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The pathogenesis of Potter's syndrome of renal agenesis

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Summary: Current views of the pathogenesis of Potter's syndrome of renal agenesis are discussed. Embryological, teratological and genetic associations between kidney and limb development are reviewed. An infant is described with lobster-claw deformity of the hands and feet, renal hypoplasia and the Potter face.

The purpose of this report is to discuss the current views of the pathogenesis of Potter's syndrome of renal agenesis[1, 2] and to emphasize certain embryological, teratological and genetic associations between limb and kidney development. The stimulus for this discussion was the birth of an infant with lobster-claw deformity of the hands and feet, renal hypoplasia and a Potter face.

The mother was a 29-year-old primiparous white Jewish woman. Both parents were in good health, there was no consanguinity, nor were there relatives with limb or kidney abnormalities. Over a 24-hour period, 10 to 11 days after her last menstrual period, the mother had taken tetracycline 1 g., which had been prescribed for pustular acne. In the third month of gestation she took 5 ml. of Dimetapp Elixir (Robins) (brompheniramine maleate 4 mg., phenylephrine hydrochloride 5 mg. and phenylpropanolamine hydrochloride 5 mg.). There was a slow leakage of amniotic fluid for two weeks before delivery. The presentation was breech. The placenta was 15 cm. in diameter and weighed 560 g.; an acute inflammatory reaction was present in the placenta and cord. Amnion nodosum was not recorded.

The infant weighed 3550 g. at birth; her length was 45 cm., head circumference was 32 cm., and chest circumference was 36 cm. (Fig. 1). The upper half of each ear was floppy, but they were not low-set (Fig. 2). Epicanthic folds were present (Fig. 3). The intercanthal distance was normal (2 cm.). The nose was flattened at the tip, the philtrum short, and the palate highly arched. Each hand had only two digits, one of which was the thumb. The left foot (Fig. 1) had two digits; the right, only one. The labia majora were enlarged.

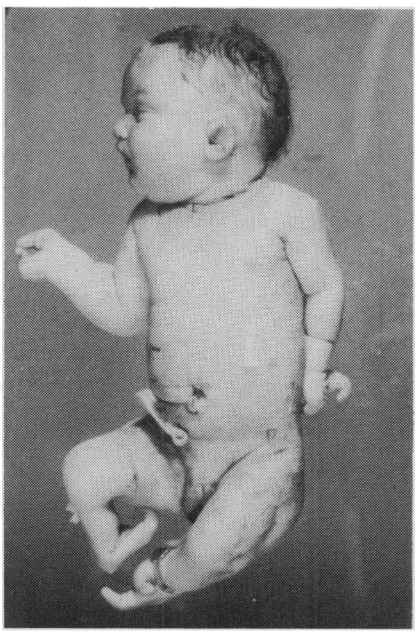

FIG. 1—Note lobster-claw deformity in all limbs of infant reported.

At birth the infant was pale, unresponsive, hypotonic, and did not cry. The Apgar rating was 5. She died of asphyxia two hours after birth.

Autopsy revealed that the lungs were minimally expanded and the kidneys and uterus were abnormal. The kidneys (Fig. 4) each weighed 5 g., measured 1.8 cm. x

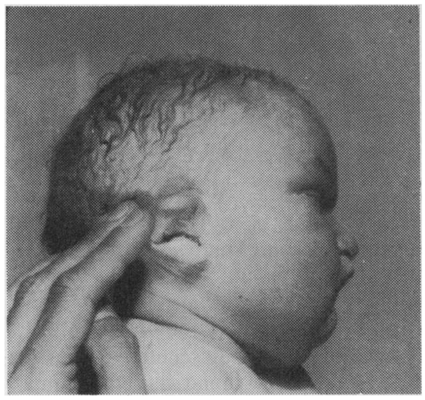

FIG. 2—Note floppy upper half of ear.

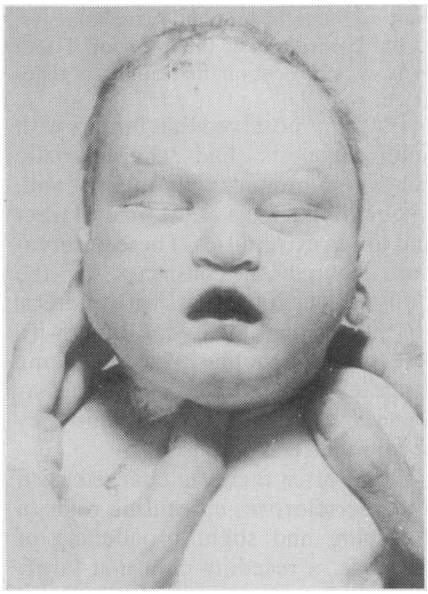

FIG. 3—Note epicanthic folds and downturned tip of nose.

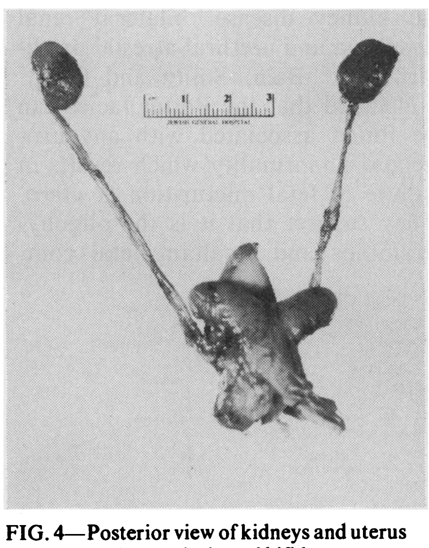

FIG. 4—Posterior view of kidneys and uterus to show renal hypoplasia and bifid uterus.

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1 cm. x 0.05 cm. and had only one papilla. The glomeruli appeared to be normal (Fig. 5), but many tubules were dilated and contained eosinophilic deposits, part of which stained with the Van Kossa stain for calcium. Interstitially, small areas of calcium deposit alternated with foci of inflammation. The uterus was bicornuate, and the adrenals ovoid in shape. The lungs were normal histologically and the Van Kossa and PAS stain revealed no abnormalities in the cartilage of the ears.

The karyotype was within normal limits.

Roentgenographic studies

A small right pneumothorax was seen on the chest roentgenogram. There was no terminal phalanx on the finger of the right hand and what seemed to be the thumb of the left hand had three phalanges. The right tibia was hypoplastic, the proximal tibial epiphysis was missing and there was no fibula or talus. The digit on the right foot had two phalanges, as did both digits of the left foot. Tooth buds were present on the skull roentgenogram.

Potter[1, 2] observed that infants with renal agenesis had characteristic facies, pulmonary hypoplasia and, frequently, defects of the genital tract and lower extremities. These observations have been confirmed by the study of over 200 infants with bilateral absence of the kidneys.[3] Infants with severe renal hypoplasia have the same range of associated abnormalities as those with renal agenesis, but they occur much less often.[4]

The Potter facies is characterized by hypertelorism, epicanthic folds, a flattening and slight broadening of the nose, a receding chin and large, low-set, floppy ears. The facies is not specific for renal agenesis;[3] it has been found also in infantile polycystic kidney disease, bilateral renal dysplasia and urethral atresia[5] or obstruction.[6] Bain, Smith and Gault[7] concluded that the Potter facies can be found associated with any urogenital abnormality which results in failure of fetal micturition *in utero.* They suggest that it is the oligohydramnios and resultant fetal compression which account for the appearance of the nose and the receding chin.[5] Evidence in support of this hypothesis is provided by the experiments of DeMyer and Baird.[8] They subjected rat fetuses to amniocentesis and observed microstomia, cleft palate and limb abnormalities, showing that development of the face and limbs can be altered in a major way by oligohydramnios. These experiments support the widely accepted view[9] that in the human infants with Potter's syndrome, the structural abnormalities of the face, lungs and limbs are secondary to oligohydramnios (Scheme I).

There is however, in our opinion, another way in which face, lung, limb and kidney defects may be associated, as shown in Scheme II.

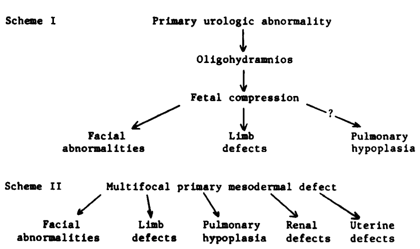
Examination of the face of a normal 18-mm. fetus[10] shows that, relative to the newborn, the ears are low set, the eyes widely separated and the mandible hypoplastic. These features are seen in many other dysmorphogenetic syndromes and probably indicate developmental retardation. Therefore an alternative explanation for the Potter face may be a primary disturbance in mesenchymal growth of the face.

Almost all infants with renal agenesis die of asphyxia within a few hours after birth. The lungs weigh less than normal and on histological examination the bronchi are prominent because of inadequate parenchymal development. In many cases the alveoli and the respiratory ducts are lined by cuboidal epithelium.[2] It is noteworthy that our patient also died in respiratory distress within a few hours after birth; however, no histological abnormalities were noted in the unexpanded lungs.

Lack of amniotic fluid in the developing fetal lung is often held responsible for pulmonary hypoplasia,[9] but Potter and Bohlender[11] described two infants in whom there was no connection between the lungs and trachea during embryonic life, yet lung development was normal. This means that circulation of amniotic fluid into the developing lung is not necessary for its normal differentiation. On the other hand it is possible[5] that compression of the thoracic cage due to oligohydramnios might be pathogenic. It is interesting to note that there is a type of congenital polycystic kidney malformation in which all the affected children die in respiratory distress within four hours after birth.[12] It would be important to know whether this is associated with oligohydramnios or pulmonary hypoplasia.

Duplication of the uterus frequently accompanies renal agenesis or hypoplasia.[4] The uterus originates as a double structure enclosed in mesenchyme and the two parts must approximate in order to fuse. A delayed or reduced growth of mesenchyme could culminate in a bicornuate uterus.

Approximately one-third of the



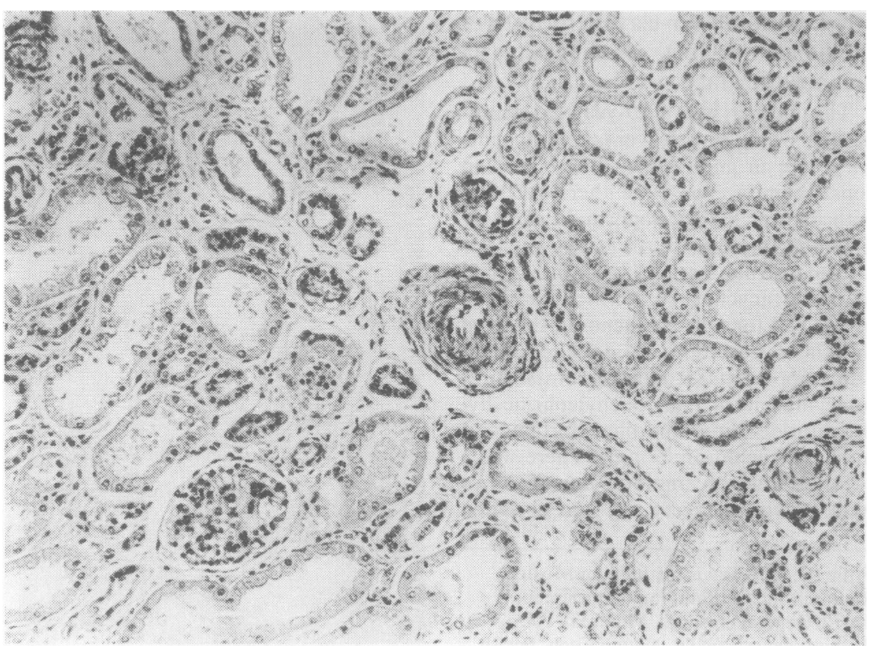


FIG. 5—Kidney of patient. Note dilated renal tubules containing deposits. (Hematoxylin and eosin)

cases of renal agenesis have limb malformations,[3] usually spade hands and talipes although more severe defects have been noted.[2] In this regard it is striking that after amniocentesis in rats[8, 13] severe limb deformities were observed. These included clubfoot, adactyly, absence of paws, short, stiff extremities and syndactyly. It has been postulated[14] that fetal immobilization can cause joint deformities and thus it seems likely that oligohydramnios could produce talipes. An alternative explanation for abnormal limb development in conjunction with urologic maldevelopment is that there is defective mesenchymal growth of the limbs. Gruneberg has shown very clearly in the mouse that some limb abnormalities seem to originate in a defect of cartilage or bone, whereas others originate in abnormally shaped foot plates observable before cartilage or bone are formed,[15] i.e. there is a defect at the mesenchymal stage of development. It seems likely that the lobster claw deformity can also originate in the mesenchymal stage. There is a very large variability in the expression of the inherited form[16] and the origin of this variability can be explained by very small changes in the shape of the foot plate at the mesenchymal stage of development. (Fig. 6).

It is provocative to examine a cross-section of a mammalian fetus at the time when hindlimb buds are starting to develop. Fig. 7 reveals that the mesenchymal condensations which are forming the metanephros

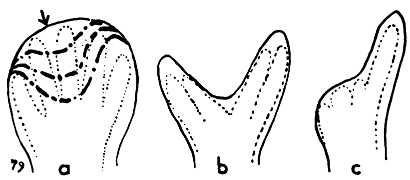


FIG. 6—Diagram to illustrate mesodermal defects leading to known types of lobster-claw malformation. (From Handbuch der Orthopädie 3, p. 468, Hohmann, Hackenbrach and Lindemann. Reproduced with the permission of Georg Thieme Verlag.)

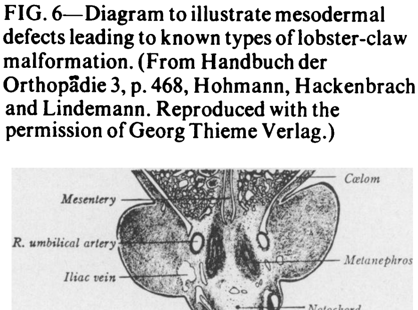


FIG. 7—Cross-section of 10-mm. pig embryo to show proximity of metanephros and hindlimb bud. (Reproduced from seventh edition of Arey's Developmental anatomy, p. 640, with the permission of W. B. Saunders Company).

and contributing to the limb bud are adjacent. At an earlier stage they probably have a common origin, so they may share a common deficiency.

Lash[17, 18] has found that mesonephros from the limb bud region of chick embryos forms cartilage in organ culture, but that mesonephros from the intervening abdominal region usually will not. He also showed that mesonephros from the limb bud region will enhance limb cartilage formation in tissue culture. Human mesonephros[19] will also form cartilage in tissue culture. The cartilage is found in the mesenchyme between the tubules. When thalidomide is added to these cultures the appearance of cartilage is inhibited.[19] Renal abnormalities are often found in necropsy studies of thalidomide infants.[20] These observations provide additional support for the hypothesis that there may be factors common to limb and kidney histogenesis.

Further evidence for the relationship of kidney and limb development is provided by the recessive mutation, wingless, in the domestic fowl, in which there is absence or reduction of the wings, leg deformities, renal agenesis and retarded pulmonary development.[21] In the mouse the gene for symmelia[22] produces sireniform abnormalities, frequently in association with small or absent kidneys. The gene for oligodactylism[15] produces either renal agenesis, horseshoe kidneys, or cystic kidneys. Dominant hemimelia in the mouse[15] is frequently associated with hydronephrosis and hydroureter.

In the human, Dieker and Opitz[23] describe three patients with limb and renal anomalies. Polydactly has been reported to be associated with polycystic kidneys in the Laurence-Moon-Biedl syndrome,[24] the Ullrich-Feichtinger syndrome,[25] a family described by Walbaum, Dehaene and Duthoit[26] and a family described by Simoupolis *et al.*[27]

To our knowledge cleft hand and foot has not been described previously with renal agenesis or renal hypoplasia. A woman with cleft feet, deformed hands and polycystic kidneys has been described by Cameron,[28] who emphasized that "abnormality of the hand and arm may be a pointer to a serious renal anomaly". We have not been able to learn the nature of the renal anomalies in the family with split hands and feet described by Temtamy and McKusick.[29] Two children with cleft hands and feet and urogenital abnormalities have been studied by Fraser.[30] One had unilateral duplication of the ureter; the other, bilateral hydronephrosis. Hydroureter was present in one individual of another family with split hands and feet and cleft palate.[31]

We believe that it is important to recognize not only that there are two different pathogenetic schemes relating kidney, limb and face abnormalities, but also that in any given individual both dysmorphogenetic schemes may be operating. A probable example of this is sirenomelia, a condition in which only one median lower limb is formed. Nearly all infants with sirenomelia have complete renal agenesis.[32] The oligohydramnios may account for the Potter face but it cannot explain the monopodia, which must therefore reflect a primary developmental defect. Similarly, in our patient the bifid uterus and the cleft hands and feet seem more likely to be the result of a mesodermal growth deficiency than of oligohydramnios.

Résumé

La pathogenèse du syndrome de Potter d'agénésie rénale

L'objet du présent rapport est de passer en revue les idées actuelles sur la pathogenèse du syndrome de Potter d'agénésie rénale[1, 2] et de souligner certaines associations embryologiques, tératologiques et génétiques entre le développement des membres et des reins. Ce qui a déclenché cette discussion a été la naissance d'un nouveau-né présentant des difformités des mains et des pieds ("en pinces de homard"), une hypoplasie rénale et un faciès de Potter.

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