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Familial Bilateral Renal Agenesis and Hereditary Renal Adysplasia*

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Abstract. This paper reports three kindreds (A, B, C) with familial bilateral renal agenesis (BRA). Etiologically, BRA is considered a multifactorially determined disorder; pathogenetically it is viewed as a developmental field defect involving absence of both kidneys and ureters in all cases, and in other cases an associated spectrum of related field defects which range from absence of the uterus and vagina to sirenomelia. In BRA, Potter's syndrome represents a symptomatic deformity complex due to oligohydramnios.

Two additional kindreds (D and E) in this paper show that unilateral absence of a kidney may occur in relatives of a propositus with severe bilateral renal "adysplasia". The former defect is designated "unilateral renal aplasia" and is presumed to be a less severe form of bilateral renal adysplasia. In these two families, and in two others from the literature, autosomal dominant inheritance seems responsible for the presence of unilateral aplasia and bilateral adysplasia in different family members; this newly recognized genetic trait is being designated "hereditary renal adysplasia (HRA)". In women with unilateral renal aplasia the associated tubal and uterine malformation may be responsible for prematurity plus an increased risk of spontaneous abortion.

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Introduction

In 1946 Potter called attention to the facial appearance of infants with bilateral renal agenesis [15, 16]. Since then the term "Potter's syndrome" has been variably applied either to the facial appearance and associated deformities of such infants alone, or to the entire condition of renal agenesis, facial appearance and associated deformities. Potter has also made the distinction between complete bilateral absence of kidneys and ureters ("complete, or primary renal agenesis") and "secondary agenesis or aplasia" in which ureteral vestiges with or without rudimentary renal tissue may be present [18, 19]. In 1965 she stated that if ". . . no kidney tissue can be identified but ureters are present, the pathogenesis is probably different (from that of primary renal agenesis) and such cases should be placed in a different category (i.e., "secondary agenesis or aplasia") [18]. In her recent book, Normal and Abnormal Development of the Kidney [19], she cited three publications on the occurrence of renal agenesis in siblings, and the fact that one of us (J.M.O.) had observed another three instances of siblings involvement. We know of only four published instances in which more than one sibling in a sibship had been affected [1, 11, 20, 23]. In this paper we are reporting the familial occurrence of presumed or proven renal agenesis and renal aplasia in five different families.

Case Reports

Family A (Fig. 1)

Case 1. This premature male infant was born to a gravida 1, para 0, 21-year-old white woman. Her pregnancy was uncomplicated until the onset of premature labor during the 26th week of gestation. She delivered a male infant who weighed 1050 g and who died immediately after delivery.

Postmortem Findings. There was asymmetry of the head due to overlap of the cranial bones and the presence of a caput succedaneum over the parieto-occipital region. The face was also asymmetrical. The nose was flat. The ears were slightly enlarged and their insertion appeared to be lower than normal. There was a bilateral clubfoot deformity. Both lungs were markedly "atelectatic and contracted". There was no appreciable functional lung parenchyma. There was a patent ductus arteriosus and foramen ovale. Both kidneys and ureters were absent. The urinary bladder was represented only as a hypoplastic tube-like structure. The testes could not be found in the scrotum or abdominal cavity.

Case 2. The second child of this family was born on March 16, 1972. At that time the mother was 22 years old and was in her 28—30th week of gestation.

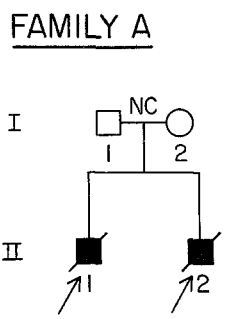

Fig. 1. Family A. NC = non-consanguineous; arrows point to propositi; diagonal slash through pedigree symbol: patient dead

Pregnancy and deliwery were uncomplicated. The male infant weighed 1160 g and had an initial Apgar score of 3; he died after 46 min.

Postmortem Findings. He had flattening of the nose, recession of the chin, "low set ears", "polydactly" of the right hand (not stated whether pre- or postaxial), ulnar deviation of the index fingers, bilateral talipes equinovarus and a "left epicanthic fold". All extremities had flexion contractures. There was bilateral "congestion" of the base of the lungs. Sections showed immature lung parenchyma. In one area there was marked cystic dilatation of the bronchi. A patent ductus arteriosus was present. Both kidneys and treters were absent; a "small round structure which resembled a hypoplastic urinary bladder" was identified in the bladder area.

Family B (Referred by Dr. R.L. Kochell, Janesville, Wis.) (Fig. 2)

Case 3 (III—19). The first pregnancy of a young and healthy, nonconsanguineous couple terminated on 1/8/1966 at 34 weeks with spontaneous onset of labor and frank breech delivery of an 1814 g male infant who died after 80 min. The baby was 42.5 cm long and at a limited autopsy he was found to have: "deformity of auricles, broad and flattened nose, redundance of skin, short neck, flexion deformity of both arms, bilateral equinovarus (deformity) of feet (bilateral), atelectasis, micrognathia, bilateral renal and ureteral agenesis, rudimentary urinary bladder, minor mesenteric anomalies with peritonealization of right colon".

The pregnancy of this 18-year-old mother had been unremarkable except for minimal abdominal enlargement and a weight gain of only 6.8 kg. She had anisocoria (right pupil larger than left) for "several years"; her left second toe was described as a hammer toe. She had never had an intravenous pyelographic study.

Her second pregnancy (III—20) terminated on 6/30/1966 at 16 weeks after several days of bleeding, cramping and passage of clots. The specimens obtained on dilatation and curettage were found to consist of placenta with empty amniotic sac and endometrial tissue.

A third pregnancy (III—21) resulted on 12/20/1967 in the birth at term of a female infant who was examined (J.M.O.) on 1/20/1969 and found to be normal. No intravenous pyelographic study has been done on her.

Her fourth pregnancy (III—22) terminated at 36 weeks on 8/12/1968 after an otherwise unremarkable pregnancy in the birth of a male infant weighing 1587 g with "low set ears", flat occiput, short, spade-like hands, webbing of the three middle digits of both hands and feet" (but not polydactyly), bilateral clubfoot

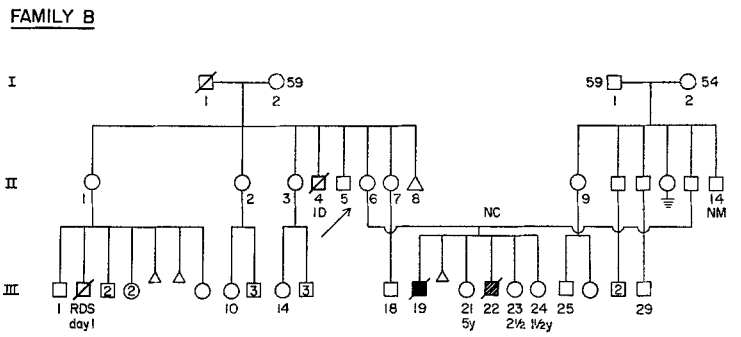

Fig. 2. Family B. Small triangle raised above sibship line = spontaneous abortion. Symbol "grounded" (as II—12): no offspring produced during years of potential fertility. NM: not married. RDS: respiratory distress syndrome. Solid color: proven case of bilateral renal agenesis; cross-hatched symbol: possibly affected. Male infant deaths (ID) in solid outline (II—4, III—2). Other Arabic numerals indicate age

deformity, and non-palpable kidneys. The infant was cyanotic, did not cry, had poor muscle tone and died after 3 hrs of respiratory failure. No autopsy was done, but the pediatrician, Dr. John R. Schroder of Janesville, Wisconsin, conceded that this child may also have had bilateral renal agenesis. Two normal girls (III—23, 24) were born recently.

Review of family history showed that the maternal grandmother had 8 pregnancies: 5 normal girls, one male infant who was born prematurely at 6 months and who died soon after birth II—4, a spontaneous abortion (II—8), and a boy who was born with a severe arthrogryposis-like condition and IQ of about 70 who is now institutionalized at Northern Wisconsin Colony and Training School at Chippewa Falls (II—5). To date, it has not been possible to examine this boy or to do an intraveneous pyelographic study on him. Mother's oldest sister had 9 pregnancies including two spontaneous abortions, three normal boys and three normal girls, as well as one male infant who died of respiratory distress on day one. Father's family history is unremarkable.

Family C (Referred by Dr. Jay E. Houlahan, Mason City, Iowa) (Fig. 3)

This family has been counseled by correspondence and is presently incompletely documented.

Case 4. The first pregnancy (IV—15) of this couple terminated in 1955 at 36—37 weeks in the birth of a male infant measuring 44.5 cm, weighing approximately 1814 g with: "bilateral renal agenesis, cryptorchidism, terminal rectal atresia with imperforate anus, pulmonary hypoplasia and patency of the ductus arteriosus. The bladder 'had the shape of a truncated cone'; it was empty and its lumen was very small. Short cord-like structures extended up its lateral margins ... these ... did not possess identifiable lumina, but their locations suggest that they represent rudimentary ureters. They did not extend to their respective renal areas."

In 1957 and again in 1961 this couple had a normal girl (IV—16, 17).

In 1963 the mother delivered a male infant at 38—39 weeks who died after 2 hrs and who is presumed to have had renal agenesis. No autopsy was done on this child, but there had been oligohydramnios.

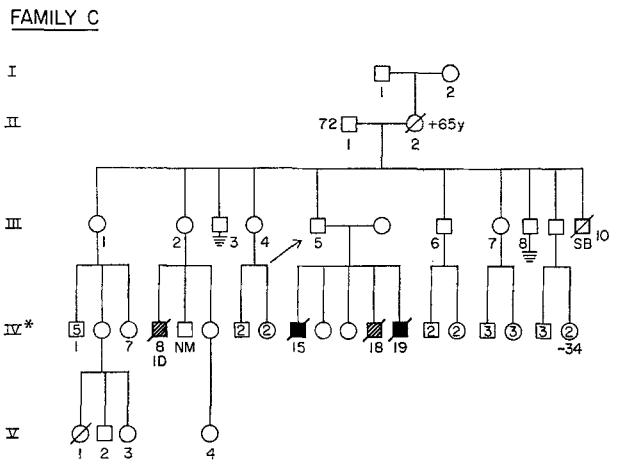

Fig. 3. Family C. I—1 and I—2 were first cousins; asterisk indicates that the order of some sibships in generation IV is not known. IV—15 is case 4: spurious ureters?

Case 5. Her fifth pregnancy terminated in 1969 in the birth of a male infant measuring 43 cm, weighing 1908 g, "with Potter's facies, large, soft and flat ears, bilateral renal and ureteral agenesis, thin, tubular bladder to umbilicus with minute lumes, cryptorchidism, and a normal gastrointestinal tract".

Mother's family history is unremarkable, but the father's family history revealed five items of possible interest. He was one of 10 siblings who were all normal except for the last who was a full-term stillborn male (III—10). Father's second oldest sister (III—2) has had a normal boy and a normal girl, and in addition a male infant (IV—8) "who died at 6 days of life and who had no lower gastrointestinal tract and no anal opening". According to the mother, this infant was operated on and autopsied and had no kidneys; however, we were unable to verify these data in the infant's chart at the Bethesda General Hospital, Fort Dodge, Iowa (former Lutheran Hospital). It was noted by the record librarian that the chart appeared incomplete; however, a check with the funeral home that handled the infant's burial supported the conclusion that he had not been autopsied. One of the father's nieces (IV—6) (daughter of a sister) had an infant girl (V—1) who "was born at 6½ months, lived only a few minutes and who had stopped developing earlier in pregnancy".

Father's maternal grandparents were first cousins; and two of father's brothers (III—3, 8) have had childless marriages.

Family D (Referred by Dr. J.F. Maser, Rice Lake, Wisconsin) (Fig. 4)

Baby boy C. S. (III—9) was the first child of a 23-year-old woman and her 26-year-old husband. The infant was delivered at 38 weeks of gestation after an otherwise normal pregnancy; it weighed 2240 g, had "collapsed lungs", a "deformed leg" and lived only 1 hr. No autopsy was done. It is possible that this child had renal agenesis.

Later in 1968 the mother suffered a spontaneous abortion at 3 months of pregnancy.

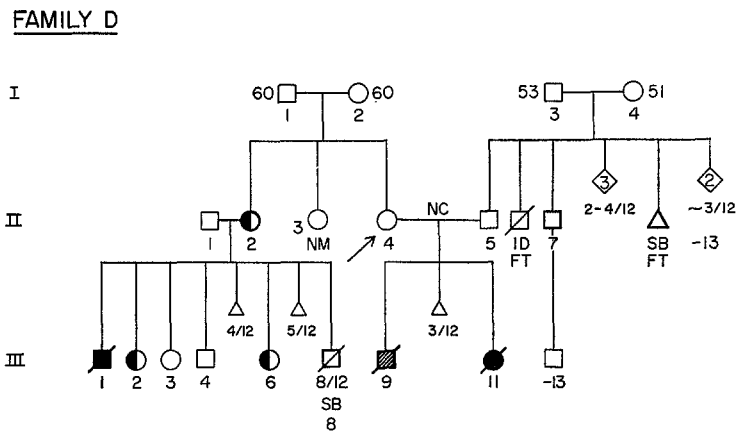

Fig. 4. Family D. Large triangle pedigree symbol on sibship line: fullterm stillborn (FT, SB) infant, sex unknown. Small diamonds (with Arabic numerals): several spontaneous abortions. Half-solid symbol (e.g. II—2): unilateral renal agenesis. Line over pedigree symbol (e.g. II—4): personally examined. III—3 has normal intravenous pyelograms

Case 6. On 12/20/1970 the mother went into spontaneous labor after an uneventful 32 week gestation and delivered a stillborn female infant (III—11) who weighed 1588 g and who was noted to have dense, bilateral cataracts. Autopsy was performed and did not reveal any abnormalities except for "complete renal agenesis". No other autopsy data are available on case 6, however, the pathologist kindly made paraffin sections of the case available; the Feulgen stain showed that the infant was sex chromatin positive.

Review of family history shows that parents were not consanguineous. The father was the first of his mother's 9 pregnancies which resulted in five early spontaneous abortions, an infant of unknown sex stillborn at term, an apparently normal term male infant who died at 3 days of unknown cause, as well as the father and his normal brother.

The mother (II—4) was the youngest of 3 sisters; she is healthy and intravenous pyelograms show that she "has a normal urinary system including two kidneys". The middle sister is unmarried. The oldest sister (II—2) is 41 years old and has had 8 pregnancies — in order of birth — a male with renal aplasia (case 7), two normal girls, a normal but enuretic male, a spontaneous abortion at 4 months, another normal girl and a spontaneous abortion at 5 months (sex unknown).

In August, 1965, she delivered a macerated stillborn male infant after a 36 week gestation at St. Joseph's Hospital in Marshfield, Wisconsin; no autopsy was done on him. Tests during a subsequent postpartum check provided evidence of a cervical carcinoma in situ, and a salpingohysterectomy was performed at the same hospital. During surgery it was discovered that her left kidney and fallopian tube were absent; she had a uterus bicornis with normal right fallopian tube. Intravenous pyelograms on two of her daughters (III—2 and III—6) show that both lack a left kidney and that their right kidney is larger than normal (Dr. J. W. Koch, Colby Clinic, Wisconsin).

Case 7. Baby boy B (III—1) was delivered after an uneventful gestation at 32 weeks from a breech position; he died after 2 hrs. He weighed 1560 g and measu-

red 42 cm. The external appearance was described as normal "except for cyanosis and rigor mortis of the knee and elbow joints". The left testis was undescended. The pathologist reports that "there was no evidence of kidneys except a firm, pea-size bit of reddish tissue at an upper end of an enlarged left ureteral structure. The urinary structures ... are not well defined except for the still-patent urachus. A rudimentary bladder sac is connected with bilateral ureter, enlarged and distended with straw colored fluid. No evidence of renal tissue is found microscopically, but the left abdominal testis is identified".

Family E (Referred by Dr. C.A. Andringa, Madison, Wisconsin) (Fig. 5)

On 7/5/1967 a presently 24-year-old woman delivered a 1644 g female infant (IV—9) who died at 2 hrs of prematurity. Examination at the time of delivery showed that she had a bifid uterus, and pyelograms revealed absence of the right kidney. In 1967 she was operated on in New York by a physician "who sewed the two halves of the uterus together". On 10/24/1968 she was delivered by caesarean section of a 3122 g male infant (IV—10) who died at 27 hrs of hyaline membrane disease at the Neonatal Intensive Care Nursery of St. Mary's Hospital Medical Center in Madison; at autopsy the kidneys were found to be normal. On 1/28/1970 she delivered vaginally but prematurely a 1928 g female (IV—11) who is living. That child has had urinary tract infections and examinations showed that she has both kidneys but bilateral ureteral reflux which is being treated with antibiotics.

Case 8. On 8/26/1972 she delivered spontaneously a 1914 g, 3 week male infant from a breech position (IV—11); there had been marked oligohydramnios. The infant had Potter's syndrome, marked respiratory distress and he died at 20 hrs. At autopsy he was found to have agenesis of the right kidney and ureter, severe hypoplasia of the left kidney and ureter with stenosis of the proximal left ureter, marked hypoplasia of the adrenal glands and iliac arteries, abdominal cryptorchidism of the right testis, severe hypoplasia of both lungs with pulmonary lymphangiectasia and bronchogenic cystic disease.

Review of mother's family history shows that she is the fifth of nine siblings who are all living and well except for the youngest (III—9) who is 14 years old

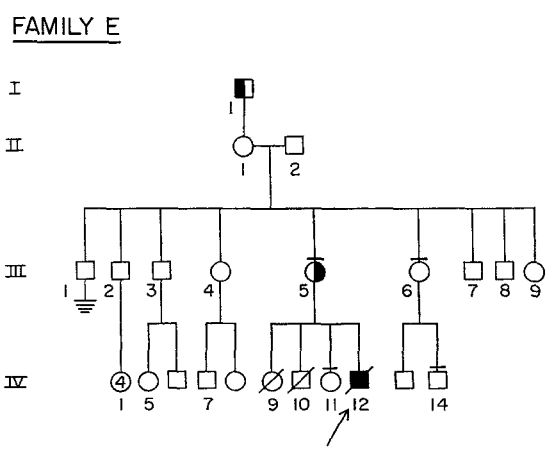

Fig. 5. Family E. See text

and who has had a chronic vaginal discharge, similar to the discharge the mother had at the same age and which she attributes to her genital malformation. The younger (IV—14) of mother's sister's (II—7) two boys is known to have a multiple congenital anomaly/mental retardation (MCA/MR) syndrome due to a deletion of the long arm of one of his number 18 chromosomes. Mother's parents (II—1, 2) are living and well, and mother's maternal grandfather (I—1) is living and well at the age of 80 years. However, at the age of 72 years, the latter developed apparently for the first time in his life a severe urinary tract infection requiring hospitalization. Intravenous pyelography at that time showed that he had only one kidney.

Documentation of families D and E is presently incomplete and will be published in greater detail elsewhere.

Discussion

Phenotypic Aspects

General Considerations. The writings of Potter [15—19] and the papers by von Stockhausen [25] and Davidson and Ross [6] deal admirably with the phenotypic aspects of renal agenesis. The term *Potter's syndrome* has been used to refer to the effects of pathogenetically non-specific absence or severe reduction of amniotic fluid (oligohydramnios); however, many persons believe that this designation should be applied only to cases of oligohydramnios of renal origin and that the presence of Potter's syndrome in a fetus or newborn infant invariably indicates renal agenesis. We have seen the Potter syndrome in a case of abdominal pregnancy, in a "dry" pregnancy (attempted abortion with continuous amniotic fluid leak till term) and in a diverse variety of cases of genitourinary obstruction without associated renal agenesis or aplasia. Potter has stated [19] that the facial appearance of these infants appears to be related to the absence of intrauterine renal excretion rather than absence of kidneys per se. Potter's syndrome, which affects primarily the face, ears, and extremities can be viewed as a symptomatic deformity complex.

A *symptomatic deformity complex* (SDC) is defined as the presence at birth of deformities which are symptomatic of an underlying functional disturbance. If the SDC is due to an anomaly (e.g. spina bifida with resulting deformities of the lower extremities) then the entire condition is designated as *anomaly-symptomatic deformity complex* (A-SDC); if an anomaly of differentiation can reasonably be explained as another manifestation of the underlying functional abnormality (e.g. cleft palate in association with oligohydramnios) the condition is designated a *symptomatic anomaly (complex)* (SAC). Most of the gross and well known congenital SDCs (the oligohydramnios SDC = Potter's syndrome, the manifold hypotonia SDCs and SDCs due to disturbances of prenatal muscle movements — a.o. the "arthrogryposes") — are etiologically

non-specific; the pathogenetic import of these manifestations should be interpreted correctly and etiology should be searched for as soon after birth as possible.

Absence or severe reduction of amniotic fluid restricts fetal movements and leads to the many diverse and well documented deformities of the extremities that are seen in infants with renal agenesis; close apposition (pressing) of the nose and auricles against the uterine wall results in flattening and pushing-over of the tip of the nose and presumably in the softness and flattening of the auricles. Potter (pers. comm. 1973) thinks that oligohydramnios does not explain all of the ear defects and that true anomalies of auricular differentiation may also be present in infants with Potter's syndrome. Flattening and congenital modeling and folding defects can be attributed to oligohydramnios without difficulty; a review of many published photos of infants with the Potter syndrome suggests to us that true anomalies of differentiation (unusual degrees of posterior angulation, "low-setness", true dysmorphogenetic defects) of the auricles, are present only in cases of renal agenesis associated with true multiple congenital anomaly (MCA) syndromes; in cases of "pure" renal agenesis they do not seem to be present with increased frequency. The frequent presence of oligohydramnios in the 18 trisomy syndrome may be a reason for the similarity of some of the ear findings in that syndrome to those of infants with pure renal agenesis. The presence of micrognathia may perhaps be attributed to diminished swallowing movements by the fetus. Cleft palate has been observed and might occur in a manner analogous to that of the rat in which amniocentesis and experimental oligohydramnios presumably causes the tongue to remain interposed between the palatal shelves with subsequent failure of these shelves to fuse [7]. The combination of cleft palate and micrognathia is known as the Pierre Robin syndrome. It is of importance to point out in this connection that the Pierre Robin syndrome is an etiologically non-specific and pathogenetically heterogeneous SAC [9] which may result not only from oligohydramnios, but which is also seen in skeletal and connective tissue dysplasias (preeminently the Stickler syndrome [9]), and in a variety of conditions associated with prenatal muscle and movement disorders. Its presence in diverse true MCA syndromes (e.g. the 18 trisomy syndrome) may reflect any one or several of the aforementioned functional disturbances and/or a true anomaly of differentiation. The fetus with renal agenesis has little or no amniotic fluid to circulate through its lungs; it is usually born with pulmonary hypoplasia and usually dies of respiratory failure before the onset of uremia. The redundancy of skin, which is remarkable in some cases, has not been explained in a satisfactory manner. The high frequency of breech presentation must also be due to oligohydramnios.

Various combinations of Potter syndrome manifestations were present in most of the cases reported above.

Bilateral Renal Agenesis (BRA). BRA was present in 5 (possibly 7) patients in families A, B and C. BRA can be viewed as a *developmental field complex* (DFC). This term is not the exact equivalent of D. W. Smith's "single syndromic malformation" [24], since the latter is applied by Smith to DFC plus SDC combinations. The DFC is defined as occurrence of two or more anomalies in a single organ, organ system or region of the body due to a single underlying developmental defect [13]. The alobar holoprosencephaly DFC is a prototypic and particularly instructive example of this class of congenital anomalies. In a developmental sequence the ultimate defect which could be implicated as the direct cause of primary bilateral renal agenesis is an anomaly of the ureteric buds, either due to atrophy after budding, or failure of the buds to sprout normally from the caudal mesonephric duct. (Hypoplasia of the bladder which is usually seen, and "agenesis" or "atresia of the urethra" which is commonly seen in bilateral renal agenesis [25, 6] presumably represents "disuse atrophy" and can be considered "symptomatic anomalies"). The caudal mesonephric duct may be the primarily defective anlage in this DFC, however, the common association of bilateral renal agenesis with absence of the trigone of the bladder, imperforate anus, terminal rectal atresia as well as absence of the vagina and uterus suggests that the DFC of bilateral renal agenesis usually involves a much more complex and extensive disturbance of embryonic induction and differentiation than simple failure of the ureteric buds to sprout and to induce metanephros normally. Potter suggests much the same in a scheme (Fig. 10 [18]) which is reproduced as Figs. 2—15 (p. 98) in her book on the kidney [19]. We think that her "field" A: "area of abnormality limited to the lower portion of mesonephric and paramesonephric ducts"; "field B": "area of abnormality [which] includes hindgut and cloacal membrane"; and "field" C: "area of abnormality [which] includes entire caudal end of embryo" represent three different degrees of involvement of *the same* developmental field:

A. The "mildest" form of this DFC (involvement of field A) then is bilateral agenesis of kidneys and ureters, usually with apparently normal Fallopian tubes but absence of uterus and vagina (or bicornuate uterus with absence of vagina) in females, and, according to von Stockhausen [25] and Davidson and Ross [6], absence of ductus deferens and seminal vesicles in males.

B. The "intermediate" degree of severity (involvement of field B) is represented by the above plus imperforate anus usually with atresia of the terminal hindgut, with or without recto-vesical or rectovaginal fistula, at times with morphological defects of the male external genitalia (hypo-

plasia of phallus, hypoplasia or absence of scrotum) or female external genitalia (hypertrophy of phallic tubercle with formation of male urethra [4, 22]).

C. The most severe degree of involvement of the same field (field C in Potter's scheme) is represented by the sirenomelic "monsters".

The same considerations apply to the alobar holoprosencephaly DFC [8] where involvement may range from arrhinencephaly with a minor midline notch of the upper lip to an apparent cyclopian defect with true alobar holoprosencephaly, a rudiment of single midline optic nerve without cyclopian eyeball, primary palate or nose.

Like the alobar holoprosencephaly DFC the renal agenesis DFC is also etiologically non-specific, and like it can be seen as a single isolated anomaly or as part of a true multiple congenital anomaly (MCA) syndrome. The former may be seen in the D1 (13) trisomy syndrome, the 13q— and the 18p— syndromes, and as an autosomal recessively inherited disorder. In case of the latter it is difficult to estimate what proportion occurs as an isolated anomaly or as part of a true MCA syndrome, since so many authors look upon the various manifestations of the Potter SDC and SAC as true primary, unrelated congenital anomalies rather than for what they are. Potter reports [19] that "in 11 of 50 infants (including 2 of 8 sirenomelic 'monsters') major cardiac malformations were present. Hydrocephalus was present in 8 infants, but in 6 was probably secondary to spina bifida or partial absence of the lower spine. In 11 additional infants (exclusive of sirenomelia) there were other abnormalities of the skeleton; in one the sacrum and in 2 the lumbar spine was absent; in 4 some of the bones of the upper extremities (radius aplasia, q.v. [16]), ribs, cervical and/or thoracic vertebrae were absent . . ." We are distinctly impressed that some of these latter cases may include the "caudal regression syndrome" seen in infants of diabetic or pre-diabetic mothers, and possibly also severe cases of the cerebro-ano-radial (CAR) syndrome and of the spino-auriculo-radio-renal (SPARR) syndrome [14]. In addition, Potter mentions two infants with webbed knees, one with arthyrogryposis and one with hyperextensibility of the knees. The only other abnormalities she cites were "harelip and cleft palate in 3; absent external ears and microphthalmia in one, diaphragmatic hernia in 2; and single umbilical artery in 6 [19]". From these data it is impossible to draw conclusions concerning the ratio of pure renal agenesis to MCA syndromes in these 50 cases.

Hereditary Renal Adysplasia. It is evident that case 7 and case 8 did not have classical BRA but rather an incomplete and asymmetrical form of renal "aplasia". Aplasia is not a strictly correct use of the term in this context, since kidney rudiments were grossly and microscopically discernible in cases 7 and 8. "Renal dysplasia" has become almost syn-

onymous with polycystic kidneys type II. Dr. Edith Potter suggests that the condition of cases 6—8 be designated the renal agenesis-aplasia syndrome. However, we agree that the term (bilateral renal) agenesis be applied solely to the entity seen in cases 1—5. To resolve various suggestions on what the condition of cases 6—8 be called and the conflicts with the existing terminology we combined aplasia and dysplasia into one word and called it: (hereditary renal) *adysplasia* (HRA). We suggest the term "adysplasia" be applied only to bilaterally paired organs, such as the kidneys, in order to avoid the objection that an absent organ cannot be aplastic. The term is to imply predominantly *asymmetric* involvement, less commonly bilateral aplasia or symmetrical degrees of dysplasia. With respect to hereditary renal adysplasia the following clinical and pathological possibilities can be tabulated in summary fashion:

	RD or RS[a]	RS or RD
1.	N?	N?
2.	N?	a
3.	N?	d1—4
4.	d1—4	d1—4
5.	d1—4	a
6.	a	a

[a] RD = right kidney, RS = left kidney, N = normal, a = aplasia, d = dysplasia.

(1) Apparently normal kidneys (on intravenous pyelography) in known HRA heterozygotes (such as II-4 in family D); the question mark is to denote the possibility that these kidneys may not be normal microscopically.

(2) Unilateral renal aplasia; the single kidney being larger than normal (as in II-2, III-2 and III-6 in family D, and I-1 and III-5 in family E).

(3) Unilateral renal dysplasia; severity of dysplasia ranging from 1 (mild) to 4 (most severe) degrees; dysplasia may be cystic?

(4) Bilaterally dysplastic kidneys; (?) may be cystic (q.v. Carbonell-Estrany, quoted by von Stockhausen).

(5) Adysplasia; as in cases 7 and 8.

(6) Bilateral aplasia; as in (?) case 6.

The observations in families D and E suggest two important practical implications. Intravenous pyelograms and careful genealogic studies should be performed in families in which a propositus has died with renal adysplasia in order to inform persons who have only one kidney of that fact for health and genetic reasons. Also the ipsilateral Müllerian duct abnormality in females with unilateral renal aplasia may predispose them to an increased risk of spontaneous abortion and premature delivery and they should be cared for in a high-risk prenatal center associated with

an intensive care premature infant nursery. Autopsy is required in all infants with Potter's syndrome in order to distinguish between BRA (which has a low empiric recurrence risk, see below) and HRA (which seems to be dominantly inherited).

In this connection the so-called *vaginal atresia (Mayer-Rokitansky-Küster or MRK)* syndrome should be mentioned. In this condition the vagina is absent; in one-sixth of (explored) cases reported by Bryan *et al.* [3] uterus, tubes and ovaries were "anatomically normal," in about one-fifth of cases there was no uterus, in 10 of 26 cases tubes and ovaries were normal but the uterus was malformed. About one-half of these women had renal and/or ureteral anomalies; in 6 of 41 women who had pyelograms there was a "solitary kidney". In 10 of Sarto's [21] 11 patients with the MRK syndrome intravenous pyelographic and surgical findings are available; in 5 the kidneys were apparently normal. Sarto's case *C6* had torticollis, abnormal thumbs, a hypoplastic bicornuate uterus, right half of uterus and Fallopian tube filled with blood, large endometrioma of right ovary, "normal" left Fallopian tube and ovary, nonpalpable left kidney; *C8* had a "duplicated left ureter and kidney" which were removed at the age of 7 years; *C58* had a hypoplastic left pelvic kidney; *C86* missed a right kidney and had a spina bifida of D11; and *C90* had congenital heart disease and a single pelvic kidney. In Sarto's study also one half of the women with the MRK syndrome had a renal and/or ureteral anomaly.

Bryan *et al.* [3] mentioned that in 1 of their 100 cases a sister had congenital absence of the vagina, and 2 of their patients had a sister with primary amenorrhea. Sarto [21] found no familial cases, but a case has come to our attention at the University of Wisconsin of a young woman with the MRK syndrome whose mother has unilateral renal agenesis. This is not an uncommon disorder; some 11 of the 50 cases in Sarto's blind cytogenetic study of primary amenorrhea had this condition [21]. Uterus and vagina are affected in the MRK syndrome as in BRA; nevertheless, the asymmetry of renal involvement, and the fact that not every woman with vaginal atresia has a gross renal developmental abnormality, the frequency of associated anomalies and occasional familial occurrence in the MRK syndrome suggest that the etiology of this condition is different from that of BRA even though the same developmental field may be affected in both conditions. In fact, the observation that the mother of a woman with the MRK syndrome had unilateral renal aplasia suggests that HRA and the MRK syndrome are etiologically related and may, in fact, be due to the same autosomal dominant mutation.

Despite the 2:1 male sex preponderance in *unilateral renal aplasia* [26], most authors consider BRA and unilateral renal aplasia different con-

ditions. Potter considers it "probable that unilateral and bilateral agenesis are caused by different mechanisms, in as much as they are accompanied by similar disturbances in the development of paramesonephric ducts. "When only one kidney is absent, the isolateral Fallopian tube is always missing, but when both kidneys are absent the Fallopian tubes are present but uterus and vagina are generally absent or abnormal" [19].

Genetic Considerations

Review of Literature. Occurrence of bilateral renal agenesis in the same sibship is rare, only 4 such cases having been reported to date [1, 11, 20, 23].

In Madisson's report [11] the mother's first pregnancy resulted in the birth of a male at 7 months of gestation; he lived for 16 days and died of unknown cause. The second pregnancy resulted at the 7th month in the birth of a stillborn male who had bilateral renal agenesis on autopsy. A third pregnancy resulted in a full-term normal female. The fourth pregnancy terminated with a full-term male infant who lived 25 min and who had bilateral renal agenesis.

The couple described by Schmidt *et al.* [23] had two normal girls and then two female infants with bilateral renal agenesis.

Baron [1] reported two consecutive male sibs with bilateral renal agenesis born to a mother who had previously delivered a full-term healthy male.

In 1971 Rizza and Downing [20] reported two consecutive female sibs with bilateral renal agenesis. This mother, too, had previously delivered a healthy female.

Other familial cases are cited by von Stockhausen [25] but are inaccessible to us except for the report by Hilson [10]. Here a woman with normal ears and normal intravenous pyelographic study had a girl who died unexpectedly at 6 years and who was found to have only one kidney (at autopsy?); two of her brothers "had left bat-ears and hypospadias but normal pyelograms, but in another the ears, penis and pyelogram were normal". This woman's brother had a "left flabby bat-ear" and a hypospadias ('hooded penis') which was ascertained after birth of his son who died at 8 hrs with the typical facies of renal agenesis and was found "at necroscopy ... to have renal agenesis ... hypospadias, and hypoplastic lungs". Von Stockhausen [25] quotes Carbonell-Estrany to have reported a 10-day-old male infant with renal agenesis; his preceding sister had died on the 3rd day of life and was found to have a hypoplastic cystic kidney. Bound studied an 8-year-old boy whose right kidney was absent and whose mother's uncle had absence of the right kidney [2].

The above personal observations and data from the literature can be sorted into two groups of cases:

A. *Patients with 'primary" bilateral renal agenesis* (BRA). This is a relatively common disorder, occurring once in about 4000 to 5000 births, with a male to female sex ratio of about 3:1. Almost all of the 400 published cases of the disorder were sporadic. Four sibships have been reported, each with two affected siblings [1, 11, 20, 23]. Our studies add another 3 families with 5 proven and 2 possible cases of BRA (families A, B and C, cases 1—5). Familial occurrence in these kindreds is apparently confined to the sibships of the propositi. In the familial cases from the literature, the sex ratio of all sibs is 6 males to 8 females, 4 of each sex being affected. In our cases (families A, B and C) the sex ratio of all sibs is 7 males to 5 females with 5, and possibly all 7 of the males being affected and none of the females being affected. To our knowledge, systematic genetic studies have not been performed on BRA; such a study has now been initiated at the University of Wisconsin. Common occurrence, predominantly sporadic and rare familial occurrence, preponderance of one sex affected, and lack of concordance in the few known pairs of twins [15, 26] suggests that most cases of primary bilateral renal agenesis represent a polygenic-multifactorial trait with "threshold" and an extremely low recurrence risk. If the male sex preponderance in this trait did reflect a significant number of cases due to X-linked inheritance or autosomal dominant mutation(s) with male sex limitation, then familial occurrence should be observed with far greater frequency (unless the trait were usually lethal at an early developmental stage). In each of the 7 sibships reported and reviewed above, the affected infants were all of the same sex: in families A, B, C and those reported by Madisson and Baron [11, 1] they were males, and in the families published by Schmidt *et al.* [23] and Rizza and Downing [20] they were females. In none of the families were males and females affected together in the same sibship. This kind of observation could also be explained on the basis of the homozygous state of two different mutations, one limited in expression to the male sex, the other to the female sex. In either case the recurrence risk would be 1 out of 8. However, the scarcity of familial observations in such a common disorder speaks against autosomal recessive determination of the majority of BRA, and reinforces our hunch (shared by Dr. C. O. Carter) that this is a multifactorial trait. As in other apparently multifactorial traits (e.g. cleft lip with or without cleft palate) male sex preponderance should suggest that female propositi should have a higher frequency of affected sibs than male propositi, i.e. that the recurrence risk following the birth of an affected female is higher than after the birth of an affected male. If, as in other multifactorially determined conditions, greater severity means greater genetic predisposition, then the recurrence risk should be greater following the birth of a "type C" (sirenomelus) propositus (especially if female) than

after a "type B" propositus in which case it should be greater than the risk following the birth of a "type A" propositus. Also, the greater the number of affected propositi in a sibship the greater should be the recurrence risk. At the present time the most common situation will be the birth of a single affected individual into a small sibship. Under the hypothesis of a multifactorial trait with a threshold beyond which there is a risk of malformation, and a risk to first degree relatives (in this case sibs only) of 35 to 40 times the population incidence [5] (estimated at 1:5000 on a crude attempt to exclude true MCA syndromes) the estimated frequency of affected siblings would be 1/140 to 1/125, i.e. less than 1%, a negligibly small risk for practical purposes.

Our sibships A, B and C are remarkable in that they consist only of affected males and normal females. To some extent this reflects undoubtedly biased ascertainment and the fact that none of these families had completed reproduction; but in part it may also reflect the same phenomenon which was discussed by Niswander *et al.* in the cleft lip/palate trait, i.e. greater liability of death for males with increasing genetic liability [12].

B. *Patients with "hereditary renal adysplasia"* (HRA) make up a second group which consists of families D and E, and the kindreds reported by Hilson [10], Bound [2], and Carbonell-Estrany (quoted by von Stockhausen [25]). The evidence from families D and E strongly suggests that this is an autosomal dominant trait with mild expression in females and severe expression in males; however, the data from these two families do not completely rule out X-linked inheritance. The genealogical evidence in Hilson's case 3 definitely excludes X-linked inheritance, but genetic heterogeneity of HRA may exist. In any event, the evidence of Mendelian determination of this trait is strong enough to suggest to physicians involved with such a family that all pertinent relatives have an intravenous pyelographic study performed on them. When this is done in families D and E one would expect with probability 0.5 for D-II-3 and E-II-1 and for each of the individuals in sibships D-III-1-6, and E-III-1-9 to show a renal abnormality. We think that D-II-4 has a high risk of having a renal anomaly, and that either one of her parents may show such an anomaly on autopsy or pyelography. This discussion assumes "complete" penetrance of the trait. The appropriate studies have been requested from collaborating family physicians and initial results confirm the presence of unilateral renal aplasia in D-III-2 and 6, but show apparently normal kidneys in D-II-4 — evidence of reduced penetrance of the renal manifestation of HRA.

Conclusions

This paper presents 8 proven and 3 possible cases of complete or

virtually complete congenital absence of the kidneys, variably associated with manifestations of the "Potter syndrome".

The Potter syndrome is a *symptomatic deformity complex* (SDC) due to oligo- or ahydramnios; this SDC can be further resolved into a *symptomatic anomaly complex* (SAC) (consisting of micrognathia, pulmonary hypoplasia, "atresia" of urethra and hypoplasia of bladder, occasionally cleft palate) and a *symptomatic deformity complex* (SDC) affecting facial appearance and shape of nose, auricles and limbs. The components of the SAC represent true morphological anomalies, the components of the SDC probably all represent deformities of initially normally developed structures; in this case both are symptomatic of a single primary underlying anomaly — namely absence or virtually complete absence of the kidneys. This produces oligohydramnios, a manifestation which need not necessarily indicate absence of kidneys, but primarily failure of renal secretions (if there are any) to reach the outside.

Most cases of *bilateral renal agenesis* (BRA) represent a limited *developmental field complex* (DFC) involving the caudal portions of the Wolffian and Müllerian ducts; more severe cases represent involvement of a larger developmental field including the hindgut and cloacal membrane; it is presumed that the most severe form of BRA is sirenomelia which represents a developmental field defect involving a major, caudal, midline portion of the embryo.

This study emphasizes the differentiation made by Potter between bilateral renal agenesis on the one hand and unilateral absence of a kidney and renal dysplasia on the other hand.

This paper contributes 3 additional sibships: A with two proven, B with one proven and one possible, and C with two proven and one possible case of BRA. Four similar observations from the literature are cited and the various genetic hypotheses pertaining to BRA are discussed. It is suggested that BRA is a multifactorially determined anomaly and the implications of that hypothesis for genetic counseling are considered in light of C.O. Carter's analysis of similar anomalies. The overall recurrence risk is probably quite small (estimated at less than 1%), but is probably higher the more severely affected the propositus and the more affected propositi for sibship. It is probably also higher in case of a female propositus than in case of a male propositus.

Families D and E of this report show that unilateral absence of a kidney and severe bilateral renal dysplasia may occur in the same kindred, that in these families these are probably the mild and severe forms of the same disorder, and that this disorder is evidently inherited as an autosomal dominant trait. We propose that this newly identified genetic condition be designated *hereditary renal adysplasia* (HRA). At least two

other previously published observations are interpreted by us as examples of dominant inheritance of renal adysplasia.

The relationship of the vaginal atresia (Mayer-Rokitansky-Küster — MRK) syndrome to BRA and HRA remains unclear; a few tentative genealogical items suggest that the MRK syndrome may also be a familial (? dominantly inherited) trait, perhaps identical with HRA.

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Note Added in Proof. "Polydactyly" in case 2, "webbing of the three middle digits of both hands and feet" in case 3, and duplication of the thumb in a recent case of BRA studied in Madison, suggests that BRA may at times represent an acrorenal developmental field defect. In Sarto's MRK case C6 an acrorenal DFC was a component of a more complex MCA syndrome. Thumb anomalies should be searched for in HRA as well.