CONGENITAL CYSTIC KIDNEY AND LIVER WITH FAMILY TENDENCY.

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So much has already been written concerning congenital cystic kidney that an additional communication upon the subject may seem to demand an apology. The author's excuse is a recent opportunity to study two cases in which the lesion was so early that they seem to offer some indication as to the pathogenesis of the condition. The cases were both new-born infants delivered in the obstetrical service of Dr. J. Whitridge Williams in the Johns Hopkins Hospital. Some interest attaches to the fact that they were both children of the same mother, being the first and second children of Mary F., an apparently healthy negro who was sixteen years of age at the time of the delivery of her first child in April, 1904. Her first confinement occurred on April 14, 1904, when a perfectly normal labor resulted in the birth of a male child 44 centimeters in length and weighing 2026 grams. The labor was clinically estimated to have occurred early in the ninth month of pregnancy. The child was placed in the incubator and seemingly did well, gaining in weight after the initial loss, but it died suddenly on the eleventh day.

The second child, a girl, was born on March 21, 1905, eleven and a half months after the birth of the first child. The child was also born prematurely, apparently toward the end of the eighth month of pregnancy. Labor was normal. The child was 42.5 centimeters in length and weighed 2005 grams at birth. It did not do well after birth but lost gradually in weight up to the time of its death when it weighed 1380 grams.

The abbreviated post-mortem protocols of both children will be found appended to this article. For the sake of convenience in description the children will be designated child "A" and child "B."

This family tendency has been previously noted a number of times, not however, in the negro race, and I emphasize it here not only to indicate the part inheritance plays in the condition but also to show that the cases here reported are related in this feature to a considerable group of cases of cystic kidney. Dunger[1] in his admirable review of the subject of congenital cystic kidney has collected eleven cases and added one of his own observation, in which the lesion has occurred in two or more members in the same generation or in two generations of a single family. To these I am able to add several others from literature in addition to the present case.

Schupmann[2] is often credited with having reported the first case showing family tendency, but a reference to his article shows, as Dunger suggests, that he reports not the occurrence of congenital cystic kidney in three children but in the third child of a mother who had given birth to two malformed children previously. This child showed in addition to the kidney lesion hydrocephalus with encephalocœle and a bicornuate uterus and double vagina. Luzzatto[3] includes Adamkiewicz[4] among those who report cases of family tendency, but I have been unable to gain access to his thesis. Virchow[5] in 1855 published the notes of a family in which the mother gave birth successively to three premature children. A post-mortem examination on the third showed bilateral cystic kidneys as the cause of the abdominal swelling. A subsequent child showed a similar condition at the autopsy, and there is little doubt that the same condition existed in the other two children which were not examined. The mother gave birth to four other children, who lived, although one died at the age of ten months as the result of acute hydrocephalus. In 1867 Wolff[6] reported a case of bilateral cystic kidney associated with hydrocephalus in the male child of a woman who had given birth to a female child, previously recorded, with similar lesion of the kidneys eleven months before. The woman had previously borne healthy children. In 1869 Brückner[7] reported two children of the same mother, the third and seventh child, with cystic kidneys and other malformations. The first of these two children showed six fingers on the right hand and seven on the left. The head was set far backward almost on the buttocks and there was also hydrocephalus with hernia of the brain. The second child showed six digits on both hands and both feet and also had

[1] *Ziegler's Beiträge*, 1904, xxxv, 445.
[2] *Organ f. d. ges. Heilkunde*, 1842, ii, 135.
[3] *La degenerazione cistica dei reni*, Venice, 1900.
[4] Inaugural Dissertation, Berlin, 1843.
[5] *Verh. d. Phys. Med. Gesellsch.*, Würzburg 1855, v, 447.
[6] *Berlin klin. Woch.*, 1867, iv, 480
[7] *Virchow's Archiv*, 1869, xlvi, 503

hydrocephalus with encephalocœle and atresia of the hymen. In 1894 Singer[8] described a family in which the first (male), fourth (male), seventh (female), tenth (female), and thirteenth (male) children showed the lesion of congenital cystic kidneys, the tumor masses causing great difficulty in delivery, resulting in the death of the children at birth. Only three of these cases were examined post-mortem, but again the presence of tumor masses in the region of the kidney leaves no doubt as to the existence of the lesion in the two unexamined cases. Carbonnel[9] has found the lesion in the kidneys of twins. Höhne[10] in 1896 reported the removal at operation of a cystic right kidney from a girl of 20 years whose mother, dying at the age of 49 years, had shown bilateral cystic kidneys, cystic liver, and cysts in the ovaries. Another child of the same woman had died at the age of 9 weeks of some kidney disease, the author suggests possibly also cystic disease. Steiner[11] in 1899 recorded two interesting families. In the first a man aged 52 died showing bilateral cystic kidneys and cystic liver. His sister also showed the condition of cystic kidneys, and his son of 10 years showed at autopsy a cystic right kidney, while several smaller children were also suspected to have the disease because of albuminuria and palpable nodular kidneys. In the second family the diagnosis of the condition of cystic kidney had been established in a man aged 46, and in a sister aged 38, while it had been demonstrated post-mortem in another sister dying at 42 years of age. In the ten-year-old son of the man a cystic right kidney had also been diagnosed. David and Jacobsohn[12] in 1900 found bilateral cystic kidneys at the autopsy on a woman 50 years of age whose sister had shown post-mortem a similar lesion. The mother of these two women who had died previously presented symptoms suggesting that she had this disease, though it was not actually determined by post-mortem examination. These authors quote Lauenstein's observation of cystic kidney in mother and daughter, as the first to denote a [family tendency, but I have been unable to find the original publication. In 1901 Beck[13] reported an operation on a woman of 55 years at which a cystic left kidney was removed. After death 11 days later the other kidney was found extensively diseased. Two sisters of the patient had died previously from the same disease, one at 40 years after an operation, and the other at 54 years. Carrez[14] records the establishment of the clinical diagnosis of bilateral cystic kidney in a woman of 48, as a result of finding at operation a large cystic left kidney in her daughter of 27. Morris[15] records the following two cases. Two children of one mother died of congenital cystic kidney, one at 6.5 months, the other at 3.5 months. Of four other children in the family 3 showed other congenital defects and one was born dead. The father of these children was the only survivor of 13 children,

[8] Inaugural Dissertation. Greifswald. 1894.
[9] Quoted by Couvelaire, *Annales de gyn. et obst.*, 1899, lii, 453.
[10] *Deutsch. med. Woch.* 1896, xxii, 757.
[11] *Deutsch med. Woch.*, 1899, xxv, 667.
[12] *Charité-Annalen*, 1900, xxv, 16.
[13] *Annals of Surgery*, 1901, xxxiii, 147.
[14] Thesis, Lyon, 1901.
[15] *Surgical Diseases of the Kidney and Ureter*, 1901, i, 656.

eleven of whom had died at birth and the other at five months. Morris quotes also the report of Bar of three successive children of the same mother, who had died of the disease. Osler[16] in 1902 reported the establishment of the diagnosis of bilateral cystic kidney in a man aged 39, whose mother had shown a similar condition at autopsy. Meyer[17] reported in 1903 the autopsies on two brothers, one 8 months old, the other two years, who had died of diphtheria. In one of these there was present an atrophic cystic kidney on the right side, and in the other a similar lesion on the left. Dunger[18] reports observing a mother aged 64 years and daughter aged 26 years in both of whom bilateral cystic kidney and cystic liver occurred. Both died of cerebral hæmorrhage.

In this list it may be noted that a number of the cases showed, in addition to the cystic kidneys, other lesions in the nature of congenital malformations, and such is the frequency of this association that it may be considered almost the rule. The list of associated malformations is long and varied. It is headed apparently by hydrocephalus, although polydactylism is of frequent occurrence. It includes varied lesions to be attributed to imperfections in development in the complicated embryonic folds of the face and perineum, such as hairlip, hypospadias, atresia of the vagina, vesico-rectal fistula, rudimentary condition of the external genitalia. Malformations of the internal genitalia are also noted. In a few cases there have been defects in the cardio-vascular system, among them absence of the ductus Botalli, defects in the interventricular septum and of the aortic valves. In one case there was situs transversus of the thoracic viscera; in another absence of the spleen.

The two cases here reported, however, showed no such gross defects or malformations. Both children though small and prematurely delivered were well-formed externally and their organs were apparently normal, grossly. On microscopical examination, however, there was found in addition to the cystic condition of the kidney, the early stage of a similar cystic condition in the liver, and in one case also in the pancreas. This brings the cases into a fairly large group of cystic kidneys. Lejars[19] collected from literature 60 cases of cystic kidney and of these 28.3 per cent. showed also the cystic

[16] *American Medicine*, 1902, iii, 951.
[17] *Virchow's Archiv*, 1903, clxxiii, 209.
[18] Loc. cit.
[19] Thesis, Paris, 1888.

lesion in the liver. Luzzatto [20] in 1900 in a larger series of cases found 43 cases or 19. 11 per cent. with the associated lesion in the two organs. This association seems important in considering the pathogenesis of the disease and will be discussed later. Turning to the kidneys themselves I shall first describe those of the second child, child "B" as they showed an earlier stage of the lesion than was shown by those of child "A."

The kidneys were normally placed in the body cavity and approximately of normal size, perhaps slightly enlarged. The ureters, bladder, urethra, and genitalia were normal. The ureters allowed the passage of a small probe with ease. The kidneys showed nothing abnormal until they were incised, when a considerable amount of urinous fluid poured out and it was found that a number of small cysts had been incised. The larger of these were about 2 or 3 mm. in diameter while there were many others scarcely visible. The cysts appeared to the naked eye to be confined almost exclusively to the medulla of the kidney, with here and there a visible cyst in the cortex. The different medullary pyramids did not appear equally affected, some of them being almost free from visible cavities. The two kidneys were affected and apparently almost equally so.

The tissues were fixed in Zenker's fluid and six sets of serial sections cut in paraffin from various parts of the organs, including a series from the part most affected as well as one from the area apparently freest from lesions. The sections showed that the kidneys in general were well formed. The cortical striation was well marked, with a normal relation between medullary rays and labyrinth, and the cortex was of normal width, measured by the number of rows of glomeruli between the capsule and the medulla which the study of numerous infantile kidneys has shown to be as a general average ten. The glomeruli were well formed and appeared normal with very scattered exceptions. In a few sections were found one or two glomeruli with a dilated capsular space. The tubules of the secreting type were also normal in appearance having a high granular epithelium and a small undilated lumen. In the medullary rays the loops of Henle appeared shorter than normal and in many places did not reach to the boundary zone. There were few cysts in the cortex until one came to a portion of the labyrinth bounding on the medulla. Here there were many elongated and oval cystic cavities lined by a fairly high cubical epithelium. By following out series of sections these could easily be found to be continuous at one end with tubules which entered the medullary rays and followed a course toward the medulla. They often joined other tubules of the collecting type. These tubules were unconnected with the loops of Henle, and were quite evidently collecting tubules, and the cysts thus corresponded to the portions of the tubular system known as the junctional tubules. The connections at the distal end of the cysts were more difficult to trace, but in several places they were found to pass over into tubules with the secreting type of epithelium.

[20] Loc. cit.

In the medulla the cystic formation reached its maximum. In many places there was scarcely a tubule found with a normal lumen. All were dilated. The cysts were larger than those of the cortex and were variously shaped, tending to be circular and were lined by high cubical epithelium. On the cortical side the cysts opened into several finger-like tubular projections which tapered rather abruptly so that in the boundary zone they were of the width of normal ducts and from here were continued as collecting tubules into the medullary rays. Toward the papilla the cysts became somewhat contracted and in favorable sections could be seen opening freely at the apex of the papilla, into the pelvis. There was no obstruction to the lumen of the ducts at the papilla. In very many places mitotic figures could be found in the lining epithelial cells of the cysts, indicating an active proliferation rather than any compression. There was, however, no evidence of numerical increase in the ducts. Intracystic papillary growths were not made out.

In the kidneys of child "B" the interstitial tissue of the medulla was not increased in amount. The walls of the adjacent cysts lay almost against each other, separated by only a few cells and strands of a rather embryonic connective tissue. The same condition held true for the cortex. In only one or two places was there a slight patchy increase in connective tissue and it was in relation to these patches that the few dilated glomeruli were found.

The sections from the part of the kidney which grossly appeared almost unaffected showed a condition similar to, but of less degree than, that in the other parts. There were almost as many cysts in both cortex and medulla, but they were smaller, resembling more a simple dilatation of the affected tubules.

There is clinical evidence that the kidney functionated, if not normally at least approximately so. The child lived 19 days and apparently passed a normal amount of urine into its napkins. Death was the result of acute gastro-intestinal infection. The sections showed also that the kidney was active and that there was no obstruction to the passage of urine through the tubules. In some of the cysts and tubules there were uric-acid deposits but not in such amount as to cause any apparent obstruction. In some of the tubules of the cortex there were hyaline casts and in one or two places such narrow casts were found projecting into the cortical cysts, demonstrating the continuity of these cysts with the tubules of the secreting type. There was precipitated albumin in some of the glomerular spaces and in the tubules, but no red blood cells were demonstrated.

The kidneys of child "A" were in general like those of child "B." They were about normal in size though the left kidney seemed slightly enlarged. This enlargement was found to be due especially to one fœtal lobule which projected above the others as a rounded pale mass. On section this was found to be much more cystic than the rest of the kidney. The cysts were large,

measuring in places 5 mm. in diameter. The tissue between them was pale and fibrous in appearance. In several places in the medulla there were small hæmorrhages, and uric-acid deposits were made out in the form of bright yellow dots and streaks. The microscopical sections showed also a marked similarity to those already described. There was, however, one important difference, and that was a new growth of connective tissue, most marked in the medulla but extending also into the portions of the cortex implicated. This connective tissue was quite richly cellular, but a Mallory connective-tissue stain showed the presence of abundant fibers which had a tendency to take a concentric arrangement about the cystic tubules. In this kidney the greater part of the cystic development was in the medulla, though the cortex was also implicated, and the cortical cysts occupied a position similar to those in the other case, in the portion of the labyrinth nearest the boundary zone. There were, in this kidney also, hæmorrhages into the interstitial tissue of the medulla.

Before treating of the pathogenesis of the renal lesion, I shall describe briefly the lesions of the other organs in so far as they have a bearing on the subject. The liver merits most attention and in the lesions of this organ again child "B" showed an earlier stage than child "A."

Grossly the liver of child "B" appeared slightly smaller than normal for an infant of that age. Superficially it was normal in appearance, the surface being smooth throughout, and the lobulation distinct. The gall bladder and bile ducts were normal. The cut surface, however, had a striking appearance and one that is apparently characteristic of this condition in its early stages. The parenchyma was quite normal in appearance, but everywhere throughout the organ the portal systems were sharply outlined as grayish translucent somewhat branched areas, resembling rather closely an oak leaf in shape. These spaces were evidently much wider than normal. There was a similar increase of connective tissue about the entering portal vessels at the hilum of the organ. The microscopical sections showed that the cause for the increase in the size of the portal spaces was a marked increase in the size and number of the ducts in them, with a slight increase in the connective tissue. This change was uniform throughout the organ. The ducts were lined by a high columnar epithelium, and were free from content other than a finely granular eosin-staining precipitate. These ducts were tortuous, were much branched, and were irregularly dilated into cyst-like spaces. In many places they could be traced to the outer limits of the lobules, where they ended in columns of liver cells of the secreting type. In other places they entered the lobules accompanied by a connective-tissue sheath, and in many places cross-sections of a duct were found, with a similar high epithelium with clear protoplasm, well inside the lobule and even close beside the central vein. The ducts with their cyst-like dilatations in the portal spaces were surrounded by an increased amount of connective tissue which was richly cellular and contained many cells of the lymphoid and plasma-cell type, as well as many eosinophiles. As stated, the condition prevailed throughout the liver, as shown by sections from various

parts of the organ. The picture offered by the liver is identical with that drawn to illustrate a case of Borst.[21]

The liver of child "A" was almost identical in gross and microscopical appearances with that of child B, the only difference being a more marked increase in the connective tissue, a difference already noted as existing between the kidneys of the two. The connective tissue in this child's liver was also less cellular and more fibrous and showed a tendency to encapsulate the ducts with concentric layers of fibers.

In the pancreas of child "B" there was found a similar hypertrophic condition of the duct epithelium. The larger ducts showed a much-folded involuted epithelium, and there were more numerous branching ducts in the spaces about the major ducts. Mitotic figures were found in the duct epithelium. The cells of the parenchyma were not so high nor so granular as those of a normal pancreas, and resembled more the duct epithelium. There was some increase in the connective tissue of the organ especially near the larger ducts. It was richly cellular and resembled the tissue about the ducts in the liver. This condition was less marked in the pancreas of child "A."

Section of the duodenum of child "B" showed a definite tendency to hyperplasia of the epithelium, though one hesitates to assign to it any important connection with the lesions of the organs described. The crypts of Lieberkühn were very deep and wide with a high coarse-appearing epithelium of an indifferent type. Some of the crypts were indeed cystic.

In the lungs of both children the terminal bronchi were extremely dilated, but there was no sacculation and the lesion was not apparently of the nature of a congenital bronchiectasis, but of a compensatory nature following incomplete aëration of the lungs.

The other organs showed no lesions which could in any way be interpreted as having a bearing on the disease of the liver and kidneys.

To summarize then, briefly, in two small children of the same parentage there was found a condition of hyperplasia of duct epithelium with a tendency to cyst formation especially marked in the kidneys and the liver, where there was also an increase in the number of ducts, but occurring also to a less degree in the pancreas and possibly in the intestine.

The attempts to explain the pathogenesis of the congenital cystic kidney have been so numerous and so varied that one is inclined to question whether pathologists have been dealing throughout with a single pathological process. Though different processes may be operative in the condition it seems

[21] *Festschrift der Phys.-Med. Gesellsch.*, Würzburg, 1899.

safe to assume that but a single one accounts for the group in which both kidney and liver are affected, and it is to this group that the present case belongs. Any light that may be gained from a study of it may accordingly, it would seem, be applied to the whole group.

If one omits the view that the cysts are formed in the interstitial tissue of the kidney which was early abandoned, and confines himself to those theories which recognize their formation either in the tubules or in the glomeruli, the attempted explanations of the pathogenesis of the condition fall naturally into three or possibly four groups:

(1) that the cysts are the result of obstruction and of retention of secretion ;
(2) that they are of the nature of a neoplasm ;
(3) that they are the result of malformation; and
(4) that the condition lies between the last two, partaking somewhat of the nature of each.

The literature of the subject has been extensively reviewed in many papers, notably those of Luzzatto,[22] Dunger,[23] von Kahlden,[24] and Busse,[25] and I shall make but brief reference to the more important opinions under the several headings of the above classification, acknowledging my indebtedness to these authors, where specific references are not given.

The great exponent of the retention theory was Virchow, and it has probably been the weight of his opinion that has gathered and held so many adherents to this view. There have been many variations in the theory, the contention being as to the nature of the obstruction. The general group of views may, however, be well summarized in the words of Henry Morris[26]: "Regarding as I do the congenital cystic kidney of the fœtus and the new born and the large polycystic kidney of the adult as essentially the same disease, both being due to dilatation, the result of obstruction, one must yet recognize different causes of obstruction

[22] Loc. cit.
[23] Loc. cit.
[24] *Ziegler's Beiträge*, 1893, iii, 291.
[25] *Virchow's Archiv*, 1904, clxxv, 442.
[26] Loc. cit.

in different cases some congenital, some inflammatory, some malformation, some traumatic, some in the kidney, some in the ureter, and some in the urethra. The affection may commence in utero or during the first months of extrauterine life, or in early childhood, or not until middle age, or advanced, or quite old age."

Virchow[27] first advocated the view that uric-acid deposits were the cause of the obstruction but in a later paper[28] advanced the theory that the lesion was the result of a fœtal papillitis or pyelonephritis which caused an increase in the interstitial tissue of the papilla. This in its contraction resulted in the atresia of the papilla and thus in the formation of retention cysts in the tubules. To this view he still adhered in 1892.[29] Frerichs attributed the cysts to retention following obstruction by casts; Bouillard and Lehmann to obstruction by uric acid and calcium salts; Klein, Rosenstein, and for a time Brigidi and Severi, to hæmorrhage from the glomerular tufts with obstruction of the outlet and dilatation of the capsule. Sabourin, Cornil, and Brault attributed the lesion to an inflammatory condition in the kidney resulting, through an interstitial new growth of tissue or cirrhosis, in a constriction of tubules and retention. The retention theory has had many other supporters who see in the cysts of the kidneys of chronic nephritis a lesion analogous to that of the congenital cystic kidney.

In 1875 Sturm[30] expressed the view that the origin of the cysts lay in the epithelium of the convoluted tubules, which at first as the result of a dilatation underwent a simple hypertrophy but later led to the putting out of bud-like processes of an adenomatous nature. By the early fatty degeneration of these constantly growing tumor-like processes, the cysts were formed. In 1876 Mihalkowicz[31] expressed the view that the condition in the kidney was analogous to the cystic disease of ovary, testicle, and breast. Chotinsky[32] could find no evidence that the

[27] *Verh. der Gesellsch. f. Geburtshülfe*, Berlin, 1847, ii, 170.
[28] *Verh. der. Phys.-Med. Gesellsch.*, Würzburg, 1855, v, 447.
[29] *Berlin. klin. Woch.*, 1892, xxix, 105.
[30] *Arch. der Heilkunde*, 1875, xvi, 193.
[31] Thesis, Paris, 1876.
[32] Thesis, Bern, 1882.

glomeruli took part in the cystic formation, but found signs, instead, of an active growth of the tubules in outgrowths from the tubules, solid cellular processes, and probably new formation of tubules. He concluded the primary factor was a hyperplasia of the tubules and of the stroma. Lejars [33] described the condition as a persistent congenital lesion, in the great majority of cases of the type of an "Epithelioma Mucoïde." In 1893 Nauwerk and Hufschmid [34] recognized buds from the tubules, intracystic papillary growths, and solid nests of epithelial cells and placed the lesion definitely in the group of adeno-cystomata. Von Kahlden [35] supported this idea, but emphasized farther the coördinate growth of the stroma analogous to that in the adenofibromata. He considered the lesion of cystic liver of the same nature. There are numerous other supporters of the theory of active growth of the epithelium of the tubules, among them Hommey, Hausmann, Albert, and Schmitz.

The frequent association of the congenital cystic kidney with malformation of various parts and organs has led to the idea that it too is to be regarded as a malformation or the result of an error in development. This view gains some support from the extreme complexity of the process of development of the genito-urinary system as a whole. Koster [36] was the first to describe the lesion as an error in development, but he based his theory on a faulty embryology. With the assumption that the tubules of the kidney grew from a separate "anlage" from that of the pelvis and joined it secondarily, he postulated a failure of union between the two parts and a consequent hyperplasia of the epithelium of the tubules with the cystic result. Hildebrand [37] has made use of quite a similar explanation on the basis of the modern dualistic theory of the formation of the kidney, i.e., that glomeruli and convoluted tubules arise from one anlage and secondarily join the collecting tubules which are an outgrowth from the pelvis. Hildebrand postulated a failure of union between these two

[33] Thesis, Paris, 1888.
[34] *Ziegler's Beiträge*, 1893, xii, 1.
[35] *Ziegler's Beiträge*, 1893, xiii, 291.
[36] Quoted by Dunger.
[37] *Archiv für klin. Chirurgie*, 1894, xlviii, 343.

systems of tubules, with a retention of secretion and cyst-formation in the convoluted portion. Ribbert[38] has made use of the same facts of development to explain the pathology of the condition, but has emphasized, instead of retention of secretion as the causal formation, a wild excessive proliferation of the cells of the tubules which fail to join, particularly of the ampulla of the collecting tubules and the portion of the other section, corresponding to the junctional tubule. He calls attention also to the point that in this active hyperplasia of the epithelium the condition bears some resemblance to a new growth. Meyer[39] and Busse[40] express a similar opinion. Shattock[41] attributed the lesion to the development of retention cysts from portions of the Wolffian body included within the kidney. Bard and Lemoine[42] expressed the opinion that the lesion was due not to a primary epithelial hyperplasia, but to a defective resistance of the walls of the tubules, in particular of the basement membrane, which allowed dilatation under the normal pressure of the secreted fluid they contained.

Quite a group of recent writers have taken what may be termed a middle position between the neoplastic and malformation theories. Thus Couvelaire[43] objects to the consideration of the lesion as a tumor of the cystoma or adenocystoma type, and concludes that the process which leads to the cystic transformation consists essentially in an exuberant but general proliferation of the epithelial cells of the excretory ducts, with a correlated reactive growth of the connective tissue. The specific character of the cells is lost. This hyperplasia and perversion in the evolution of the cellular elements take place while the organ is developing and is to be considered as a malformation in that sense. Borst,[44] though retaining the lesion among the cystic adenofibromata, considers the process as an error of development,

[38] *Verh. der deutsch. path. Gesellsch.*, 1899, 2te Tagung, 187.
[39] *Virchow's Archiv*, 1903, clxxiii, 209.
[40] Loc. cit.
[41] *Trans. of the Path. Soc.*, London, 1886, xxvii, 287.
[42] *Arch. de méd.*, 1890, ii, 151.
[43] *Annales de gynêc. et d'obstet.*, 1899, lii, 453.
[44] Loc. cit. and Die Lehre von der Geschwülsten, 1902, p. 596.

not in the sense of Ribbert, but in a disturbance of equilibrium between the growth of epithelium and connective tissue, the *sine qua non* for the normal development of an organ. In the cystic liver and kidney, he postulates a failure of the epithelium to develop in a normal way, as the result of a pathological agent, and to possess an increased power of growth. As a result, the connective tissue is invaded. Luzzatto [45] concludes that the pathogenesis of the cystic kidney is not uniform: that in a small number of cases—the shrunken cystic kidneys—the lesion is a result of an interstitial nephritis of fœtal origin; that in the more common type it is to be regarded as either a malformation or a tumor of congenital origin, between which he is unable to draw a sharp line. Still he is inclined to include four congenital cases of his study under the fibrocystadenomata, and a fifth under malformations, due to an excessive development of connective tissue in the organ.

Dunger [46] recognizes an inflammatory type, but also places the more common in the unsettled province between congenital neoplasms and malformations. He considers the primary factor, however, an error in development, with a secondary proliferation of the epithelial and connective tissues.

In considering these theories from the standpoint of the cases here presented, one notices first that the kidneys offer no evidence whatever in support of the obstruction and retention theory. The urinary path was open throughout from pelvis to urethral orifice. The children lived eleven and nineteen days respectively and passed urine freely. In the kidney the microscopical sections showed the orifices of the ducts of Bellini free and if anything wider than normal. In the kidneys of child "B" there was practically no increase in the interstitial tissue to cause constriction of the tubules. The tubules were in great part free from other than fluid content, and uric-acid deposits and casts, though present, were for the greater part in the least dilated tubules.

While studying these cases, the author has had opportunity

[45] Loc. cit.
[46] Loc. cit.

to compare the picture afforded by the congenital cystic kidney with that of a congenital hydronephrosis following a stricture of the ureter (Autopsy 2504), in a child which lived but a few days after delivery. The sections of the two lesions were entirely different. In the hydronephrosis there was but moderate dilatation of the ducts of the pyramids, with beginning flattening of the papilla and a beginning proliferation of the interstitial tissue near the mouths of the ducts. There was no indication of active growth of the epithelium. Further, the dilatation of the tubules consequent on the damming back of the urine was noticed not only in the medulla, but also in the cortex, in the convoluted tubules where the lumen was wide and the epithelium somewhat flattened, and even in the glomeruli where the capsules were considerably dilated. In the congenital cystic kidneys, on the other hand, the tubules of the secreting type in the cortex and the glomeruli, with very few exceptions, were entirely unaffected.

These cases then give absolutely no support to the theories which refer the lesion to obstruction and retention. There is as little evidence afforded to support the idea of any malformation or error in development of the kidneys in the sense of Hildebrand and Ribbert—that is, of a failure of the two sets of tubules to join with each other. The glomeruli and cortical tubules were well formed and apparently normal in number. The loops of Henle were possibly somewhat shorter and less well developed than in kidneys of an equal age, but this was the only possible deviation from the normal. If there were a failure of union, one would expect a dilatation of the convoluted tubules or glomeruli due to retained secretion. But in these kidneys no such dilatation was found, and, though the cystic formation was diffuse throughout the kidney, there was anatomical and physiological evidence that the urinary path from glomerulus to pelvis was free.

The sole malformation, if it may be called such, was an active proliferation of the epithelium of the collecting ducts of the medulla and of the junctional tubules in the cortex, chiefly in the inner part. Of such active proliferation, there was positive evidence in the numerous mitotic figures found in the epithelial

lining of the cysts in child "B." The absence of an increase of connective-tissue growth in the kidney of this child and its presence in that of the other seems evidence also that such sclerosis is a secondary phenomenon. In the kidney I was unable to satisfy myself that there was an excessive formation of tubules. In the liver, on the other hand, where that point is more easily determined from the architecture of the organ, the ducts were not only larger than normal but much more numerous, and in many cases penetrated the lobules almost to the central vein. There seems no question that one must consider the processes in the two organs as essentially the same, and this suggests the possibility that some of the cystic tubules in the labyrinth of the kidney cortex, which clearly showed a connection with the ducts of the medullary rays, but which much less rarely could be found to continue into tubules of the secreting type, were new-formed tubules, analogous to those ducts of the liver which penetrated the lobule. The condition in some particulars thus resembles a neoplasm, yet it is as readily considered a malformation in the sense of an abnormal power of growth of the duct epithelium. If one accepts the Cohnheim theory for the origin of certain tumors in the congenital misplacement of tissues, an error in development, there is no sharp line between the two conditions. However, it seems to the author scarcely appropriate to term the congenital cystic kidney an adenocystoma. Instead of a localized growth more or less sharply outlined from normal tissue, one finds here a diffuse and widespread influence affecting the conducting tubules generally in the kidney, liver, and pancreas, and even possibly in the intestine. The occurrence of multiple tumors in the body is not unusual, but it is to be regarded more or less as a coincidence, and in no group of tumors do we have as constant bilateral occurrence as in congenital cystic kidneys, or as frequent an association as is found between that lesion and the cystic liver. Further, in the several organs the abnormal tubules were directly connected with normal parenchyma, and in the kidney there seems physiological and anatomical evidence that in the cases here reported the cystic tubules carried on their normal function of carrying away the secretion from the parenchyma of the

organ. That this functional activity persists for any great length of time I do not maintain. It is readily seen that the increase in the size of the cysts, their encroachment on each other, and the coördinate growth of connective tissue might soon lead to obstruction of a great number of tubules and ducts. This, however, would be a secondary effect.

Primarily, then, one finds evidence of an epithelial hyperplasia in ducts which otherwise appear normal. This leads at first to a general cylindrical increase in the size of the ducts, but gradually there is a greater dilatation at points in the ducts less fixed by the architecture of the organ, and cystic tubules are the result. The expansile force must at first be the normal pressure of the secreted urine, a force which secondarily becomes much greater owing to the mutual pressure of the dilated tubules and consequent obstruction of some of them at various points. It may be objected that a primary weakness of interstitial supporting tissue has not been excluded as the stimulus to the epithelial hyperplasia. To explain why one finds the cystic formation instead of intratubular epithelial growths in case of a primary epithelial hyperplasia, one must assume that the normal urinary pressure is greater than the resistance offered by the supporting kidney tissue. However, that there is any abnormal weakness of this tissue does not necessarily follow, and in fact the specimens offer no evidence of any deficiency in the supporting membrane of the tubules. The tortuosity of certain dilated ducts in the boundary zone, where there appears to be the greatest resistance to expansion, seems an added point in the favor of a primary epithelial process. The position of the lesion in pathological classification would seem to depend on a definition of terms. If it be a neoplasm, it differs from the conditions usually included under that term. If it be a malformation, it is one only in the sense of Couvelaire and Borst—a disproportionate activity in the growth of the epithelium. The frequent occurrence of associated malformations of other parts and organs would appear to indicate that the condition bears a closer relation to malformations than to new growths in the commonly accepted interpretation of the latter term.

From the marked hereditary and family tendency shown in the disease, one is led to search for the etiological factor in the parents. Where the condition has appeared in two generations it has generally been transmitted from father to son and from mother to daughter. Where it appears in several members of one generation, several successive children of either sex may be affected or healthy children may intervene. In one case, Singer's, there was a definite regularity in the appearance of the disease, every third child of thirteen having shown cystic kidneys. The condition then in the parent which determines the lesion in the child is not always operative. What this factor is must for the present be left undetermined.

The abbreviated autopsy protocols of the two cases are as follows:

AUTOPSY No. 2291. April 28, 1904. Post-mortem examination on Baby F. (child "A"), aged 11 days.

The body is that of a small but well-formed colored male infant, 44 cm. in length. There is some desquamation of the epidermis from the arms and hands, and there are signs of nasal discharge. The abdominal cavity shows a slight excess of clear fluid with marked œdema of the retroperitoneal tissues. The pleural and pericardial cavities are normal.

The heart is of about normal size, and, except for marked distension of the coronary veins, is normal throughout.

The lungs are of pinkish color, deepening to a red in the posterior portion, and crepitate throughout. On section they show marked congestion of the vessels, and the cut surface is moist.

The spleen measures 4 x 2.5 x 15. cm. and is dark red in color. On section the pulp is increased in amount, obscuring the architecture of the organ; Malpighian corpuscles visible.

The liver is about normal in size with smooth regular surface. On section it has a dark purplish color, mottled with areas of light grayish translucent appearance, which are leaf-like in shape. These areas seem firmer than the liver parenchyma. There are scattered throughout the organ also, small light colored areas which are just visible. The limits of the lobules cannot easily be made out. There is an increase in the connective tissue about the larger vessels. The gall bladder and ducts appear normal.

The pancreas, stomach, and intestine show no definite lesions.

The kidneys are described on page 276.

Adrenals, testicles, and epididymes show no lesions.

The lines of ossification in the femur and tibia are sharp, clean cut, and regular

Aorta and branches are normal.

Microscopical examination. With the exception of the organs described no lesions of importance were found.

Liver. See page 278.

Pancreas. The secreting parenchyma is well formed. Many of the cells contain clear spaces and vacuoles. The ducts are prominent in the section, are dilated, are more branched, and seem comparatively more numerous than in other pancreases of this age.

Kidney. See page 277.

Anatomical diagnosis. Congenital cystic kidneys and liver; catarrhal enteritis. Acute splenic tumor.

AUTOPSY 2515. April 10, 1905. Baby F. (child "B"), aged 19 days.

The body is that of an emaciated colored female child, 42.5 cm. in length. There are no external lesions.

The serous cavities show no lesions.

The heart is of about normal size, and the cavities are filled with rather thick unclotted blood. The valves, endocardium, and myocardium are normal.

The left lung is of light pinkish color, is dry on section, and crepitates throughout. The right lung resembles the left.

The spleen is enlarged and measures 5 x 3 x 1.5 cm. On section the pulp, which is of dark brownish red color, seems increased in amount. The Malpighian corpuscles are enlarged.

The liver is small measuring 10 x 5.5 x 3 cm. The surface is smooth and glistening and the organ seems normally formed. The color is a deep brown. On section the brownish surface shows everywhere leaf-like grayish translucent areas, apparently representing enlarged portal spaces. Otherwise the architecture of the organ cannot be made out. The gall bladder contains a small amount of thick greenish bile. The ducts appear normal.

The pancreas appears normal in size and texture, with no increase in its stroma.

The stomach is distended. Its mucosa is swollen, injected, and covered with thick mucus.

The intestine shows a greenish fluid fæcal content, and considerable mucus on its epithelial surface. The mucosa is injected at intervals throughout its length, and is swollen and velvety.

Mesenteric lymph glands are enlarged, opaque whitish in color, and soft and moist to the touch.

The left kidney is slightly enlarged, and measures 5 x 2.7 x 2.5 cm.; the right measures 4.5 x 2.8 x 2.4 cm. For description see page 275.

The adrenals show no lesion. The bladder and genitalia are normal throughout.

The lines of ossification at the lower end of the femur and upper end of the tibia are sharp and clean cut, not thickened or irregular.

MICROSCOPICAL EXAMINATION—Liver. See page 277.

Pancreas. See page 278.

Duodenum. See page 278.

Kidney. See page 275.

The lesions in the other organs are not of interest.

Anatomical diagnosis. Congenital cystic kidney, liver, and pancreas; acute catarrhal gastro-enteritis; acute splenic tumor; acute mesenteric lymphadenitis.