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# POLYCYSTIC DISEASE OF THE KIDNEYS AND INTRACRANIAL ANEURYSMS. THE ETIOLOGY AND INTERRELATIONSHIP OF THESE CONDITIONS: REVIEW OF RECENT LITERATURE AND REPORT OF SEVEN CASES IN WHICH BOTH CONDITIONS COEXISTED.

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The finding of two abnormalities, each of which may be of congenital origin, in the same patient, is considered to be additional evidence of their congenital character, such anomalies being frequently multiple. Polycystic disease of the kidneys and aneurysms of the intracranial arteries have both been attributed to congenital defects and their simultaneous occurrence is therefore of interest.

## ETIOLOGY OF POLYCYSTIC KIDNEY.

Numerous theories have been advanced as to the etiology of polycystic kidneys, and these have been frequently reviewed (*e.g.*, Norris & Herman, 1941). The earliest investigators believed that it resulted from obstruction of the tubules by deposition of salts or by inflammation, either non-specific or syphilitic. Others have believed that the condition is neoplastic in origin and more recently it has been suggested that there is a defect of organiser activity resulting in overgrowth of one tissue, a condition of hamartosis. A developmental defect was first suggested in 1895 by Mutach who thought that such a defect was preventing union of the developing renal anlagen. In 1923 Kampmeier demonstrated that in the normal development of the kidney the second to fourth generations of uriniferous tubules are temporarily attached to similar generations of collecting tubules but later become separated from them. These uriniferous tubules may become cystic before undergoing atrophy or reuniting with later generations of collecting tubules. He believed that persistence of these embryonic cysts results in single cysts and that pressure of some of these cysts may give rise to polycystic disease by interfering with the normal genetic course and confluences of other tubules. This theory has been widely accepted, but more recent work suggests that it does not cover all the facts. Norris and Herman (1941) have pointed out that there is evidence that, for a long period in foetal life, development of the kidneys is normal and also that some of the cysts develop from

collecting tubules. They consider that in the case of polycystic kidneys a much greater part of the metanephros than is normal is provisional and that degeneration of the nephrons following cystic enlargement is an abnormal extension of the process which occurs normally in the case of the mesonephros and probably also in the first units of the metanephros. Norris and Tyson (1947) believe that a similar origin for cystic disease of the liver and pancreas can be demonstrated.

It is well-known that those affected with polycystic kidneys can usually be placed in one of two clinical groups, those in whom the condition is found at birth or soon after, and those in whom it does not appear until middle or late life. Although there are at least thirty-eight cases in the literature in which death occurred between two and twenty years, there is no doubt that there is a very real gap in the age incidence. This has led to a reluctance to accept a congenital basis for the disease in older persons. Most observers have found no significant difference in the histology of the two groups, but Lambert (1947) demonstrated in his cases that while in infants the cysts are blind and functionless, those in adults communicate with excretory tubules and the renal pelvis and retain their functional activity. He believes that this is the cause of the longer duration of life in the adult type. Those who support a single origin for all polycystic kidney disease attribute the gap in the age incidence to the ability of the renal parenchyma to hypertrophy sufficiently to preserve a reasonable renal function until secondary vascular changes occur.

A family history of the condition is found as frequently among adults as infants and Cairns (1925) considered that, in the family he studied, there was evidence of a tendency for the disease to appear earlier in successive generations. However, Fergusson (1949) could find, in a review of 84 families, no example of adult and neonatal disease in the same family. He considered that adult cases tend to show inheritance on the lines of Mendelian dominance, the neonatal as recessive characters, and suggested that there might be two types of congenital polycystic kidney of different etiology. He referred to the experiments of Hinman and Hepler (1925) who produced solitary cysts by simultaneous occlusion of the collecting tubules and interference with the vascular supply to the same portion of the kidney : he referred also to the series of unilateral polycystic kidneys collected by Howze and Hill (1949) in which there were renal vascular malformations.

The only experimental production of polycystic kidneys has been by Bagg (1925) who irradiated one generation of mice over the abdomen and studied their descendants. Three cases of unilateral polycystic kidney were produced, two of which were associated with eye defects. There were many cases of inherited absence of one kidney. He considered that the inheritance was on recessive Mendelian lines.

Associated abnormalities are extremely common in the neonatal group, being frequently of sufficient severity to prevent life. In adults, apart from cystic disease of certain other organs, they are uncommon. One-third of cases have cystic liver and congenital cysts are occasionally found in lung, pancreas and spleen. The family recorded by Cairns (1925) had an associated hereditary history of myopia. The syndrome described by Lindau (1931) may be mentioned here. In this syndrome haemangioblastomata of the brain are associated with cystic disease of the pancreas and frequently with cysts of the kidneys ; in addition the kidneys may show tumours described as adenoma or hypernephroma. The nature of the renal cysts does not appear to have been clearly elucidated, but Weber (1931) did not consider they were identical with those of polycystic kidney and Lindau stated that the abdominal lesions never gave rise to symptoms. It should be noted that the development of malignancy is rare in polycystic kidneys. Walters and Braasch (1933) reported nephrectomy for malignancy in three cases, and Melilow and Gile (1940) and Bobbitt (1943) reported single cases of hypernephroma. Wells (1936) had a case of intracystic papilloma. In the case of Hayward (1946) the polycystic disease was found only in the kidney affected by the tumour and may have been secondary. Tomoff (1937) described a case in which the diagnosis was made radiologically but without confirmation. A further example was found in the present series :

A man aged 64 had noticed a lump in the left hypochondrium four years previously. This had increased steadily in size and for four months he had had increasing pain in the left side. He had no urinary symptoms apart from nocturnal frequency of micturition. He had contracted syphilis at the age of 17 for which he had not received treatment until he developed dyspnoea on exertion and occasional swelling of the ankles at the age of 40. He died suddenly three days after admission.

At autopsy, there was syphilitic scarring of the first part of the aorta and aortic valve with involvement of the coronary orifices, the left coronary being completely obstructed. The aorta was dilated.

The left kidney weighed 2800 g. and measured 32 by 16 cm. There was a large cyst occupying the lower pole and numerous smaller cysts occupying the upper pole of the organ. Many of the cysts contained altered blood. The central part of the kidney was occupied by a tumour growth which was invading the cysts at each end. The growth was white in colour and showed numerous areas of necrosis and haemorrhage. The right kidney was slightly enlarged (190 g.). The capsule stripped with difficulty leaving some small depressed scars. The cut surface appeared congested but the normal markings were well maintained.

The liver was of normal size (1700 g.). Scattered throughout its substance were numerous cysts varying in size from 0.5 to 4 cm. in diameter. Some of the cysts contained altered blood, the remainder clear fluid. The liver substance was otherwise normal.

The pancreas was of normal size ; several small cysts containing clear fluid projected from its surface.

Microscopically, the renal cysts were lined by columnar epithelium of varying height which in places showed numerous large vacuoles. In some areas there was heaping up of the epithelium with the formation of papillary ingrowths into the cavity of the cysts. This appearance merged with the frank papillary adenocarcinoma which formed the central tumour mass. In places this showed a close resemblance to renal tubular structure.

Although only one kidney was affected, the presence of cysts in the liver and pancreas shows that this was a true case of polycystic disease

in which malignancy had developed. The rarity of such an occurrence is evidence against the theory that polycystic disease is neoplastic in origin.

On the other hand Clemmesen (1942) described a family in which the father died with a probable diagnosis on clinical grounds of polycystic disease complicated by hypernephroma. One son had hypernephroma of the right kidney and cystic disease of the left kidney, although the description does not suggest a true polycystic disease. Five other children had polycystic disease and the twin of one of these had a hypernephroma. Clemmesen considered that there might be some relation to Lindau's syndrome and that the development of both hypernephroma and polycystic kidneys might be related to events in the third month of foetal life.

### ETIOLOGY OF INTRACRANIAL ANEURYSMS.

The congenital basis of some intracranial aneurysms was first suggested by Eppinger in 1887, and this has gradually gained increasing acceptance. For long syphilis was held to be an important cause and although some writers now wholly deny the existence of syphilitic intracranial aneurysms Wilson (1940) considered that so extreme a view was unjustified. Other granulomatous lesions are rare causes but one case in the present series showed a large aneurysm of the basilar artery and another of the left superior cerebellar artery which were associated with a tuberculoma in the left lobe of the cerebellum and were considered to be due to tuberculous involvement of the arterial walls.

Acute bacterial infection has also lost favour as a cause of aneurysms. Turnbull (1918) considered that of 44 aneurysms 29 were congenital and 15 embolic. Cushing, as late as 1923, said that ' most aneurysms in young people are unquestionably of mycotic origin.' More recent writers accept only a small proportion as mycotic, *e.g.*, Dandy (1944) 4.5 per cent.

Most disagreement has been on the role of arteriosclerosis. In the analysis by McDonald and Korb (1940) of 1,125 aneurysms in the literature, 50 per cent were considered to be arteriosclerotic. Strauss *et al.* (1932) attributed 9 of 11 cases to arteriosclerosis and Schmidt (1930) 11 of 23. The latter considered that even if congenital abnormalities or weakness from places of lower resistance played a part, the importance of atheroma was indisputable and he accepted those cases as arteriosclerotic in origin in which there was evidence of arteriosclerosis micro- or macroscopically.

On the other hand Dandy (1944) found only 16.2 per cent of 108 cases to be due to arteriosclerosis and Martland (1939) reported 38 aneurysms of congenital origin to one arteriosclerotic. Symonds (1923) thought that most aneurysms were of congenital origin and Richardson and Hyland (1941) state that the vast majority are of ' berry ' type although a third of their cases showed arteriosclerosis. They state that in subarachnoid haemorrhage from ruptured aneurysms ' arteriosclerotic arteries are

uncommon. Severe cerebral arteriosclerosis may produce elongated dilatations of the arteries of the Circle of Willis, particularly in the basilar and internal carotid vessels. Such dilatations may be sufficiently great to warrant the term " fusiform aneurysm ".' They also say that the berry aneurysm may ' be seen in a wide range of ages and may be associated with healthy cerebral arteries or with varying degrees of cerebral arteriosclerosis.' Tuthill (1933) considered that there was no basis in the position, multiplicity or histological appearances on which a distinction could be made between congenital and arteriosclerotic aneurysms.

Nathan and Angrist (1943) point out the frequency with which sclerotic changes are found in the area of the aneurysm even when there is no sclerosis elsewhere and quote an example in a boy of 12 years. They classified aneurysms as arteriosclerotic if there was marked general arteriosclerosis in addition to the local lesion. They found 15 ' berry,' 10 mycotic, 2 syphilitic and 8 arteriosclerotic aneurysms and 1 traumatic (arterio-venous) aneurysm. They attribute the high proportion of mycotic aneurysms to careful microscopic examination of any small haemorrhagic areas in cases of infection ; and they consider that the diagnosis of syphilitic aneurysm can only be made or excluded by histological examination.

Among those who accept a congenital basis for the aneurysms there is a divergence of opinion as to the nature of the congenital abnormality. In 1930 Forbus reported the finding of defects of the media of the vessel wall at arterial branchings ; this was present both in cases with aneurysms and without. He considered it a common finding due to development of muscular tissue on branch vessels independently of that on the main vessel. He also found defects on other small vessels of the body. Similar defects had been noted previously (Turnbull, 1918 ; Duguid, 1925) and have frequently been confirmed since then, although Tuthill (1933) considered them to be artefacts. Glynn (1940), however, found the media defects in 80 per cent of preparations of cerebral vessels, whether aneurysms were present or not, and contrasted this with the low proportion of aneurysms. He also found the defects to be more common in adults than in infants. He believed that resistance to stretching depends on the elastica rather than the media and that aneurysms develop in the intracranial vessels because the elastic layer there is almost entirely concentrated in the internal lamina where it is readily injured by atheroma and other focal degenerations. Forster and Alpers (1945) consider that there is a tendency for the elastic membrane in the wall of an aneurysm to degenerate but that the degree of degeneration varies widely and is no guide to the original nature of the aneurysm. Carmichael (1945) found large defects of the media extending to 1 or 2 sq. mm. to be frequent, occurring in 27 of 40 preparations examined. He considers

that either the internal elastic lamina or the media alone can prevent undue extension of the lumen and that the wall will not yield if the outer coat is supported by one substantial inner layer, whether of muscle, elastic tissue or fibrotic intima.

If aneurysms develop from the media defects described by Forbus they should arise solely at the point of bifurcation of an artery. Dandy (1944) considers that they do not necessarily arise at such a site, although usually in close proximity to it. He believes that aneurysms are remnants of embryonic vessels, as suggested by Bremer (1943). Windle (1888) collected 200 cases of arterial anomalies of the Circle of Willis, and Fearnsides (1916) noted their frequency in other vertebrates. Slany (1938) found that 14 of 26 cases of aneurysm showed such abnormalities. Padget (1944) found that the anomalies are due to persistence of embryonic vessels and that incomplete involution of these vessels is related to the formation of aneurysms. She found that variations of the Circle of Willis are twice as frequent in cases with aneurysm as without and that this ratio is even greater in considering those Circles in which the abnormal vessels are larger than normal.

Riggs and Rupp (1942), who found the high proportion of 131 aneurysms in 1437 consecutive autopsies, also noted a high degree of association of aneurysms with congenital anomalies of the Circle of Willis. They found that all their aneurysms were at arterial branchings and that there were no aneurysms in 102 children under 10 years of age although media defects were present. They consider that these findings support the views of Forbus, in that the defects would later give rise to aneurysms and that structural malformations by producing local alterations in the vascular dynamics might provide a mechanical basis for the development of aneurysms in congenitally weak portions of the vessel wall.

The presence of congenital anomalies in other parts of the body is not common; the best known is coarctation of the aorta. Abbott (1928) found that of 200 cases of this condition 18 died of subarachnoid haemorrhage and 5 of these had ruptured aneurysms; 2 others had unruptured aneurysms. Wright (1949) found a total of 16 proved cases of the association in the literature, and of these 11 died of rupture.

## PREVIOUS REPORTS OF POLYCYSTIC DISEASE WITH INTRACRANIAL ANEURYSM.

The association of polycystic kidneys with cerebral aneurysm was first remarked on by Dunger (1904). He wrote that 'strikingly often—by comparison with the extreme rarity of polycystic kidneys—we find in this condition aneurysmal appearances, particularly in the region of the arteries of the brain.' He reported one case, quoted one from Borelius (1901) and mentioned three others in a personal communication from Schmorl. He stated further that 'in the literature on cystic kidneys,

aneurysms have been frequently noted ' but these have not been traced. There is no mention of intracranial aneurysms in the autopsy reports summarized by Sieber in his review of the literature in 1905. Dunger speculated as to whether the aneurysms were the result of hypertension or a special toxin or were a congenital anomaly.

Fearnsides (1916) found two unruptured aneurysms in a patient with polycystic disease who had died of uraemia, and Katz and Muhe (1924) reported a further case of ruptured aneurysm. O'Crowley and Martland (1939) found ruptured ' congenital, berry ' aneurysms in thirty-eight of fifty-four cases of subarachnoid haemorrhage. In three of these thirty-eight cases polycystic kidneys were present, while two showed hypoplasia of one kidney, one having also stenosis of the abdominal aorta, one had aberrant adrenals and one showed the presence of Chiari's network in the right auricle. A further nine cases of subarachnoid haemorrhage were attributed to ruptured hypoplastic cerebral arteries, one case having associated subaortic stenosis and one a congenital cyst of the lung (Martland, 1939).

Snapper and Formijne (1939) reported two cases, but one of these can only be considered a probable case of aneurysm as she survived. McDonald and Korb (1939) reported one case in which the polycystic disease was unilateral and Wilson (1940) noted the presence of polycystic disease with accessory spleens and abnormality of the lungs in a case.

Forster and Alpers (1943) found the association in an infant of thirteen weeks. This and Fearnsides' case are the only ones in which rupture has not occurred. Madonick *et al.* (1946) reported one proved case and one in which two episodes of subarachnoid haemorrhage had occurred with recovery for five years ; in view of the absence of hypertension and uraemia they considered that an aneurysm was probably present. Sahs and Keil (1943) found two examples in twelve cases of ruptured aneurysm.

Suter (1949) reviewed these cases, except those of Sahs and Keil, and added two further cases of his own. In a series of 5,960 autopsies he found twenty-three cases of ruptured aneurysm and four unruptured. He found five cases of polycystic disease in the same series and in two of these ruptured aneurysms were simultaneously present.

Nathan and Angrist (1943) reported a case in which hypertension had been known to be present for many years ; histological examination of the ruptured aneurysm showed an extensive zone of necrosis in the wall with an acute inflammatory reaction at the neck of the aneurysm, greater than would have been expected as a result of the rupture. This case occurred in a series of thirty-six aneurysms, twenty of which were ruptured berry or arteriosclerotic aneurysms.

Kartagener and Gruber (1947) refer to a personal communication from Uehlinger quoting a case.

Magee (1943) mentioned the finding of polycystic kidneys in one of fifty-eight autopsies for subarachnoid haemorrhage; aneurysms were found in forty-three of these cases but it is not clear if an aneurysm was shown to be present in the case with polycystic disease. A similar doubt exists in the cases of Ask-Upmark and Ingvar (1950). They found ruptured aneurysms in twenty-eight of forty-seven autopsies with five cases of polycystic kidney and four other cases of congenital renal anomaly. They found no cardiovascular anomalies.

Other cases of subarachnoid haemorrhage occurring with polycystic kidneys have been reported in which no aneurysm was found (*e.g.*, McGregor, 1926; Bell, 1935; Oosting, 1944; Mayers, 1948). Lambert (1947) noted rupture of a vessel in the brain or meninges in four out of seven cases and considered that some might have been due to aneurysms. The influence of hypertension and vascular degeneration cannot be excluded in these cases but in McGregor's case, for example, the patient was a sailor aged 22 in whom the vessels of the Circle of Willis were noted to be otherwise healthy.

Of other series of cases of subarachnoid haemorrhage, Hyland (1950) with forty-four cases of aneurysm in fifty-five autopsies, Helpern and Rabson (1950) with sixty-four in ninety-five, Taylor and Whitfield (1936) with thirty-three in forty-three and Hamby (1948) with forty-four in forty-seven make no mention of the kidneys, although the last remarks the absence of coarctation of the aorta. Many of Dandy's hundred and eight cases of intracranial aneurysm did not come to autopsy and no renal abnormality is recorded; in one case the presence of coarctation of the aorta led to the diagnosis of an aneurysm.

It may be seen that, if the cases of subarachnoid haemorrhage of Magee and of Ask-Upmark and Ingvar are considered as all due to ruptured aneurysm, fourteen cases of polycystic disease were found in six reported series of aneurysms, amounting to two hundred and fourteen cases, an incidence of 6.5 per cent. On the other hand four series of one hundred and eighty-five cases of proved aneurysm did not report any abnormality of the kidneys and this would give an overall rate of 3.5 per cent. It is not known, however, whether in these series the absence of any report of renal abnormality can be taken to imply that none was present.

The frequency of aneurysm in a series of cases of polycystic kidney is much less documented, the only figures available being those of Suter (1949) who found two ruptured aneurysms in five cases of polycystic disease. It is evident that this is too high a proportion owing to the smallness of the series; Bell (1935) considered that intracranial haemorrhage was relatively uncommon with polycystic kidney. Sieber (1905) found seven cases of apoplexy in ninety-eight fatal cases in the literature; Coombs (1903) found five cases in forty-four museum specimens. Rall and Odel (1949) reported four cases of cerebral haemorrhage, including an infant with birth trauma, in forty-six autopsies.

PRESENT CASES.

The following case, in which the diagnosis of intracranial aneurysm has not been proved, drew attention to the possible association of the two conditions ; it presents in addition certain features of interest.

*Case* 1. Miss M. P. was admitted to the Royal Infirmary, Glasgow, on 19th April, 1935. She was then aged 21 years. Four days earlier she had developed a sudden severe frontal headache, accompanied by dizziness and vomiting. The headache persisted and she vomited again the following day, but not thereafter. She had no significant previous history. Her father had died at the age of 51 of kidney disease.

On admission she had severe frontal headache, especially on moving the head. Nuchal rigidity was present and Kernig's sign positive. Knee and ankle reflexes could not be elicited. Ophthalmoscopic examination showed some congestion of the vessels and the edges of the discs were ill-defined and hazy. B.P. 140/70 mm. Hg. No masses were palpable in the abdomen and there was no abnormality in the urine. W.R. negative.

Lumbar puncture on 20th April revealed cerebrospinal fluid (C.S.F.) under increased pressure and containing blood. Xanthochromia was present. Some lymphocytes, epithelial cells and many red blood corpuscles were seen. Culture was sterile.

On 24th April she was still complaining of lightness and dizziness of the head with a sensation of pins and needles deep in the frontal region. The temperature had risen to 104°F. but was beginning to settle. All reflexes were present and the fundi were normal. A further lumbar puncture revealed the C.S.F. still under pressure and pale straw in colour.

On the evening of this day she developed a sudden left hemiplegia. This was not accompanied by any confusion of mind or disturbance of vision but was followed by incontinence of urine and faeces. Lumbar puncture the following day showed the pressure of the C.S.F. to be rather lower and the colour somewhat paler.

On 27th April there was complete flaccid paralysis of the left side with no disturbance of sensation. The left plantar response was extensor and the abdominal reflexes were absent on the left side. She lay with her head turned to the left and complained of neck pain on attempting rotation. The temperature had been falling steadily but slight pyrexia persisted until 14th May. On lumbar puncture on 10th May the C.S.F. was clear. Movements of the left arm and leg began to appear on 24th May and she was discharged on 9th July with a residual spastic hemiplegia. Fine movements of the left hand had not returned but she was able to walk with support.

She continued to report at intervals until February, 1944. She had some pain in the paralyzed limbs and complained of right-sided headache but was otherwise well. B.P. in February, 1944, was 140/80 mm. Hg.

On 2nd December, 1947, she was admitted to the Eastern District Hospital, Glasgow. For the previous three years she had had pain in the right hypochondrium. Her appetite had been poor and she had had occasional vomiting. One year previously she had had some difficulty with micturition and her urine had been said to be ' not right.' For the past ten days she had been breathless, dizzy and faint.

On admission blood pressure was 170/120 mm. Hg. A mass was felt in the left lumbar region extending to the level of the umbilicus and the right kidney was palpably enlarged. Urine : S.G. 1008-1014 ; no abnormalities. I.V.P. : two large cystic kidneys, more marked on the right side. Blood urea 36 mg.%. Serum albumen 6.4 g.%, globulin 1.45 g.%. Blood pressure varied from 148/80 to 200/100 mm. Hg. She was discharged on 12th January, 1948, but was readmitted on 26th August, 1948, having fainted two weeks previously and suffering from headache, vomiting and diarrhoea. The previous findings were confirmed.

In July, 1949, she was seen as an outpatient, complaining of general tiredness, breathlessness on exertion and at night. B.P. at this time was 210/130 mm. Hg.

She was readmitted to the Royal Infirmary on 21st October, 1950, being now aged 36 years. She had had a severe attack of pain in the left side of the abdomen six weeks earlier and one in the right side one week before admission. For the past two years she had had flushings, dizzy turns, occasional vomiting and dull aching pain in the right flank. She was always thirsty and stated that she drank at least one quart of water during the night. She had noticed increased swelling of the abdomen for the past month. The left ankle was always slightly swollen but no other oedema had been noticed. She continued to have occasional headaches.

On examination the abdomen appeared convex and enlarged. There were palpable masses on both sides ; that on the right extended from the costal margin almost to the inguinal region, the medial border being two inches lateral to the umbilicus ; that on the left extended from the costal margin to the level of the umbilicus, with which its medial border was in line. Both masses had a nodular character. The apex beat was palpable in the fifth left interspace 4½ inches from the midline. The rhythm was regular apart from occasional extrasystoles. The sounds were pure and of good quality. B.P. varied between 165/95 and 175/105 mm. Hg. There was some impairment of air entry at the base of the right lung and scattered rhonchi were present throughout both lungs. There was no change in the residual hemiplegia. The urinary output was from 40 to 65 oz. daily, S.G. 1006-1010. A trace of albumen was present and granular, epithelial and hyaline casts were seen. X-ray chest : cardiac contours within normal limits and clear lung fields. E.C.G. : left axis deviation. I.V.P. : large kidney masses ; concentration was poor but the presence of polycystic disease was evident. Blood urea : 80 mg.% ; 67 mg.%. Calvert's urea concentration test : maximum 1.09% ; minimum 0.55%. Serum albumen : 5.0 g.%, globulin 1.89 g.% The abdominal pain improved and she was discharged on 15th November, 1950.

The age of this patient at the time of the subarachnoid haemorrhage makes it extremely probable that the underlying lesion was an aneurysm. The occurrence of a second haemorrhage which was apparently entirely intracerebral does not affect this diagnosis. Richardson and Hyland (1941) reported two fatal cases in which initial subarachnoid haemorrhage with temporary recovery was followed by a recurrence of bleeding entirely into cerebral tissue without further subarachnoid haemorrhage being found either on lumbar puncture or at autopsy. Robertson (1949) has also stressed the frequency of gross cerebral damage from ruptured intracranial aneurysms, finding it in fifty-six of ninety-three post-mortem specimens.

Most authors accept the ability of an aneurysm to thrombose and so prevent further bleeding. Wechsler and Gross (1948) however do not agree with this and they believe that vascular malformations are a more common cause of subarachnoid haemorrhage than is recognised, finding this in six of ten cases they report. Martland (1939) found ruptured hypoplastic arteries to be the cause in nine of fifty-four cases. On the other hand Hyland (1950) found angiomata in only two of fifty-five cases and thinks that ' it seems doubtful whether they cause subarachnoid haemorrhage with any frequency except possibly in children.' He concludes that ' the accumulated evidence from autopsy, arteriographic studies and exposure at operation, in other large series as well as our own, indicates a sufficiently high incidence of demonstrable aneurysms as the cause for this clinical syndrome to warrant consideration of the prognosis in unverified cases in the terms of aneurysm.'

The case described above is of particular interest in that there was no evidence of any kidney lesion at the time of the haemorrhage and nothing to suggest it for at least nine years later. Most cases of the association have been demonstrated at autopsy but, in the two cases (Madonick *et al.*, 1946 ; Snapper & Formijne, 1939) which survived, the presence of polycystic kidneys was demonstrated at the time of the subarachnoid haemorrhage. It would appear that the renal lesion in this case could

have played little part in the onset of rupture. It is notable that there has been no further bleeding despite the hypertension present for the past three years, although Hyland considered that the presence of hypertension made a further fatal attack more probable.

In order to elucidate further the frequency of the association of cerebral aneurysms and polycystic kidneys, the autopsy reports of the Royal Infirmary, Glasgow, for the years 1934-48 and of the Western Infirmary, Glasgow, for the years 1925-45 and 1947 were examined. As may be seen from the table the two series showed a very close agreemert in the incidence of both lesions.

TABLE 1.
Analysis of autopsy reports from two Glasgow infirmaries.

| | Boyal Infirmary 1934 — 1948 | Western Infirmary 1925 — 1945 1947 | Total |
|---|---|---|---|
| Autopsies .. .. .. | 5617 | 5628 | 11245 |
| Polycystic kidney .. .. | 17 | 19 | 36 (0.32%) |
| Non-infective aneurysms | | | |
| Total .. .. .. | 74 | 74 | 148 (1.3%) |
| Ruptured .. .. | 73 | 71 | 144 |
| Polycystic kidney with aneurysm .. .. .. | 2 | 4 | 6 |

In addition to the one hundred and forty-eight non-infective aneurysms, there were five aneurysms due to infection; three (two ruptured) were associated with subacute bacterial endocarditis, one (ruptured) with post-operative septicaemia and one with tuberculoma as previously mentioned. Multiple aneurysms were noted to be present in ten cases. In one case a ruptured ' berry ' aneurysm was associated with an angiomatous mass on the cerebral surface. Arieti and Gray (1944) in reporting a similar case discussed its relation to Lindau's disease.

There were twenty-eight cases in which subarachnoid haemorrhage was not shown to be due to rupture of a ' berry ' aneurysm. In one it occurred from a cirsoid aneurysm and in one from a cavernous haemangioma (intra-cerebral haemorrhage having also occurred). Four cases were associated with haemorrhagic disease, one with subacute bacterial endocarditis, one with cholesteatoma and one with prematurity. In nineteen no specific cause was found, although vascular sclerosis or hypertension was present in nine; in eight the presence of an aneurysm was definitely suspected although none was found.

Of the one hundred and sixty-seven cases of subarachnoid haemorrhage in which there was any probability that an aneurysm might have caused

the bleeding aneurysms were found in one hundred and forty-seven (88%). The incidence of aneurysms over the series of autopsies (1.3%) is comparable with most recorded figures, although Riggs and Rupp (1942) reported finding 9 per cent. The small number of unruptured aneurysms found is doubtless due partly to the fact that examination of the brain was not performed in many cases with no cerebral symptoms and partly to the ease with which an unsuspected small aneurysm may be overlooked. There is also the possibility that in some cases a weakness of the vessel wall may develop into an aneurysm only shortly before rupture.

Polycystic disease was present in six cases (4%) of intracranial aneurysm. In another case one kidney was congenitally absent. No congenital cardio-vascular anomalies were recorded.

Conversely, 16.6 per cent of the cases of polycystic kidney died from subarachnoid haemorrhage from or associated with aneurysms. Two further cases died from subarachnoid haemorrhage in which no aneurysm was demonstrated. In only sixteen of the thirty-six cases was the head examined and although no aneurysms were found in those in which haemorrhage had not occurred it should be noted that unruptured aneurysms were present in three cases in which it had. Six cases of multiple cysts of the kidney were not considered to be true polycystic disease and have been excluded. In one of these death occurred from a ruptured intracranial aneurysm.

Other abnormalities found with polycystic kidneys were polycystic liver in eight cases, a congenital cyst of the lung in one case and cystic pancreas in one case. In one case there was the rare combination of congenital absence of one kidney and polycystic disease in the remaining one. This was in a female who died at the age of 23 of uraemia ; the head was not examined. Only two other recorded cases of this have been traced (Coombs, 1903 ; Carlson, 1946).

*Case* 2. Male, 43 years. Three years previously he had been in hospital suffering from haematuria ; the diagnosis at that time was said to have been hypernephroma. He had continued to have haematuria at intervals. For the past six months his vision had been failing and for the past month he had had constant frontal headache with occasional vomiting and his ankles had been swollen. He had collapsed suddenly on the day of admission, was admitted in coma and died shortly afterwards. His blood pressure was considered to be high but was not recorded by manometer.

*Post-mortem examination.* Kidneys R. 1100 g., L. 1350 g. Both organs showed very marked enlargement, measuring each about 26 cm. in length. This was due to polycystic disease, the cysts being of varying size up to that of a walnut. Most of them contained dark brown fluid consisting of changed blood. Brain : There was extensive subarachnoid haemorrhage on the base of the brain and extending along the right Sylvian fissure to the right hemisphere. An aneurysm 0.5 cm. in diameter was present on the right middle cerebral artery 5 cm. from its origin and this aneurysm showed a large rupture in the wall. The haemorrhage from this rupture had torn up the brain substance of the right hemisphere and extended into the right lateral ventricle. Another small aneurysm, unruptured, was present on the anterior communicating artery. The vessel walls were otherwise healthy. The heart showed well marked concentric hypertrophy with slight dilatation of the right ventricle. There was oedema of the lungs.

*Case* 3. Male, 42 years. There was a history of a kidney illness twelve years previously. Since then he had had occasional attacks of haematuria. He became disorientated, lapsed into coma and was admitted the following day. B.P. 240/70 mm. Hg. He died shortly after admission.

*Post-mortem examination.* R. kidney 1200 g., 11 by 25 cm., L. kidney 900 g., 12 by 21 cm. Both organs were the seat of very marked cystic disease. The cysts varied greatly in size, many being large ; maximum diameter 6 cm. Some of the cysts contained purulent material. Very little renal tissue was left. The ureters were healthy. Brain : An extreme degree of subarachnoid haemorrhage had occurred over the entire brain. The source of this haemorrhage was not observed but there was a small unruptured aneurysm on the left side of the Circle of Willis and it seemed probable that the haemorrhage originated in another such lesion. The heart showed slight hypertrophy. Other organs were normal.

*Case* 4. Female, 61 years. No history of previous illness known. She collapsed suddenly and was admitted in coma. She improved and was able to answer questions after two days but developed a right hemiplegia and died twelve days after admission.

*Post-mortem examination.* Kidneys R. 260 g., L. 280 g. The increase in bulk was associated with their being polycystic. Liver : 1040 g. Numerous cysts were present, especially on the lower border anteriorly, 0.5—4 cm. in diameter. There were smaller cysts in the substance of the right lobe. The cysts contained clear watery fluid and the lining was thin and glistening. Pancreas : healthy. Brain : There was massive subarachnoid haemorrhage especially in the left parietal region but extending from the frontal to the occipital poles and also to the right side. There was much haemorrhage at the base of the brain with rupture to the subdural space. The surface of the brain was not greatly damaged but the inferior aspect of the left temporo-sphenoidal lobe was involved. There was no ordinary cerebral haemorrhage in the region of the basal ganglia. The left middle cerebral artery was the site of aneurysmal dilatation (1.25 by 0.8 cm.) 2 cm. from its origin from the Circle of Willis. The aneurysm was almost completely thrombosed but was ruptured on its posterior aspect. At the corresponding point on the opposite side there were small swellings on the artery, as also on several neighbouring vessels, probably commencing aneurysms. There was a small aneurysm on the anterior communicating artery. On histological examination the origin of the aneurysms from Y junctions was confirmed. The thrombus was recent ; there was considerable atheroma. The heart was hypertrophied.

*Case* 5. Female, 28 years. Cystic disease of the left kidney had been diagnozed two years previously. For three weeks she had had frontal headaches and vomiting. She collapsed suddenly and died five hours later.

*Post-mortem examination.* L. kidney 1135 g. It contained numerous cysts and very little renal tissue remained. R. kidney 400 g. There were several cysts with a moderate amount of renal tissue. Brain : There was subarachnoid haemorrhage on the left side. At the junction of the left middle cerebral artery with its inferior lateral frontal branch there was a pyriform sac the size of a pea which was ruptured on its superior aspect. No other aneurysms were seen.

*Case* 6. Male, 34 years. He had felt out of sorts for two days and then collapsed suddenly. He was admitted in coma with periods of acute delirium. Blood pressure was not obtained. There was slight nuchal rigidity and Kernig's sign was positive. Reflexes were increased and the right plantar response was extensor. Optic neuritis was present in both eyes and a recent haemorrhage below the left disc. On lumbar puncture the cerebro-spinal fluid was under high pressure and uniformly blood-stained.

*Post-mortem examination.* R. kidney 625 g., L. kidney 510 g. Both kidneys showed a marked degree of congenital cystic disease. In the right kidney the cysts reached a large size, up to 2 inches in diameter. The contents had the usual serous or blood-stained character. Brain : There was widespread subarachnoid haemorrhage. The cerebral vessels were sclerotic. On the left middle cerebral artery at the origin of its inferior lateral frontal branch there was an aneurysm about a quarter of an inch in diameter with a small orifice on its medial surface. There was a small patch of atheroma at the junction of the vessels. Massive haemorrhage had spread to the region of the left internal capsule and had ruptured into the lateral ventricle. The heart was hypertrophied. Other organs were normal.

*Case* 7. Male, 26 years. Five years previously he had received a blow on the head and had been unconscious for one day. Since then he had had seizures associated with headache and possible loss of consciousness with increasing severity. He collapsed while watching a football match with twitching of both arms and right leg He died three hours later.

*Post-mortem examination.* Kidneys (1600 g. together) showed the typical appearance of congenital cystic disease, the cysts on the whole being of large size. The remaining renal tissue was small in amount. Skull : The bones and dura were healthy. There was widespread subarachnoid haemorrhage especially around the basal cisterns. The cerebral arteries showed no evidence of general disease. The arrangement of vessels in the Circle of Willis was normal. There was an aneurysm on the right anterior cerebral artery, 1 inch from its origin, $\frac{1}{8}$ inch in diameter with a wide rupture on its undersurface. There was no intracerebral haemorrhage. There was hypertrophy of the left ventricle. Other organs were normal.

Suter (1949) calculated the expected frequency of the association by chance in his series as 0.02 in 5,960 autopsies and found two cases. The possibility of chance is greater in the present series, the proportion of ruptured aneurysms and polycystic kidneys found both being higher; 0.47 cases of chance association might be expected instead of the six cases found.

Of the cases in which the sex is known, twelve have been male and eight female. The average age at death from rupture of the aneurysm in those cases in which the age is known is 41.3 years. In this series the average age at death of all cases of ruptured non-infective aneurysm is 46.1 years. This difference is not significant and it cannot be said that the presence of polycystic kidneys results in rupture of an aneurysm at an earlier age.

The influence of hypertension on the development of an aneurysm from some underlying congenital anomaly or on rupture of an aneurysm is difficult to assess. In eleven proved cases in which the blood pressure was noted it was found to be raised. In all except one of these, however, it was estimated after the onset of subarachnoid haemorrhage and it is well known that this may cause a transient hypertension. On the other hand hypertension is found frequently with polycystic kidneys. Schacht (1931) found a systolic pressure of over 145 mm. Hg. in 61 per cent, and diastolic over 90 mm. Hg. in 55 per cent of cases, the proportion being even higher in cases coming to autopsy. The unproved recovered cases reported here and by Madonick *et al.*, are the only two in which normal pressures have been recorded. Five of the six cases found here showed some degree of cardiac hypertrophy, suggesting previous hypertension. In the case reported by Forster and Alpers (1943), in which death occurred at the age of thirteen weeks, there seems no doubt that a common congenital etiology must have been present. The recovered cases with normal pressure add support to the view that this is also true of other cases.

## SUMMARY AND CONCLUSIONS.

*Summary.*

The more recent literature on the etiology of polycystic kidneys and of intracranial aneurysms is reviewed, and previous reports of the association of the two lesions are recorded.

A case of subarachnoid and cerebral haemorrhage at the age of 21 is reported, in which evidence of polycystic renal disease developed over 9 years later and in which there has been no recurrence of haemorrhage over a period of 16 years despite the development of hypertension.

In 11,245 autopsies six cases of polycystic kidney associated with intracranial aneurysm were found. The relationship was present in 4 per cent of cases of aneurysm and 16.6 per cent of cases of polycystic kidney, while 22.2 per cent of cases of polycystic kidney died from subarachnoid haemorrhage.

*Conclusions.*

It is concluded that polycystic kidneys and intracranial aneurysms are associated more frequently than would occur by chance. Although hypertension and vascular degeneration may play some part in the development of the aneurysms, it is more probable that there is a common etiology and therefore support is given to the congenital origin of both intracranial aneurysms and the adult type of polycystic disease.

Although coarctation of the aorta is more widely known as an associated finding with intracranial aneurysms, the association with polycystic disease appears to be more common.

Subarachnoid haemorrhage, frequently from ruptured aneurysm, is a not uncommon cause of death in polycystic disease.

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