ANIMAL MODEL OF HUMAN DISEASE

Potter's Syndrome

Animal Model: Amniotic Fluid Deficiency and Fetal Lung Growth in the Rat

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Biologic Features

Experimental oligohydramnios induced in rats during the last trimester of pregnancy was found to produce hypoplastic lungs, cleft palates, and limb deformities.

Sprague–Dawley rats of known gestestional age underwent operation on Day 16 or 17 of pregnancy. Individual amniotic sacs were punctured with an 18-gauge needle. The pregnancy was then allowed to continue to term, with amniotic fluid draining into the maternal peritoneal cavity through the fistula produced by the needle puncture. Reaccumulation of small amounts of amniotic fluid due to closure of the fistula was found in the sacs of 13% of the fetuses.

At term (Day 21.5) there was growth retardation of the fetuses whose amniotic fluid was drained on Day 16 but none in those drained on Day 17 (Figure 1). Absolute lung weights in both experimental groups were decreased, with the most severe hypoplasia in the Day 16 group (Figure 2). Lung weight:body weight ratios in both groups were reduced, with no difference between the Day 16 and Day 17 fetuses (Figure 3). There was no consistent qualitative histologic difference in the lungs from control and experimental animals. Cleft plates were present in 81% of fetuses whose amniotic fluid was drained on Day 16. No cleft palates were found in those animals which underwent operation on Day 17, the day on which palate closure is complete. Malformations of the extremities, principally, partial syndactyly and, more rarely, resorption of digits, were present in

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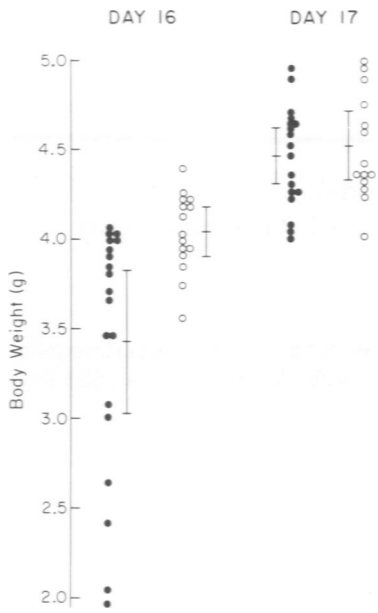

Figure 1—Body weight at term of animals operated on during the 16th or 17th day of gestation. Significant growth retardation was found in the experimental fetuses (*solid circles*) compared with control animals (*open circles*) ($P < 0.001$) in the Day 16 surgical group. No growth retardation was found in the Day 17 surgical group. Mean weights and a 95% confidence interval for each group are indicated by horizontal lines.

35% of experimental animals. Placentas and membranes showed no evidence of amnion nodosum. Needle puncture of the amniotic sac resulted in 33% fetal mortality. No mortality was encountered in the littermate controls.

These observations demonstrate that amniotic fluid is necessary for

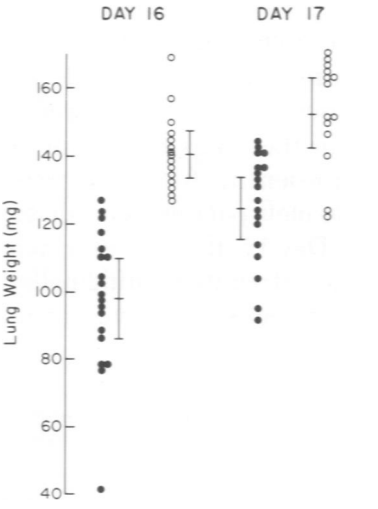

Figure 2—Absolute lung weights indicate lung hypoplasia in the Day 16 and Day 17 experimental groups. The duration of oligohydramnios influenced lung size at term, with a more significant decrease in lung weight in the Day 16 animal group ($P < 0.001$) than in the Day 17 group ($P < 0.01$). *Solid circles*, experimental animals; *open circles*, controls.

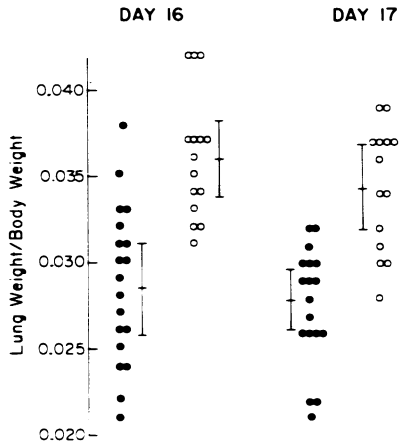

Figure 3—Lung weight:body weight ratios illustrating significant lung hypoplasia in both experimental groups. The *P* value (based on the inverse transform of the transformed mean [11]) is less than 0.001 for Day 16 animals and less than 0.01 for Day 17 animals. *Solid circles*, experimental animals; *open circles*, controls.

normal lung growth and that experimental deficiency of amniotic fluid in the third trimester of pregnancy is associated with pulmonary hypoplasia.

Comparison With Human Disease

Potter's syndrome is associated with intrauterine renal nonfunction due to either renal agenesis or maldevelopment. It is characterized by a constellation of changes, including oligohydramnios, pulmonary hypoplasia, increased incidence of cleft palate, and bony malformations. The possibility of a causal relationship between the oligohydramnios and the induction of anomalies has been suspected on clinical grounds [1,2] but has not been confirmed experimentally.

Amniotic fluid is largely derived from fetal urine in the latter stages of pregnancy.[3] Its volume is primarily determined by the relative rates of fetal intestinal absorption and fetal urination,[4,5] with a minor contribution from the lungs.

Results of experiments in which the role of amniotic fluid in fetal development was examined have focused exclusively on skeletal abnormalities.[6-10] The cleft palates and limb defects produced in rats with oligohydramnios led us to postulate that removal of amniotic fluid might also be used to study the pulmonary component of Potter's syndrome. Our experiments with chronic deficiency of amniotic fluid as the only variable have confirmed the relationship of the major nonrenal components of Potter's syndrome to oligohydramnios. In humans, oligohydramnios is due to renal nonfunction; in this model, it is achieved by amniotic fluid leakage.

Usefulness of the Model

Needle puncture of rat amniotic sacs is a simple and effective technique to induce chronic oligohydramnios, pulmonary hypoplasia, and other nonrenal components of Potter's syndrome. This model allows another approach to the study of the role of amniotic fluid in the development of congenital malformations and, in particular, the relationships between the aqueous fetal environment and pulmonary growth and development.

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