Hare lip |
| Cheilognathoschisis | Cranio-rachischisis |
| Short limbs | Microcephaly |
| Osteogenesis imperfecta | Vestigial tail |
| Large ears | Abnormal ribs |
| Turmschädel | Bifid tongue |

Malformations of the viscera

| | |
|---|---|
| Cystic liver | Cystic pancreas |
| Oesophageal atresia | Oesophageal diverticulum |
| Absent spleen | Accessory spleens |
| Situs Inversus | Malrotation of gut |

/Hypoplasia.....

| | |
|---|---|
| Hypoplasia of gallbladder | Absent gallbladder |
| Meckel's diverticulum | Intestinal diverticulum |
| Atresia of bowel | Atresia of rectum |
| Imperforate anus | Cystic lung |
| Trachea-oesophageal fistula | |

The following authors have described these malformations in either single case reports or groups of patients: Meckel (1822), Virchow (1869), Boynet et al (1903), Dunger (1904), Bunting (1902), Herxheimer (1906), Rosenow (1911), Shukowsky et al (1912), Staemmler (1921), Bugbee et al (1924), Hook et al (1925), Teuscher (1926), Davis (1928), Roscher (1933), Hennemann (1945), Bell (1950), Campbell (1951), Potter (1952), Bigelow (1953) and Bocian et al (1955).

Of special interest is the syndrome described by Gruber (1934) and elaborated by Pohlmann (1935) as acrocephalo-syndactyly and dysencephalia splanchnocystica. It usually includes encephalocoel, polycystic kidneys, cystic pancreas, frequently polydactyli and sometimes ocular defects and arhinencephaly. This association of malformations was frequently observed and a few cases collected from the literature. It was also found to occur in infants of one mother on several occasions. Gruber mentioned a possible relationship between this syndrome and tuberous sclerosis.

/Of.....

Of special interest may also be the association of portal tract fibrosis with polycystic kidneys described by Parker (1956) but previously also noted by Kanthack et al (1892).

Present series

(See tables VII and VIII). Of a total number of 16 stillbirths and infants below 1 year, 13 came to autopsy. Of these, 9 had associated malformations and one of the cases not coming to autopsy, also had associated developmental defects. Malformations were observed in:

Urinary tract - 5 cases

Musculoskeletal system - 1 case

Gastro-Intestinal system - 2 cases

Central nervous system - 2 cases

Cardiovascular system - 1 case

The malformations observed most frequently in association with polycystic disease of infants in this small series are consistent with those found by other authors in much larger groups of patients.

One fact emerges from this and that is that the type and degree of malformation is quite different in the adult and infantile form of the disease.

TABLE VIII

DATA ON INFANTS AND STILLBIRTHS WITH CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEY DISCOVERED AT AUTOPSY

| NO. | NAME | AGE | SEX | RACE | PATH.NO. | RENAL FINDINGS | ASSOCIATED ANOMALIES | COMMENT |
|---|---|---|---|---|---|---|---|---|
| 62 | Baby McC. | 1 day | Male | Coloured | 21/1945 | Normal sized bilateral polycystic kidneys | Left uretero-vesical-obstruction | |
| 63 | S.G. | 2 months | Female | European | 115/1945 | Bilateral polycystic kidneys | Hydrocephalus, webbed digits, polydactyli, cerebral haemispheres asymmetrical, skull sutures abnormal, blue sclerotics | |
| 64 | Baby B. | Stillbirth | Female | Coloured | 39/1946 | Magaloureter, bilateral polycystic kidneys of large size | Deficient calcification of skull, spina bifida, cleft palate, polydactyli | Large abdomen noted at birth |
| 65 | W.L. | 25 days | Male | European | 270/1947 | Bilateral small polycystic kidneys | Narrowed uretero-vesical orifices and ureteral dilatation | |
| 66 | Baby M. | Stillbirth | ? | Coloured | 376/1947 | Bilateral small polycystic kidneys | Narrowed uretero vesical orifices | |
| 67 | Baby W. | Stillbirth | Female | European | 41/1949 | Bilateral polycystic kidneys of spongy appearance | Cystic liver | Two sibs died of congenital defects but no post mortems done |
| 68 | Baby S. | 1 day | Male | Bantu | 24/1953 | Small cystic kidneys | Nil | Large amount of functional tissue |
| 69 | Baby S. | 1 day | Female | Coloured | 79/1953 | Normal sized kidneys. Medullary cysts only | Nil | |
| 70 | Baby N. | 1 hour | Male | Coloured | 249/1953 | Bilateral large polycystic kidneys | Obstruction in penile urethra. Dilated bladder and ureters + undescended testes | |
| 71 | Baby H. | 1 day | Female | Coloured | 284/1953 | Bilateral polycystic kidneys | Nil | |
| 72 | Baby G.H. | 4 hours | Male | Bantu | 417/1953 | Large bilateral polycystic kidneys | Short thumbs, polydactyli, cystic pancreas, accessory spleen, malrotation of gut, abnormal thoracic skeleton. | |
| 73 | Baby J.D. | 3 hours | Male | Coloured | 560/1953 | Bilateral large polycystic kidneys | Large annular foramen ovale. Cysts in right broad ligament. | |
| 74 | W.C. | 4 weeks | Male | Coloured | 17/1956 | Bilateral large polycystic kidneys | Nil | |

## THE ASSOCIATION OF POLYCYSTIC DISEASE OF THE KIDNEY WITH VON HIPPEL-LINDAU DISEASE AND TUBEROUS SCLEROSIS

The fact, that cystic kidneys may be associated with malformations of a more widespread nature, has frequently been commented on.

The possibility that the complex malformations described by him as acrocephalosyndactyli and dysencephalia splanchnocystica may be related to tuberous sclerosis and von Hippel-Lindau disease, was mentioned by Gruber (1934) and also by Rümler (1934).

Moolten (1943) discussed this question at some length and grouped tuberous sclerosis, polycystic kidney disease, von Hippel-Lindau disease and neurofibromatosis together as disseminated hamartiosis. He considered all these conditions to be caused by defective embryonic organiser activity.

The association of these two conditions with cystic kidneys has been described under the heading of classification of cysts. Only the main features will be indicated although some repetition may be necessary.

### von Hippel-Lindau disease

The oldest report of the occurrence of cerebellar cyst, cysts of the kidney and pancreas in the same patient is that of Pye-Smith (1884).

/Lindau.....

Lindau (1926), however, first described the disease entity: Haemangioblastoma of the retina and nervous system, cysts of the kidney and pancreas, benign tumours of kidneys, pancreas and adrenals occurring together in various combinations.

von Hippel-Lindau disease has frequently been described in several members of a family. Rochat (1927), Craig et al (1941), Tonning (1952), Moller (1952) and by Bird et al (1953) in a South African family. From the reported series it seems to follow a dominant mode of inheritance.

It is not difficult to understand why this disease has been compared with the adult form of polycystic kidneys, with its associated liver- and pancreatic cysts and occasional intracranial aneurysms (Clemmesen, 1942; Köhler, 1947; Nielsen, 1950; Bigelow, 1953). For the same reason analogous features between von Hippel-Lindau disease and acrocephalo-syndactyly and dysencephalia-splanchnocystica were pointed out (Gruber, 1934; Rümler, 1934; Donat, 1935).

It is distinctly uncommon for these patients to present clinically with symptoms due to their renal lesions (Lindau, 1926; 1931; Cushing et al, 1928).

The only exceptions are the patients described by Davison et al (1936) and Donat (1935). The patient of Davison et al had a part of a cystic pancreas removed after it presented as

/an.....

an abdominal mass. Later both kidneys became enlarged but at autopsy were found to be affected by multiple single cysts.

Donat's patient had an enlarged kidney clinically and at autopsy a kidney with multiple single cysts were found.

In a family with von Hippel-Lindau disease, Moller (1952) found a boy of twelve who developed haematurea and the kidney removed at operation showed multiple single cysts but not true polycystic kidneys and no evidence of angiomatosis. This is probably the only case in which the renal lesion (if this is von Hippel-Lindau disease) caused haematurea (Lindau (1952) in a personal communication to Moller).

The reasons for rejecting the two cases quoted by Dalgaard (1957) as evidence that polycystic kidneys may occur in a patient with von Hippel-Lindau disease have been stated.

From a search of the literature it can be concluded that polycystic kidneys have never been conclusively shown to be present in von Hippel-Lindau's disease. The kidney lesions in this disease are non-specific (Lindau, 1952). Even in his earliest descriptions of the disease, bearing his name, Lindau pointed out that the cystic changes in the kidney did not resemble polycystic disease.

No cases of von Hippel-Lindau disease were encountered in

/this.....

this series.

Tuberous sclerosis

The presence of cysts in the kidney as well as other lesions of the kidney have frequently been described in tuberous sclerosis (Bundschuh, 1912; Inglis, 1954; Potter, 1952; Stewart, 1939 and in numerous other reports).

It is well known that this condition occurs in families.

The association between true polycystic disease of the kidney and tuberous sclerosis has been reported in infants only on two occasions (Eliakis, 1937; Inglis, 1954).

The case described by Eliakis deserves further comment. A new-born female child with typical bilateral congenital polycystic kidneys had a rhabdomyoma of the heart. The child's brother died at the same age and of the same conditions. A sister aged 6 had polycystic kidneys.

No evidence of this disease could be found in the present series.

# S E C T I O N  V I

## GENETIC FEATURES OF POLYCYSTIC KIDNEY DISEASE.

## THE INHERITANCE OF POLYCYSTIC KIDNEYS

### Historical background

The first description of polycystic kidneys in members of one family was that of Meckel (1822). The two newborn infants were children of one mother and had multiple associated malformations - meningocoel, spina bifida, club feet and polydactyli.

It is remarkable that almost all the descriptions of polycystic disease occurring in families, published during the nineteenth century, concerned siblings with the congenital form of the disease. The following authors reported this type of familial polycystic kidney disease during that period: Schupmann (1842); Adamkiewicz (1843); Virchow (1855); Carbonel (1865); Burger (1867); Wolff (1867); Brückner (1869) and Singer (1894). Of these authors Adamkiewicz and Virchow described different members of one family and Burger and Wolff different members of another family.

The congenital form of polycystic kidney disease is only rarely encountered in families, as compared with the adult form. Up till the present only 32 proved and 3 probable instances could be found in the world literature.

It is difficult to find a satisfactory explanation for the fact that familial occurrence of polycystic kidneys was first discovered in infants. Many of these case reports, mentioned

/obstructed.....

obstructed labour as one of the complications occurring in their cases on account of the large size of the abdomen in some of these children. This may have drawn attention to the disease as a woman was not likely to forget the previous similar episode. Many of these children were stillborn and stillbirths apparently formed a very large part of the post mortem material in the previous century.

According to David et al (1900) the credit for the first description of polycystic kidneys occurring in adults belonging to the same family should go to Lauenstein, but this reference could not be traced.

Steiner (1899) was the first, however, to stress the fact that polycystic kidney disease had a strong hereditary tendency and that this fact could be used as an aid in the diagnosis of this disease. He also described two families in which the disease occurred in adults but noted, in each family, a child of 10 who may have had the disease in an early phase.

Since that time families with polycystic kidneys have been reported on numerous occasions, and familial incidence has been mentioned in clinical studies, so that a vast literature has accumulated about this subject. The literature may be conveniently divided into 4 large groups:

/(a).....

(a) Reports of single families

A number of large single families, with polycystic kidneys transmitted through several generations, have been described (Bull, 1910; Crawford, 1923; Cairns, 1925; Cumming, 1928; Morganti, 1949) to mention only a few.

The description of families with the disease has served the purpose of drawing attention to the hereditary nature of the disease. As such, is a family with the disease, a mere curiosity and can give us no clear picture of the disease in the general population.

If, in addition, the affected members should only be reported, or affected and non-affected are not all examined a distorted view of the mode of inheritance may be gained.

On the other hand, studies on linkage with other factors can be done on a family with the disease with relative ease. Such information gained, may hold for that particular family only, but may be a valuable contribution to the question of gene-linkage.

(b) Collections of reports on families

In 1904 Dunger could collect 11 examples from the world literature in which polycystic disease of the kidneys occurred in families and added one family of his own. He grouped the

/adult.....

adult and the congenital form of the disease together in this collection. Cairns (1925) collected 23 families from the world literature and added another family of his own in which the disease occurred in 3 generations. He divided the patients with the disease in one generation into adult and congenital types. Cairns was the first author who made an attempt to analyse the genetic material available and to determine such factors as anticipation, dominance, sex-linkage and lateney in the inheritance of polycystic kidneys.

Werner (1940) made a large scale collection of reports of the familial occurrence of this disease and brought together information on 109 families with the disease, concerning 350 affected individuals. He assumed a dominant mode of inheritance to be at work in the adult form of the disease and a recessive mode of inheritance in the congenital form.

Werner emphasized the fact that the adult and congenital forms of the disease do not occur in the same families. The isolated case in adults was considered by him to be caused by an irregular dominance or to be determined by factors which are not hereditary in nature.

Fergusson (1949) collected 84 families covering 305 affected individuals who were not described by Werner and added 6 families of his own to this material. He was the first

/author.....

author who made an attempt to determine linkage of polycystic kidneys with other known inherited factors so that a potential case may be detected by means of this. He had no success but opened a new field of study in this disease.

(c) Clinical descriptions of polycystic kidneys, with familial incidence being mentioned

As the hereditary natures of polycystic kidneys became better known, attention was paid to this aspect of the disease in most of the large series of reports on this disease from medical or surgical clinics.

It is obvious that the hereditary aspect is not always investigated to the same extent by different authors. This may, in part explain the wide variations in frequency with which a family history of polycystic kidneys is reported by different authors.

Davis (1928) found a family history of polycystic kidneys in 37% of his patients and Cumming (1928) in 36% of his patients.

Rall et al (1949) found a definite family history of polycystic kidneys in approximately one third, and a history suggestive of polycystic kidneys in a further quarter of their 207 patients.

Newman (1950) found only 5 patients with a family history

/of.....

of polycystic kidney disease in his series of 57 patients.

In contrast to this, Goldstein (1951) found that 27 patients had a definite family history of polycystic kidneys and 9 had a family history suggestive of polycystic kidneys in a series of 36 patients.

Simon et al (1958) found a definite family history of polycystic kidneys in 66 cases and a suggestive family history in 85 cases in their series of 366 cases. In 55 there was definitely no family history and in 160 it was not mentioned in the records.

(d) Statistical genetic studies

This was carried out for the first time by Arrigoni et al (1954) who tried to determine the hereditary nature of the disease without selection of material. They used 24 patients admitted to a urological clinic as basis for their analysis. Of these 24 patients 16 were found to be members of 15 families with polycystic kidneys. This material was then used for genetic analysis.

The work of Dalgaard (1957) is a monumental work in this respect and will probably become the standard of reference on the subject of inheritance of polycystic kidneys.

His basic material consisted of 242 propositi on 232 of whom

/genealogical.....

genealogical investigation was carried out. Of these 242 propositi only 15 had familial incidence of polycystic kidneys reported in their case records, while a family history of kidney disease was found in a further 26 cases. As a result of the investigation of Dalgaard the presence of polycystic kidneys was revealed in the families of 162 propositi.

The vast material was analysed on a statistical basis and the methods employed are beyond reproach.

## THE ADULT AND CONGENITAL FORM OF POLYCYSTIC KIDNEY DISEASE OCCURRING IN THE SAME FAMILY

When a hereditary influence was recognised a factor in the aetiology of polycystic kidney disease, all these patients, whether they were adults or newborn children with the disease, were considered as suffering from the same disease entity.

Cairns (1925) was the first author to classify all the cases of polycystic disease occurring in one generation into two main groups i.e. adults and infants. Marquardt (1934) and Werner (1940) differentiated between the two types and described a different mode of inheritance for them.

The literature was searched to determine whether the adult and congenital forms of polycystic kidney do occur in the same family. Several families have been described in which this has apparently occurred. These reports have never been convincing or adequately substantiated.

Höhne (1896) described a female aged 49 years with polycystic kidneys, whose daughter was operated at the age of 20 years for polycystic kidneys and another child had died at 9 weeks of kidney disease.

Zeit described a family in which the disease occurred in 3 generations and in the third generation a child one year of age,

/was.....

was found with the disease and 3 other children probably had the disease. The exact reference to this communication could not be traced but this author was quoted by Barnett (1917) and Morissey et al (1924).

Forsman (1913) described a child and a foetus with congenital polycystic kidneys born to a healthy mother whose sister may have had polycystic kidneys.

Moolten (1943) reported a child dying at the age of 2 weeks of bilateral congenital polycystic kidneys. The child's mother had several operations on the kidneys but the nature of her renal lesion was not definitely known.

Kretschmer (1948) described a child of 5 months with congenital polycystic kidneys. The father and mother were quite well but one maternal aunt had albuminurea at the age of 13 years and there was a strong family history of Bright's disease and hypertension.

Hilson (1957) described a family with polycystic kidneys and abnormalities in position and shape of the external ear. A female with polycystic kidneys had a child who died within a few hours after birth of kidney disease but no autopsy was performed.

Comment

From these reports it is quite clear that the adult and

/congenital.....

congenital form of polycystic kidneys have never definitely been proved to occur in the same family.

They do indicate that more careful examination of the young children of adults with polycystic kidneys should be done and that relatives of infants with congenital polycystic kidneys should be fully investigated.

Only in this way can the problem of the mode of inheritance of congenital polycystic kidneys be solved.

POLYCYSTIC DISEASE OF THE KIDNEYS IN ADULTS AND CHILDREN OCCURRING IN THE SAME FAMILY

Children with the disease in families in which adults are known to suffer from the disease have been described fairly frequently and are well substantiated.

Children in the age group 1-10 years have been described by Savera (1946) in two families with polycystic kidneys occurring in adults. Both children were 2 years old and belonged to the third generation with the disease.

Fergusson (1949) described it in a boy of 5 and Hilson (1957) in a boy of 6 years; both children of parents with polycystic kidneys. Halbertsma (1932) and Weidner (1938) reported such cases of 10 years of age and 2 similar patients who probably had polycystic kidneys, were described by Steiner (1899).

The patients of Shapiro (1929) was 13 years old and the patient of Jungmann (1922) was 14 years old.

Young (1946) described a patient aged 14 years with polycystic kidneys but it was not proved beyond doubt the patient's grandmother did have polycystic kidneys.

Present series

5 Patients between the ages of 15-18 years were found. They were all asymptomatic and discovered because their whole family was investigated.

/Comment.....

Comment

Polycystic disease of the kidneys occurring in children, belonging to families, in which the adult form of the disease is known to occur, are probably examples of the disease coming to an early expression.

It has frequently been found that adults date their symptoms from adolescence (Osler, 1915). One is certainly not justified to conclude from these scanty isolated examples that anticipation occurs in later generations with the disease, as many of these patients were asymptomatic and were either chance findings at autopsy (Savera, 1946) or were found because a family was investigated for the disease (Shapiro, 1929; Fergusson, 1949).

The patients described by Jugman (1922), Halbertsma (1932) and Weidner (1938) were symptomatic.

Polycystic kidneys in infants and children in the same family

This is apparently very rare. Lightwood et al (1932) described a family in which four siblings were affected. Only 3 are described in detail and they were $1^{10}/_{12}$ years, 4 years and $1^{11}/_{12}$ years old. The first one died and the diagnosis was confirmed at autopsy. The others were alive and were clinically diagnosed.

In the family described by Eliakis (1937), 3 siblings were affected. Very little information is given about two of them.

/The.....

The eldest was 6 years old and had polycystic kidneys. A newborn girl had polycystic kidneys and a rhabdomyoma of the heart. A boy also died directly after birth with similar findings.

Comment

The older members of these families are probably examples of the congenital form of the disease with enough functional renal tissue to allow them to live to this age.

Difficulties in human genetic studies with special reference to polycystic kidneys

These problems have been well formulated by Kemp (1951).

Certain universal problems in human genetics will probably never be solved, such as the relative long duration of human reproductive life, the limited number of offspring and the inability to obtain selected matings.

In tracing the family history of a patient one is always liable to err on account of unknown illegitimacies and adoptions which occurred (Savera, 1946).

A disease which only comes to expression relatively late in life and causes the death of the carrier in a relatively short period of time does not allow one observer to examine personally more than 2 or at the most 3 generations. This is to some extent true of polycystic kidneys.

/When.....

When one deals with a disease, which has such well marked features that a layman's evidence can be accepted as proof of its presence, one's task is somewhat easier in tracing it in deceased members of whom no medical records are available (polydactyli, colour blindness, cleft palate). There is no such prominent sign by which a layman may know polycystic kidneys to be present. Haematurea is a fairly common and dramatic symptom but does not occur in all patients with the disease and members of a family with polycystic kidneys may have haematurea from other causes. Patients are often told by their attending physicians that their kidneys are enlarged or "floating" and this can be an indication that polycystic kidneys may have been present.

When case records are consulted of deceased members of a family, features are not mentioned and one is left in doubt whether the particular feature was absent or not looked for. In patients with polycystic kidneys the diagnosis may never be made unless an autopsy is performed.

The only satisfactory method of investigating a family for a particular disease, is by personal examination of all members of that family. This is difficult in South Africa where a relatively small european population is widely dispersed over a very large country, often in parts which are accessible with difficulty.

/Most.....

Most of these problems are greatly augmented when genetic studies are to be carried out in the non-european and more specifically the bantu population.

## GENETIC MATERIAL IN THE PRESENT SERIES

### Clinical Cases

From the records of 14 adult patients with polycystic kidneys admitted to Groote Schuur Hospital a definite family history of polycystic kidneys were obtained in 2 and a family history of kidney disease in 1.

One patient, (No. 38), H.T.B. (table V), a female aged 42, with a family history of kidney disease had died since her discharge from hospital but a number of her relatives were traced and it was defnitely established that, in her family, polycystic kidneys had been present in her own generation and in that of her mother. This family could unfortunately not be investigated as most of the members are living in the Transvaal and the Orange Free State.

Patient (No. 39) D.T. (table V), a female aged 41, had 2 sisters with polycystic kidneys.

Patient (No. 51) G.H.M. (table VI), a female aged 63 had 2 sisters who died of polycystic kidneys and her daughter suffered from renal symptoms.

To these may be added, 4 patients belonging to family I who were all admitted to Groote Schuur Hospital at one time or another. All gave a history of polycystic kidney disease in their families. A total of 7 patients with a family history of

/polycystic.....

polycystic kidneys or even of kidney disease, but at that time, they did not know that they belonged to a family with this affection.

Thus out of a total of 20 patients seen clinically as cases of polycystic kidneys, 7 (35%) gave a family history of polycystic kidney disease.

Family I

This family was discovered and investigated because several patients, belonging to a small community, within a geographically isolated part of South Africa, were found to have polycystic kidneys. They did not know that they were related and proof was only found of this after a genealogy had been worked out (see table IX).

Criteria for diagnosis

Only those patients who had definite radiological signs and at least one suggestive clinical sign such as albuminurea, an enlarged kidney or hypertension, were regarded to be suffering from the disease. Two patients did not have the diagnosis confirmed by radiology but they had such outspoken clinical signs that they were considered as definite cases of the disease. Case No. 5 (V 5, table IV), J.N.R. and Case No. 26 (VI 23, table IV), both had typical enlargement of a kidney and albuminurea.

/Case.....

Case 5 also had a massive haematurea which was followed by anurea and death in uraemic coma.

Radiological evidence alone was only accepted as diagnostic, if it was outspoken and indisputable.

Patients who probably suffered from polycystic disease of the kidney in family I

In this group are included those patients about whom sufficient information was not available to warrant an indisputable diagnosis of polycystic disease of the kidneys.

The fact that two of the fairly constant features of this condition are enlargement of the kidneys and haematurea, has been of some help in tracing these patients through information obtained from relatives.

Patients IV 3 and IV 15 (see below) have been described so well that they could almost be included in the group of patients regarded as definitely suffering from the disease.

European male, M.H.M. (Patient II 2, table IX). The history was obtained from two of his daughters. He suddenly experienced severe haematurea at the age of 69 years, became anuric and died 13 days later in coma. This patient was married twice (see table IX) and children from both these marriages have developed the disease.

/European.....

## KEY TO TABLES IX AND X

Unaffected male

Affected male

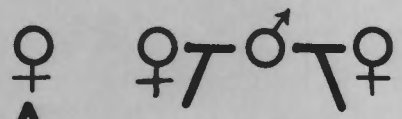
Unaffected female

Affected female

Male. Died in infancy

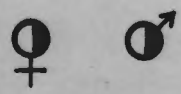
Female. Died in infancy

Sex unknown



Individual married twice

Dizygous twins

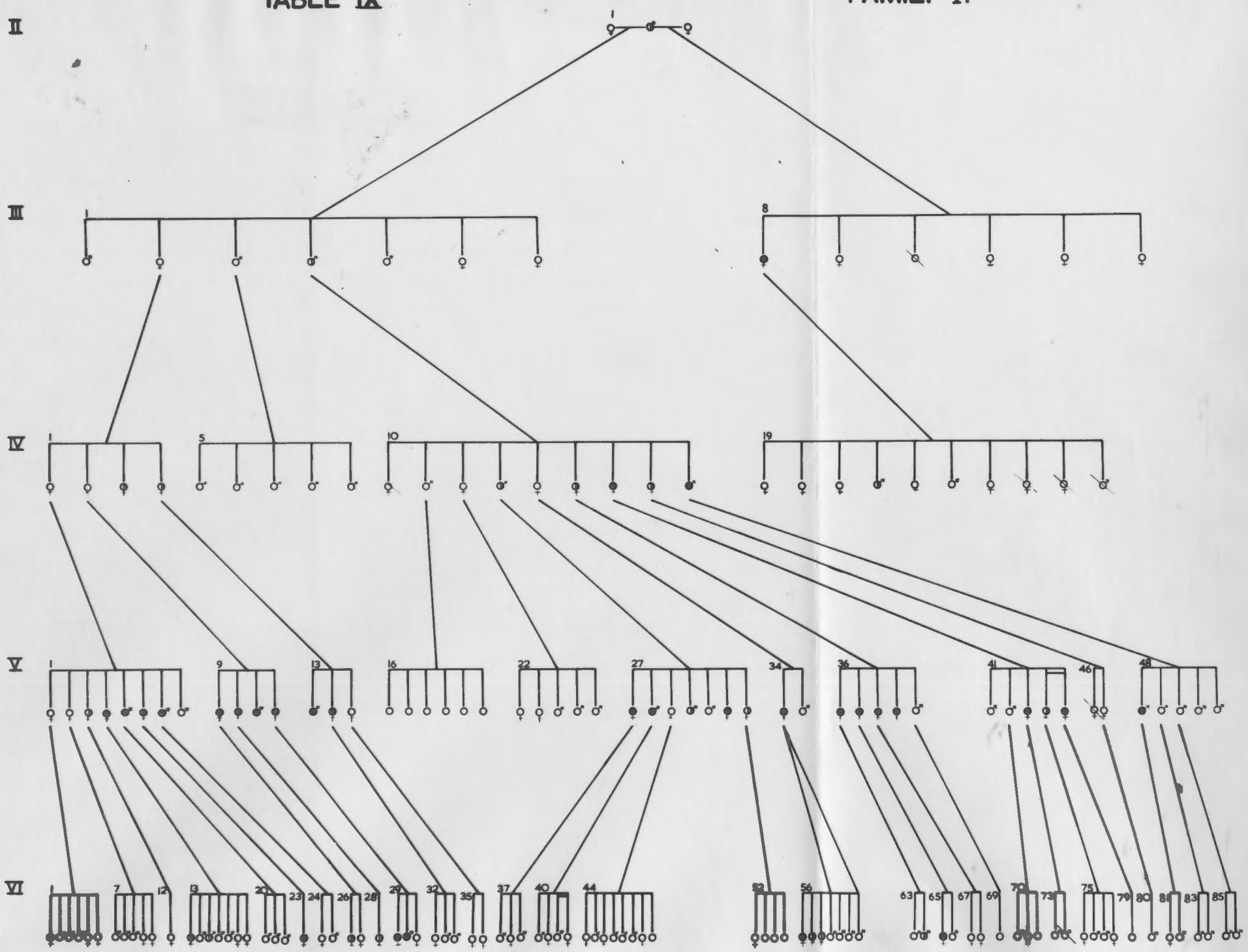


In generations II, III and IV Individuals who probably suffered from polycystic disease of the kidneys

In generations V and VI individuals regarded as potential sufferers from polycystic disease of the kidneys

# TABLE IX

## FAMILY I.



European male, H.L.M.C.M. (Patient III 4, table IX). Several of his children state that he was quite well till the age of 58 when he suddenly developed severe haematurea. His condition gradually deteriorated and he died a few months later in coma.

European female, E.D.S. (Patient IV 3, table IX). Single. This patient had a kidney operation in the New Somerset Hospital in 1921. The hospital records could not be traced. She was told by the surgeon who operated on her that her kidneys looked like a bunch of grapes. She had several episodes of haematurea during her life, complained of continuous dragging abdominal pain and died suddenly at the age of 50 years.

European female, S.F.M.D. (Patient IV 4, table IX). Married. This patient never had haematurea but had a "floating kidney". Kidneys were later said to be enlarged. Had terminal anurea and died in coma.

European male, H.P.M. (Patient IV 13, table IX). Had a sudden severe painless haematurea at the age of 57. He was quite well till that time but afterwards steadily deteriorated and died in coma six months later. History was obtained from his wife.

European female, E.D.O. (Patient IV 15, table IX). The information about this patient was obtained from her children and from the private practitioner who attended to her during her illness.

At the age of 43 she had a sudden severe episode of

/painless.....

painless haematurea. She was examined radiologically at Worcester Hospital and she was told that she had cysts in the kidney. She gradually deteriorated and died at the age of 50 years. In the last stages of her illness her kidneys were both massively enlarged with irregular nodular surfaces.

European female, S.G.M. (Patient IV 17, table IX). Married. Very few details are available about this patient. She died in 1927 of an infection of the face. Her one kidney was removed in the New Somerset Hospital before 1921. The hospital records could not be traced.

European male, J.B. (Patient IV 22, table IX). Married. Patient died of malignant hypertension at the age of 53. There is a past history of "inflammation of the kidneys" in childhood. An I.V.P. was never done and it was believed that he had chronic nephritis as the primary cause of the hypertension. Post mortem examination was refused.

Patients considered to be potential sufferers from polycystic disease of the kidneys

Those patients, who show minimal evidence of kidney abnormality such as albuminurea, hypertension or suggestive changes on intravenous pyelography, are included in this group.

It is quite likely that one observed these patients very critically and with a great deal of suspicion. If they were

/seen.....

seen without any details about their family background being known, they would probably not have evoked any comment.

All the young patients with albuminurea were tested for orthostatic albuminurea but the presence of this factor could not be proved in any of them.

The majority of these patients were personally examined by the author (see table IX).

European female, C.E.S.R. (Patient , table IX), aged 50 years. She is asymptomatic. Blood pressure 160/90 and has ++ albumin in the urine. The pyelographic signs are suggestive but not definitely diagnostic. Two brothers and two sisters have polycystic kidney disease.

European male, M.M. (Patient V 30, table IX), aged 36 years. No history or physical finding, indicative of polycystic kidneys, but has a + albuminurea. Intravenous pyelography was not done. Two of his sisters and one brother has polycystic kidney disease.

European female, C.E.C. (Patient V 33, table IX), aged 29 years. Sister of previous patient. She is asymptomatic. No abnormality found on examination except a trace of albumin.

There are very suggestive changes on the intravenous pyelogram but re-examination was not possible as she is pregnant.

/It.....

It is of some interest, from the point of view of associated malformations, that her daughter (VI 52) had a choledochus cyst. This was treated by choledochojejunostomy at the age of 6 months (Mr. J.H. Louw) and the child is active and well at the age of 8 years. The mother did not want to bring her for pyelographic examination.

European female, E.J.S. (Patient V 44, table IX), aged 34 years. No symptoms directly attributable to polycystic kidney disease. Has had an elevated blood pressure with her last pregnancy and this has apparently persisted (child 5 years old). Blood pressure 180/100. Albumin +++. The changes on the intravenous pyelogram do not allow a definite diagnosis of polycystic kidneys to be made. Her twin sister has the disease.

European female, C.E.G. (Patient VI 1, table IX), aged 32 years. She has no complaints which could indicate any genito-urinary disturbance. Blood pressure 160/90. She has a trace of albumin in the urine and on the intravenous pyelogram there are suggestive changes but not enough to be certain of the diagnosis.

European male, H.J.P.L. (Patient VI 15, table IX), aged 18 years. On routine examination for admission to a pension scheme, he was found to have albuminurea. He had no complaints, has never had haematurea. He was not hypertensive but his left kidney was slightly

/enlarged.....

enlarged, and the presence of albumin in the urine was confirmed on several occasions. He never attended for pyelographic examination.

European female, M.G. (Patient VI 26, table IX), aged 18 years. No complaints suggestive of polycystic disease. Has a blood pressure of 150/100-110 and ++ albuminurea. The X-ray changes are suggestive of early polycystic changes.

European female, M.C.P.G. (Patient VI 28, table IX), aged 9 years. No symptoms or signs of importance except a + albuminurea which was present intermittently. Two years later there was a slight enlargement of the right kidney but intravenous pyelography done 2 years apart showed no abnormality.

European female, B.W.S. (Patient VI 57, table IX), aged 14 years. No complaints of note and examination revealed no abnormality except an albuminurea of + which was present on repeated testing over several years. The intravenous pyelogram does not show any definite changes on which a diagnosis can be based.

European female, J.C.S. (Patient VI 58, table IX), aged 12 years. No complaints whatsoever and no other abnormal physical findings. An intermittent trace as + of albumin in the urine.

European male, F.H.C. (Patient VI 64, table IX), aged 21 years. There were no indications of disease

/in.....

in this patient on examination or on interrogation but it is showed in the intravenous pyelogram that there is very definite evidence of distortion of the calyceal architecture.

The male/female ratio of affected members in this family is 8:22.

Two pairs of twins occurred in this family. First pair: Two dissimilar females Patients V 44 and V 45, table IX) aged 34, of whom one has polycystic kidneys and the other is regarded as a potential sufferer from the disease.

The second pair (VI 42 and VI 43, table IX), a brother and sister aged 4 years who were normal on clinical examination but who were not examined radiologically.

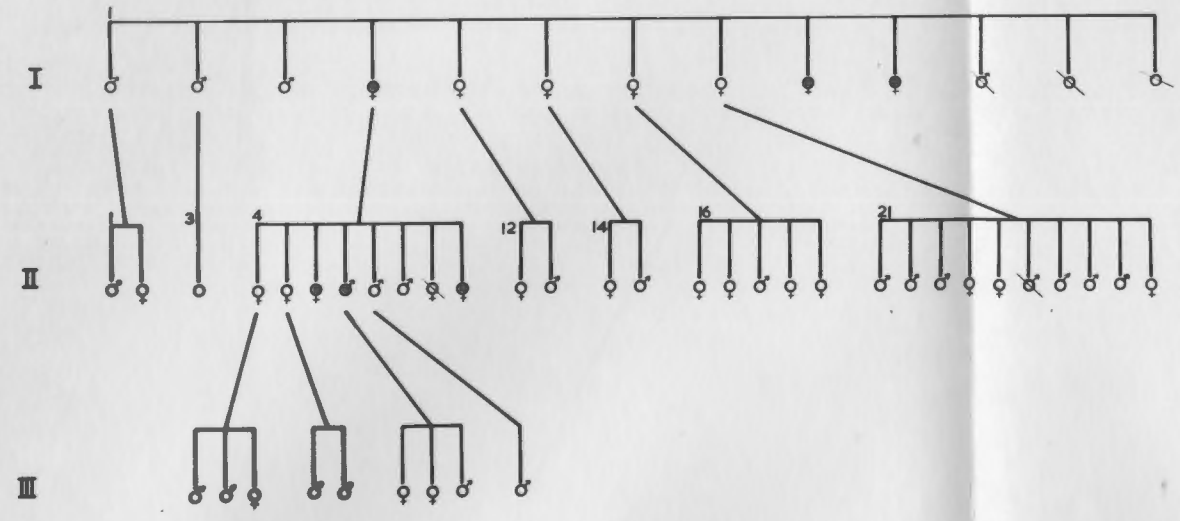
There was no consanguinity in this family.

Family II

(See table X). The presence of polycystic kidneys in this family was indicated to the author by a urologist. Very little information could be obtained from them and the table is merely given as another example of the familial occurrence of polycystic kidneys in South Africa.

TABLE X

FAMILY II



## GENETIC ASPECTS OF THE CONGENITAL FORM OF POLYCYSTIC KIDNEY DISEASE

The mode of inheritance in the congenital type of polycystic kidneys have been assumed to be recessive (Marquardt, 1934; Weiner, 1946). Dalgaard (1957) thought that the large spongy type may have a recessive heredity.

As definite evidence, that a disease is caused by a recessive gene, is usually taken a high degree of intermarriage among parents of affected individuals. No author could so far find any evidence of consanguinity in parents of children with polycystic kidneys.

In a search of the literature only one example of consanguinity could be traced. Teilhaber (1899) described congenital polycystic kidneys in two children whose mother was married to her uncle.

Of special interest also, are the cases reported by Teuscher (1926). Two sisters each had children with congenital polycystic kidneys and meningocoels. One woman had one such a child and the other two. Unfortunately the mothers were not examined.

Bachrach (1934) described a female who married twice and from each of these unions a child with congenital polycystic

/kidneys.....

kidneys was born.

Savera (1946) put forward a very strong plea that the mode of inheritance in congenital polycystic kidneys may be an irregularly dominant one.

Twin studies in congenital polycystic kidneys

Isolated reports of twins in which one or both were affected with congenital polycystic kidneys have appeared sporadically.

Dalgaard (1957) was the first to collect 7 pairs suffering from this disease. He thought that this material may help to clarify our view on the hereditary nature of congenital polycystic kidneys.

We cannot add any new twin material from our own series but would like to draw attention to three other twin pairs described in the literature, not mentioned by Dalgaard.

Busse (1904) described the kidneys of one member of a pair of twins, of which the other was apparently normal. The affected child also had hydrocephalus but no statement on the sex or zygosity is available.

Meader (1907) described a male with deformed hands and feet, polydactyli, cystic liver and meningocoel. The twin sister was normal.

Stickel (1909) quoted by Adrian et al (1913) described one

/of.....

of a pair of twins with large bilateral polycystic kidneys which necessitated evisceration to make delivery possible. Apparently the other child was normal.

The total number of twin pairs described in the literature is probably 10. Other authors describing it are: Carbonel (1865); Berner (1913); Schneider (1928); Hernandez et al (1930); Gruber (1934); Röwer (1936) and Lambert (1943).

Associated malformations and their linkage with congenital polycystic kidneys

Should one consult the list of malformations which have been found in association with congenital polycystic kidneys, it is striking that only a limited number of these have been linked in association with congenital polycystic kidneys in families.

Sibs with polycystic liver and kidneys have been described by Bunting (1902), Lightwood et al (1932) and Marquardt (1934).

Polycystic pancreas occurred in one of Bunting's and both of Marquardt's patients.

The complex of malformations described by Gruber (1934), acrocephalo-syndactyli and dysencephalia splachnogcystica was elaborated by Pohlmann (1935) and has been described in siblings on several occasions.

The entire complex need not accompany polycystic kidneys.

/Polycystic.....

Polycystic kidneys with associated meningocoel or meningo-encephalocoel have been described by LeLievre et al (1924) and Teuscher (1926) in a family with congenital polycystic kidneys.

Present series

No example of congenital polycystic kidneys occurring in a family was found. In one case, Patient No. 62, Baby W. (table VIII) a history of congenital deformities in two other sibs was obtained but these infants did not come to autopsy so that no conclusions can be drawn from this case. The histology of the kidneys and liver in this case are shown in figures III and IV respectively.

It is not possible from available material to state whether the congenital type of polycystic kidney disease occurring in families belonging to a distinct and definite pathological type as suggested by Potter (1952).

As Dalgaard (1957) also noted, it is remarkable that the vast majority of sibs with congenital polycystic disease had very large kidneys.

Whether this type of polycystic kidney disease is due to the influence of a recessive or an irregularly dominant gene and whether such a gene may show a pleiotrophic effect and thus cause the other malformations which ~~is~~ are so frequently associated with the kidney lesion cannot in our opinion, be stated with any

/certainty.....

certainty. It may well be that the diffirent types of polycystic kidneys as described in the section on pathology has different modes of inheritance.

If this disease is caused by a recessive gene then this gene is far more lethal than the dominant one (Savera, 1946).

## GENETIC ASPECTS OF THE ADULT FORM OF POLYCYSTIC KIDNEY DISEASE

As indicated previously, the comprehensive work of Dalgaard (1957), which covered such a large number of families and was carried out in such ideal conditions for genetic study, will not easily be surpassed. There can be very few other countries, where such a mass of well documented genetic material can be brought together as in this outstanding Danish project. His material has been the only published so far which allows unbiased statistical analysis.

This work of Dalgaard appeared at a time when we were already in progress with the present project. In the light of what has been done by Dalgaard very little has remained to be done to clarify the genetic problems in this disease.

For the sake of completeness, however, we will give a review of the literature on this subject.

### Dominance

The fact that polycystic disease of the kidney may be found in successive generations of a family, has brought many authors to the conclusion that the mode of inheritance must be a dominant one (Marquardt, 1934; Wenner, 1940; Savera, 1946; Cannon, 1947; Fergusson, 1949).

From our own observations it seems very likely that a disease which can be carried through 4 or 5 generations must be

/caused.....

caused by a dominant gene.

In an exacting genetic statistical analysis of his material Dalgaard (1957) found that this disease shows a regularly dominant pattern of heredity due to a single gene.

Penetrance

This is a statistical concept, and refers to the frequency with which the characteristic expression of a gene or genotype is manifested among those who pocess the gene (Sorsby, 1953).

This is exceedingly high in the pathological-anatomical sense as the penetrance may reach nearly 100% if the individual lives to be 80 years of age (Dalgaard, 1957).

From studies on the concordance and discordance between the two sides of the body he also confirmed this high penetrance of the gene producing polycystic kidneys.

He tried to use twin material to estimate the penetrance of the gene for polycystic kidneys but correctly concluded that the twin material, as reported in the literature, and found in his own series was not suitable for statistical analysis.

The adults of twin pairs described in the literature are those of Love et al (1902), Reason (1933), Weidner (1938), Clemmesen (1942), Arrigoni et al (1954), Wiedemann (1953), Simon et al (1955), Dalgaard (1957).

/Present.....

Present series

To these observations we may add a twin pair found in our series.

European female, D.M. du T. (Patient No. 23 (V 44), table IV), aged 34 years. Had no symptoms but was found to have polycystic kidneys on pyelographic examination at the age of 29, when the family was investigated. At that time her blood pressure was normal and only a trace of albumin could be detected in the urine. No other clinical abnormalities were detected in the patient. At present she has bilateral large kidneys, a fair amount of albumin in the urine and a blood pressure of 170/100.

European female, E.J.S. (Patient V 45, table IX), aged 34 years. Twin sister of the patient just described. This patient has had an elevated blood pressure during her last pregnancy (at the age of 29) and her blood pressure has remained raised ever since.

On clinical examination the kidneys are not palpable, the blood pressure is 180/100 and she has a large amount of albumin in the urine. Intravenous pyelography has been repeated at an interval of 2½ years and no definite evidence of polycystic kidneys could be found although suspicious changes are present.

They are dissimilar as they have completely different physical features, eye colour, hair colour and blood groups.

/These.....

These two patients are merely added as a further contribution to the twin material in polycystic kidneys of adults.

Comment

From the various sources quoted, it is evident that polycystic kidneys are caused by a dominant gene with a very high degree of penetrance.

Incomplete penetrance of the gene in the heterozygous state i.e. irregular dominance apparently does not exist in this condition. This may appear to be present because polycystic kidneys show a very wide variability in expression and the disease may be present without being clinically detectable by any means.

In this way, it may seem as if the disease has skipped a generation but in most cases where this was found, the examination of the "unaffected" person, was not complete.

In our personal observations this disease was usually inherited from an affected parent by an affected child. If it appeared to skip a generation it was due to inadequate information being available about that patient. If information was available to the effect that the patient was quite well, this cannot be accepted as evidence that the patient did not have polycystic kidneys.

/Intra-family.....

Intra-family correlation

This was described in polycystic kidney disease by Clemmesen (1942) and Dalgaard (1957). The last named author determined the intra-family correlation in 30 siblings comprising 75 individuals and found a significant sib-relationship for the ages of diagnosis.

Comment

Intra-family correlation is one of the features of an abiotrophy. The fact that it has been found in such a way as described by Dalgaard, is another reason for regarding polycystic kidneys in adults as an abiotrophy. Intra-family correlation may be determined by various factors.

"Affected members of a family share not only the same pathogenic gene, but to a large extent a similar genetic constitution and to a certain extent also a similar environment. These are all factors that tend to produce uniformity and similarity in clinical malformations within a particular group and help to explain variation as between different family groups. Individual variations within a group, however, do occur not unfrequently, as different members do not, of course, have an identical total genetic constitution or environment" (Sorsby, 1953).

/Our.....

Our material was not suitable for determination of this feature as the group was too small for comparisons to be made and an adequate control group was not available.

Expression

That the disease may vary widely in its clinical nature, severity and age of onset and rate of progress is a fact which has been frequently commented upon.

In the one family described here a remarkable difference in expression was found even in relatives with the disease. One patient may live to the age of 80 and be asymptomatic while another may suffer severe disability from this disease at an early age.

Intra-family correlation may exist but individuals belonging to different families and sporadic cases may show a wide variety of clinical features as became evident from the clinical discussion of polycystic kidneys.

Anticipation

Cairns (1925) thought, on evidence of his own observations and on collected material, that the disease occurred at a younger age in the later generations suffering from this disease.

Werner (1940) also discussed it but warned that if a family is examined because some member has been found to have polycystic

/disease.....

disease, the disease is discovered in the later generations at an early age while they are still asymptomatic.

Dalgaard (1957) used the age of death as an index for determining anticipation as the age of diagnosis is displaced in time due to changes in diagnostic technique.

He could not find any indication that anticipation had occurred in his material.

In our series the period of observation is too short and the information on the earlier generations too scanty to come to any conclusion.

The carrier state in polycystic kidneys and gene linkage

The term "genetic carrier" has been applied to an apparently normal person who servesas the transmitter of an inherited disorder (Neel, 1953). Polycystic disease is caused by a dominant gene which only comes to expression fairly late in life and shows a very high degree of penetrance. On account of the high penetrance the number of carriers of this disease are probably equal to the number of patients who will later develop the disease. They may never experience symptoms on account of its presence due to the mild degree to which it comes to expression. As will be discussed later, the genetic carrier is the problem in the control of polycystic kidneys by genetic hygienic measures.

As we have seen earlier, the detection of the disease in

/its.....

its earliest stages is usually, if not always, impossible. The carrier can therefore not be detected by clinical means.

As an alternative to the clinical approach it has been suggested that where the gene, responsible for a pathological condition, is linked to one producing a harmless trait (for example, a serological characteristic), one could use the latter gene to "tag" the former (Neel, 1953).

Linkage studies have not, so far, proved to be of great practical value.

Sex linkage

Dunger (1904) believed that the disease was transmitted from father to son and mother to daughter but this theory was disproved very soon.

Cairns (1925), Cannon (1947) and Arrigoni et al (1954) found no evidence of sex linkage.

The disease is certainly not Y-linked as it does not occur in men alone.

There is no difference in the sex-ratio of the sufferers from this disease to suggest that the disease is X-linked. One would then expect twice as many females as males in the population with polycystic kidneys.

Fergusson (1949) found more females than males in his families.

/In.....

In family I there are far more females than males affected but this can probably be explained by the greater number of females in the family as a whole and the greater number of females examined.

No evidence of partial sex linkage could be found.

Linkage of polycystic kidneys in adults with blood groups

The genes for the blood groups are probably, at this stage, the most suited for use as marker genes. The frequency with which they occur in the population, their independent segregation and their known mode on inheritance make them very useful in this respect.

Taste-ability for phenylthiocarbamide (P.T.C.) ranks almost with this.

Secretor characteristics probably also satisfies the criteria mentioned.

Fergusson (1949) was the first to investigate the linkage of polycystic kidneys with blood groups, secretor, taste ability for P.T.C. and various physical features. He could not establish any definite relationship.

Dalgaard (1957) had the blood groups: ABO, MNS, P, Rh. Lewis, Duffy and Kell, done on as many of his patients as possible. He could find no close genetic relation in any comparison between the gene for the blood group and the disease.

/He.....

He stated that the gene for the disease either lies on another autosometo the blood group genes investigated or that they are a considerable distance apart, if they lie on the same autosome.

Present series

(See table XI). Blood groups (ABO, MN, P, Rh, Duffy, Kell) were determined in 41 members of family I.

These patients were also tested for taste ability for P.T.C. (Taster leaflet method).

The secretor property was also determined in a number of individuals.

From table XI it can be calculated that there is a statistically significant relationship between blood group A and polycystic kidneys and Rh (C) and polycystic kidneys.

Due to the limited number of individuals examined, there can be no definite conclusion to these results. A far greater group of individuals will have to be examined to eliminate selection and to enable an evaluation of the results according to the method of Penrose (1946) as described by Dalgaard (1957).

Linkage with other known genetically determined factors

Fergusson (1949) first made an attempt to find if any genetic linkage existed between the inheritance of polycystic

/disease.....

TABLE XI

THE ASSOCIATION OF POLYCYSTIC DISEASE OF THE KIDNEYS WITH OTHER KNOWN INHERITED FACTORS IN FAMILY I

| NAME | GENEALOGICAL NUMBER | SEX | POLYCYSTIC KIDNEYS | GROUP B | GROUP A | Rh. | | | | | M | N | P | $F^y$ | K | SECRETOR | TASTE ABILITY FOR P.T.C. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | D | C | E | c | e | | | | | | | |
| H.C.B. | III 8 | F | + | - | - | + | + | | - | + | + | - | + | - | - | | + |
| M.M.S. | IV 21 | F | - | - | - | + | + | - | - | + | + | - | + | + | - | | + |
| H.C.M. | IV 23 | F | - | - | + | + | + | - | + | + | + | - | + | + | - | | + |
| M.H.B. | IV 24 | M | - | - | - | + | + | - | - | + | + | + | + | + | - | | + |
| J.E.v.N. | IV 25 | F | - | - | - | + | + | - | + | + | + | + | + | - | - | | + |
| M.C.P.R. | V 6 | F | + | - | - | + | ?- | - | + | + | + | + | - | - | - | - | + |
| M.P.J.R. | V 7 | M | + | - | - | + | - | + | + | + | + | + | - | - | - | | - |
| M.J.G. | V 9 | M | + | - | - | + | - | + | + | + | + | + | - | - | - | - | - |
| M.C.G. | V 12 | F | + | - | - | + | - | + | + | - | + | + | ++ | - | - | - | - |
| J.H.D. | V 13 | M | + | + | - | + | + | - | - | + | + | + | - | - | - | | - |
| E.D.C. | V 14 | F | + | - | - | + | + | - | - | + | + | + | - | + | - | | + |
| S.F.G. | V 15 | F | - | + | - | + | + | - | - | + | + | + | + | + | - | | - |
| H.P.M. | V 28 | M | + | - | + | + | - | + | + | + | - | + | + | + | - | | - |
| C.E.L. | V 29 | F | - | - | - | + | + | - | + | + | + | + | + | - | - | | + |
| M.J.B. | V 32 | F | + | - | - | + | + | - | + | + | + | + | + | - | - | | + |
| C.G.P. | V 34 | F | + | - | - | + | + | - | - | + | + | + | +++ | - | - | | + |
| C.E.C. | V 36 | F | + | - | - | + | - | + | + | + | + | + | ++ | + | - | | + |
| H.P.C. | V 37 | F | + | - | - | - | + | - | + | + | + | + | +++ | - | - | | + |
| E.S. | V 38 | F | + | - | - | + | - | + | + | + | + | + | + | + | - | | + |
| F.S. | V 39 | F | + | - | - | + | - | + | + | - | + | + | +++ | + | - | | + |
| J.O. | V 40 | M | - | - | - | + | - | + | + | + | + | + | ++ | - | - | | + |
| W.J.G. | V 41 | M | - | - | - | + | + | + | + | + | - | + | ++ | - | - | | + |
| H.M.G. | V 42 | M | - | - | - | + | + | + | + | + | - | + | + | - | - | | - |
| C.E.v.d.V. | V 43 | F | + | - | - | + | + | - | + | + | - | + | + | - | - | | + |
| D.M.duT. | V 44 | F | + | - | - | - | - | - | + | + | - | + | ++ | - | - | | + |
| E.J.S. | V 45 | F | P | - | + | + | - | - | + | + | - | + | +++ | - | - | + | + |
| H.P.M. | V 48 | M | + | - | - | | + | - | - | + | - | + | + | - | - | | ? |
| L.H.M. | V 49 | M | - | - | + | + | + | - | + | + | + | + | + | - | - | + | + |
| P.A.M. | V 50 | M | - | - | + | + | + | - | + | + | + | - | + | - | - | + | + |
| O.A.M. | V 51 | M | - | - | + | + | + | - | + | + | - | + | + | - | - | + | - |
| C.R. | VI 20 | F | + | - | - | | - | + | | + | + | + | | | | | + |
| M.C.P.G. | VI 28 | F | - | - | - | + | + | - | - | + | - | + | +++ | + | - | | + |
| M.C.P.G. | VI 29 | F | + | - | - | + | ?+ | + | + | + | + | - | ++++ | + | - | | + |
| N.J.G. | VI 30 | M | + | - | - | + | - | - | - | + | - | + | + | + | - | | - |
| C.E.S. | VI 56 | F | + | - | + | + | + | - | + | + | + | + | + | - | - | | - |
| B.S. | VI 57 | F | P | - | + | + | + | + | - | + | + | + | ++ | - | - | + | + |
| J.C.S. | VI 58 | F | - | - | + | + | + | - | - | + | + | + | + | - | - | + | + |
| I.B.C. | VI 63 | M | - | - | + | + | + | - | - | + | + | + | ++ | - | - | + | + |
| F.C. | VI 64 | M | P | - | + | + | - | + | + | - | + | + | ++ | - | - | + | + |
| E.D.C. | VI 65 | F | + | - | + | | - | - | + | + | - | + | + | + | - | + | + |
| D.S. | VI 75 | F | ? | - | + | - | - | - | + | + | + | + | + | + | - | | |

disease of the kidneys and physical factors such as eye colour, ear shape etc., but he could find no evidence of it.

Myopia in several members of a family with polycystic kidneys was found by Cairns (1925) but he could find no linkage between the two conditions.

White (1929) described polythelia in a family with polycystic kidneys but no statistical analysis of the association of the two conditions was given.

Savera (1946) found that a member of this family with polycystic kidneys had a turmschädel and haemolytic anaemia but could not trace these anomalies in other members of the family.

Low set and deformed ears were described in a family with polycystic kidneys by Hilson (1957).

Present series

No physical factor was found to be linked with the inheritance of polycystic kidneys although patients were examined for this (eye colour, iris pattern, ear shape, hyperextensibility of phalanges, hairgrowth on the dorsae of the middle phalanges of the fingers, hair colour etc.).

None of the entities described by other authors could be found in this family.

A number of cases of spina bifida occulta were observed

/when.....

when the X-rays were examined. On account of the description of Keyzer et al (1952) of this deformity in a family in which infants suffered from congenital polycystic kidneys, we tried to determine whether it had any significant relationship to polycystic kidney disease of adults.

In a total number of 50 X-rays, 18 had polycystic kidneys and 23 had spina bifida occulta. Seven patients had both abnormalities combined. No significant relationship was found to exist between these conditions in the present material.

Comment

It does not seem as if great success awaits the attempts at establishing gene-linkage. Only by careful observation of clinical associations and descriptions of large genealogies may this problem eventually be solved.

In a potential sufferer from polycystic kidneys, it would be ideal to have such a "marker" property, by means of which the presence of the gene for this disease may be established.

Dalgaard (1957) suggests that the syndrome of malformations: polycystic kidneys - polycystic liver - congenital aneurysm of the intracranial arteries, is caused by a single gene with wide variation in the last two components.

## NOTE ON THE DIFFERENCE BETWEEN THE ADULT- AND CONGENITAL FORMS OF POLYCYSTIC KIDNEY DISEASE

At this stage it may be advisable to indicate why a differentiation has been made between the adult and congenital forms of polycystic kidney disease.

(a) There is a completely different mode of inheritance in the two conditions and they do not occur in the same family.

(b) The malformations associated with the congenital form of this disease are of a more widespread and more severe nature than those found with the adult form of the disease.

(c) The two conditions occur at two distinct age-periods with no acceptable evidence that the congenital form gradually merges into the adult form or that the adult form is even congenital in nature.

(d) There are histological differences between the two types of renal lesion.

THE ISOLATED CASE OF POLYCYSTIC KIDNEY DISEASE

All patients with polycystic kidneys do not belong to families with a tendency to this disease.

It is likely that many more patients have a family history of this disease than is ordinarily suspected.

A family history which is taken in a hurry is not of much use. Patients may be quite ignorant about a disease which does exist in their families because they have no contact with their relatives or because the disease has not become clinically manifest. On the other hand, a patient may die from one of the complications of polycystic kidneys without the primary condition ever being suspected.

Arrigoni et al (1954) found 16 cases out of a total of 24 to be propositi of 15 families, in which polycystic kidney disease occurred.

They thought that the existence of isolated cases could, in part at least, be explained by variable expression of the gene for polycystic kidney disease. The parents of a patient may have had the disease and not have experienced symptoms of it.

Comment

One has to agree with Cairns (1925) that more intensive investigation of the relatives of "isolated" cases have to be provided before they can be accepted as such.

/It.....

It is possible, as Werner (1940) suggested that not all cases of polycystic kidneys have a genetic background.

## ADVICE TO PATIENTS WITH POLYCYSTIC DISEASE OF THE KIDNEYS

The aims, problems and methods used in genetic hygiene have been fully discussed by Dalgaard (1957).

It may be of interest to note that his work is reported from a country with a relatively small population where a central registry for hereditary disease exists. According to Danish law a person may, on his own application, be sterilized, or a female may have her pregnancy terminated if there is a definite risk of transmission of a severe genetically determined disorder.

When such measures are provided, genetic hygiene can play a considerable part in preventive medicine; but otherwise, as in most other countries, genetic hygiene must play only a very minor part.

### Factors to be considered when patients with a genetically determined disease is to be advised

The work of Dalgaard (1957) and of Frazer (1954) have done much to clarify this rather difficult and problematical subject.

(a) The mode of inheritance of the disease in question

If it is dominant, then the carrier will in all probability be heterozygous for the gene so that 50% of his children will be

/affected.....

affected and 50% will be normal.

Should all such persons be prevented from having children, it would be possible to eradicate the disease carried by them, in one generation. Only those cases occurring as a result of spontaneous mutation will then exist.

If a recessive mode of inheritance is at work, the affected person will be homozygous for the recessive gene. If the carrier of a recessive gene should be prevented from having offspring it will have only a very limited influence on the frequency of the gene in the general population. Only 25% of the offspring of parents with the recessive gene for a disease will have the disease and 50% will be normal carriers.

(b) <u>The statistical risk that the offspring will be affected</u>

The empirical figures given above for dominant and recessive modes of inheritance, is no adequate answer for a patient who wants to know about his hereditary disease.

The exact nature of the disease should first be determined. Variations in expression, intra-family correlation, if any, the age of onset and the degree of penetrance in that family are all important.

As Dalgaard (1957) remarks, this is not only genetical a problem but a genetical-clinical problem to be settled by persons trained to in genetics.

/(c).....

(c) The seriousness of the defect

It is clear that in the more severe cases genetic hygienic measures will have to be considered more frequently. Authors have varied in their opinion about the severity of the defect in polycystic kidneys (see the opinions of Wiedemann (1938) and Werner (1940) below).

(d) How much is a child desired?

This may influence the opinion given to a patient if other measures like adoption are not acceptable.

(e) Conscientious objections

Religious objections to contraception and other hygienic measures may also force one to take a risk which would not be allowed otherwise.

(f) What is the risk to the mother?

A woman with renal functional impairment or with renal function existing in a precarious ballance, pregnancy may precipitate renal failure. This contra-indicates pregnancy and may force one to terminate pregnancy and even to advise sterilization. Toxaemia of pregnancy occurring in the early stages of pregnancy may also necessitate therapeutic abortion and sterilization.

(g) What is the risk to society?

Polycystic kidney disease is too rare to be a social burden

/at.....

at the moment. One can well imagine that in the future, the malformations may increase in frequency due to better management of complications like infection etc. and a greater number of these patients living to produce offspring. This can only be limited to a certain degree by negative eugenic measures as many of these patients cannot be diagnosed by any means till they have advanced to an age at which they have produced children. New cases will continue to arise due to mutations.

(h) The attitude of patients to their genetic constitution

There may be a feeling of shame or they may feel that a social stigma may be attached to them. Careful management is necessary as this may cause disruption of an otherwise satisfactory marriage.

Genetic counselling advised by previous authors

In 1900, David et al stated that patients with polycystic kidneys should be advised not to marry, or at least, not to have children. Shapiro (1929) thought that patients with this disease should be informed of the risk of transmitting it to their children and that marriage should be discouraged.

Braasch et al (1932) stated that, on the basis of the strong hereditary tendency, progeny should be limited, and, in some cases, sterilization may well be advocated.

Steglich (1935) raised the practical problem that the

/disease.....

disease has its onset so late in life that by the time it is diagnosed the patient, especially if it is a female, is at the end of her reproductive life so that sterilization would be of very little benefit indeed. On the other hand a person, in whom the diagnosis had been made at an early age on account of symptoms or family investigations, would not find advice against parenthood acceptible at a stage when he was apparently in perfect health.

Weidner (1938) regarded polycystic disease of the kidney as a severe disabling hereditary disorder and thought that, as much, it demanded sterilization.

Werner (1940) did not think that sterilization had a place in the management of this condition at all. The severe congenital form would eliminate itself on account of individuals suffering from it not being viable. The adult form appeared at an advanced age, ran a symptomlous course in many instances and many patients had relatively little trouble from it. He believed that they ought to be allowed to have children.

Authors who do not differentiate between the adult and the congenital form of the disease believe that the parents should be examined if they desire to have more children after one child with congenital polycystic kidneys has been born (Campbell, 1951).

/As.....

As pointed out already, the two diseases do not occur in the same family and examination of the parents will not enable one to estimate the risk of a future child having polycystic kidneys.

Personal experience and opinion on the question of genetic hygienic measures

In South Africa, no legal measures are in existence for the management of patients suffering from severe genetically determined disorders or carriers of such disorders.

One has, on a number of occasions, been approached by young members of this family who knew about the disease and who wanted to know whether they were suffering from it and what they were to do.

Advice against marriage in a young person who is apparently quite well is a difficult and problematical action to take. If such a patient has the disease and knows about it, from personal experience of relatives suffering from it, the whole question ought to be discussed openly. All the risks for children to have the disease, dangers to the patient and chances of a normal offspring have to be stated frankly. Such a patient can discuss the problem with the prospective marriage partner and if the partner can also consult the physician an

/acceptable.....

acceptable solution may be found.

A young married couple without children of whom the one partner is found to be suffering from the disease, can be advised on contraceptive technique to prevent pregnancy. On two occasions, young adults, who were found to have the disease, on their own asked advice about contraceptive technique so as not to have any further progeny.

Only if a patient is symptomatic and has been diagnosed as suffering from this disease, can the hereditary nature of the disease and its risks be explained. One can only put the facts before these patients in as balanced a way as possible, and leave the final decision to them.

To advise all of these patients not to have children would, from the point of view of society, be the correct thing to do. In the future, this disease should become a burden to society, this may become imperative.

At the moment it may be asking rather much in the way of personal sacrifice from these unfortunate individuals to preclude all from parenthood.

From a humanitarian point of view, it may be thought that suffering may be prevented in future generations if a carrier should not procreate. It is impossible however, to weigh the suffering of one individual against the years of

/freedom.....

freedom from symptoms and useful lives led by others with this disease.

Carrier state

This is probably the most difficult question to settle of all: Should a patient, who is an asymptomatic carrier of the disease be told that he has polycystic kidneys?

We have no curative therapy for polycystic kidneys and in the author's opinion it would be cruel to inform a patient of a disease which is in many instances a death sentence. We are in agreement with Dalgaard (1957) that extreme circumspection is to be exercised in reporting the diagnosis and prognosis to a potential sufferer from this disease.

Birch-Jensen (1954) and Higgins (1952) believe that carriers should be searched for in families with the disease and diagnosis should be told to them and prophylactic measures should be instituted.

In the author's opinion it would be better to leave these unfortunate people in ignorance till they ask about the disease, or till they develop symptoms and then follow the course outlined above.

In advising patients with this disease, one has to tread that elusive path between over-optimism and frank pessimism so that they may treat their malady with the necessary consideration without becoming neurotically incapacitated at an age when they could live happy and useful lives.

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