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The lungs in congenital bilateral renal agenesis and dysplasia

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SUMMARY A detailed quantitative analysis was made of the lungs from 8 infants dying with bilateral renal agenesis or dysplasia. Total lung volume was reduced in all cases, particularly in those with renal agenesis. In both groups there was a reduction in number of airway generations, indicating interference with development at between 12 and 16 weeks' gestation. The alveoli in each acinus were reduced in size and, in some cases, number—although their stage of differentiation was normal for age—pointing to a disturbance of growth during later fetal life also. As liquor is largely non-renal in origin at least up to 16 weeks' gestation, it seems that there are factors other than the oligohydramnios interfering in early lung growth in these cases, such as reduced proline production by the kidney.

The concurrence of bilateral renal agenesis and pulmonary hypoplasia was first recognised by Potter (1946) and later confirmed by others (Davidson and Ross, 1954; Sylvester and Hughes, 1954; Carpentier and Potter, 1959; Potter, 1965). Later it became apparent that lethal pulmonary hypoplasia was also a consistent feature in babies with no renal function at birth because of bilateral renal dysplasia with or without cyst formation (Ashley and Mostofi, 1960; Bain and Scott, 1960). The underlying mechanism remains obscure although many have suggested that the pulmonary hypoplasia is secondary to oligohydramnios and thoracic compression *in utero*. Siblings are only rarely affected (Buchta *et al.*, 1973; Whitehouse and Mountrose, 1973; Cain *et al.*, 1974; Hack *et al.*, 1974) and there are few reports of both members of a twin pair being affected (Mauer *et al.*, 1974). Oligohydramnios is almost universal, breech presentations and premature labour are frequent, stillbirth is not uncommon (Ratten *et al.*, 1973), and early neonatal death due to respiratory insufficiency is almost inevitable in those born alive. Babies surviving for any time often develop a complicating pneumothorax or pneumomediastinum (Liberman *et al.*, 1969; Renert *et al.*, 1972; Stern *et al.*, 1972; Bashour and Balfe, 1977) and a chest *x*-ray taken at this time may be almost diagnostic (Leonidas *et al.*, 1975). In a series of 49 cases of bilateral renal agenesis, Potter (1961) found at necropsy that the degree of pulmonary hypoplasia varied, but in extreme cases alveoli were almost completely lacking. Reale and Esterly (1973) found a reduced lung to body weight ratio in 20 infants with a variety of renal anomalies. This was greatest in those cases with bilateral agenesis. They also found in some, a reduction in the number of alveoli within each acinus, assessed by the method of Emery and Mithal (1960).

The nature of the hypoplasia in the lungs from infants with congenital diaphragmatic hernia (Kitagawa *et al.*, 1971) and rhesus isoimmunisation (Chamberlain *et al.*, 1977) was analysed by precise morphometric techniques after injection of the pulmonary artery and inflation of the lung. In both conditions the number of airway generations and their accompanying arteries are reduced as well as the total number of alveoli. In the present study, these quantitative methods have been applied to lungs from infants with bilateral renal agenesis or dysplasia. Using these methods, it is possible to analyse type and degree of hypoplasia and the timing of interference with development.

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Case material

The lungs from 8 patients with abnormal kidneys were studied and the diagnosis and main features are shown in Table 1. Cases 1 and 2 had bilateral renal agenesis. Case 1 also had sacral agenesis, gross rotation of both lower limbs, and rectal atresia. Three infants (Cases 3–5) were diagnosed as having the typical features of sirenomelia (Duhamel, 1961) which included in these cases bilateral renal agenesis. Cases 1–5 are all referred to as having renal agenesis. Cases 6–8 had renal dysplasia, the kidneys consisting of a mass of watery cysts with no renal tissue (Pathak and Williams, 1964). Case 7 also had hydrocephalus and was thought to have the Dandy-Walker syndrome (D'Agostino *et al.*, 1963). Case 6 was one of twins, the other being anencephalic. In all patients it was reported that little or no liquor was present at birth and amnion nodosum (Landing, 1950) was proved in Cases 1, 2, 5, 7, and 8. All 8 showed evidence of postural moulding. Two babies were stillborn, 5 died of respiratory insufficiency, and one (Case 7) from intracranial haemorrhage. The longest period of survival was 18 hours.

The 2 infants with renal agenesis born before the 31st week of gestation were of normal weight for age but the weight of the others with agenesis was reduced to the 5th centile or less. The infants with renal dysplasia were of normal body weight, except for Case 6 which was on the 10th centile, probably because it was one of twins. In the 4 infants in which it was measured, combined heart and lung weight was reduced. Pressure-volume curves (Reynolds *et al.*, 1968), obtained on all but Case 4, showed that all lungs were reduced in volume, particularly those with renal agenesis. The relationship of volume to pressure change was normal in Cases 2, 3, 7, and 8 showing normal alveolar stability. In Cases 1, 5, and 6 although there was some residual air indicating that surfactant was present, there was a relatively rapid decline in volume with decreasing pressure.

Methods

The pulmonary arteries of the 8 cases were injected with a barium sulphate and gelatine suspension at 60°C and at a water pressure of 100 cm. Arteries were filled and fully distended down to precapillary level. The airways were inflated with buffered formol saline at a pressure of 45·5 cm water and the lungs and heart left to fix for at least one week. The lungs were studied, using quantitative techniques as described by Hislop and Reid (1970). These studies included measurement of inflated lung volume, measurement of lung length and pulmonary artery size on arteriograms, and tracing airway branching pattern by serial reconstruction. The maturity of the alveoli was assessed, size was estimated from the number per unit area, and to estimate alveolar number per acinus the radial alveolar count, as described by Emery and Mithal (1960), was used. Wall thickness of pulmonary arteries was measured and the degree of extension of muscle along the arterial pathways assessed by identifying arteries according to their accompanying airways and their size (Davies and Reid, 1970). After fixation, the hearts were dissected and weighed using the method of Fulton *et al.* (1952).

Results

The morphological findings are summarised in Table 2.

Table 1 *General necropsy findings*

Case no.	*Sex*	*Gestational age (weeks)*	*Survival time (min)*	*Body weight*		*Inflation volume (ml)*	*Alveolar stability*	*Diagnosis*	*Comment*
				(kg)	*(Centile)*				
1	M	29	15	1·2	50	3	?N	Bilateral renal agenesis	Rectal atresia and sacral agenesis
2	M	33	18 hours	1·25	5	9	N	Bilateral renal agenesis	Bilateral hip dislocation
3	F	30	10	1·44	50	7	N	Sirenomelia and bilateral renal agenesis	
4	M	38	Stillborn	1·71	<5	10	—	Sirenomelia and bilateral renal agenesis	
5	F	41	Stillborn	2·19	<5	5·5	?N	Sirenomelia and bilateral renal agenesis	
6	F	38	70	2·49	10	14	?N	*Bilateral multicystic renal dysplasia	Identical twin anencephalic
7	F	39	25	3·17	50	16	N	†Bilateral polycystic kidneys	Hydrocephalus with Dandy-Walker deformity. Sibling also affected
8	F	41	120	3·63	75	18	N	Bilateral multicystic renal dysplasia	Right hip dislocation

*Royer *et al.* (1974); †Goldston *et al.* (1963)

Table 2 *Morphological findings*

Case no.	*Gestational age (weeks)*	*Lung volume (ml)*	*Airway no.* (normal 20–25)*	*Alveolar maturity size*	*Radial alveolar count*	*Artery size*	*Arterial wall thickness*	*Arterial muscle extension*		*Total ventricular weight (g)*
								By size	*By position*	
1	29	12 (55)†	—	N ↓↓	2·5 (2·6)‡	↓	N	↑	↑	3·25 (3·7)§§
2	33	17 (70)	16	N ↓	2·3 (3·7)	N	↓	↑	↑	1·68 (5·2)
3	30	14 (60)	17	N ↓↓	2·1 (2·6)	N	↓	↑	↑	3·75 (4·0)
4	38	18 (80)	—	N ↓↓	2·7 (3·6)	↓	↓	↓	↓	5·66 (12·1)
5	41	19 (110)	—	N ↓↓	3·1 (4·4)	↓	(↓)	Normal	↓	3·87 (12·3)
6	38	30 (80)	—	N ↓↓	3·5 (3·6)	↓	Normal	Normal	Normal	7·58 (12·1)
7	39	22 (95)	20	N ↓↓	2·5 (3·6)	↓	↑↑	↑	↑	11·71 (12·2)
8	41	25 (110)	18	N ↓	3·0 (4·4)	↓	N	↑	↑	10·91 (12·3)

*Normal values. Hayward and Reid (1952); †Hislop (1971); ‡Emery and Mithal (1960); §§ Hislop and Reid (1972a).
↑—increase in size, number or extension to the periphery; ↓—decrease in size, number or extension to the periphery.

Lung volume. All lungs were greatly reduced in volume. In Cases 1–5 the reduction was greatest, the volume being similar to that of a fetus of about 24 weeks' gestation, and in none was it more than one-quarter of the expected volume. In Cases 6–8 the volume was equivalent to the normal lung at 28 weeks' gestation. In all cases lung length was appropriate for volume.

Airways. In Cases 2, 3, 7, and 8 the posterior basal airway to the left lower lobe was traced from hilum to terminal bronchiolus by dissection and microscopical serial reconstruction. While the normal number of airway generations for this segment is 20–25 (Hayward and Reid, 1952), in all 4 pathways the number was reduced to between 16 and 20 generations. It seemed that the bronchi (the airways which develop first and have cartilage in their wall) were normal in number while the bronchioli (which appear later and lie distal to the cartilage plates) were considerably reduced. Unlike the others, Case 7 had a more nearly normal number of bronchioli. In addition, in Cases 1–5, microscopical examinations showed bronchi abnormally close to the pleura, indicating relative reduction in volume of the respiratory region and of the number of peripheral airways. In Cases 1 and 2, the cartilage plates were large for the size of the airways. In Cases 6–8 distribution of airways was normal.

Alveoli. The development of the alveoli was assessed by their stage of maturation, their number, and size. Judged by gestational age, the lungs should have been in the terminal sac stage of development (Boyden, 1975). At the beginning of this stage, at 24 weeks' gestation, the saccules are simple in outline; by its end, at birth, primitive alveoli are seen in their walls as shallow indentations. In all lungs the alveoli were of normal type for age but were smaller than normal.

Radial alveolar counts showed that in Cases 2, 4, 5, 7, and 8 the number of alveoli in each acinus was more than 1 SD below the normal mean (Emery and Mithal, 1960). In the other 3 cases it was below the mean but within the normal range. As the reduced number of airway generations means a reduced acinar number, it may be assumed that in all lungs the total number of alveoli must be reduced. Thus reduction in alveolar number and size both contribute to the reduced total lung volume.

Pulmonary arteries. From the arteriograms, the overall branching pattern and size of the pulmonary arteries were assessed (Fig. 1).

In Cases 2 and 3 the arteries were normal in size for age of the fetus. In the other 6 lungs the arteries were reduced in size for age, although in each the arteries were large for the volume of the lung. This relative increase was greater in the infants with renal agenesis and in these the arteries appeared large, tortuous, and crowded. This was confirmed microscopically, where large vessels were found close to the pleura. The arteriograms of the renal dysplasia lungs showed normal distribution of vessels and no relative increase in size of peripheral arteries.

Arteries accompany airways and the reduction in the total number of preacinar conventional arteries mirrored reduction in airway number. Supernumerary arteries were present but appropriately reduced in number. The number of arteries per unit area within the acinus was less than normal in the lungs associated with renal agenesis but seemed normal in those with renal dysplasia.

Muscularity of pulmonary arteries. In cases of agenesis (Cases 1–5) the wall thickness of the pulmonary arteries was less than the normal fetal level except in one, the youngest, in which it was at normal fetal level. In case 2 the walls were as thin as in a normal adult—1–2% in the larger vessels.

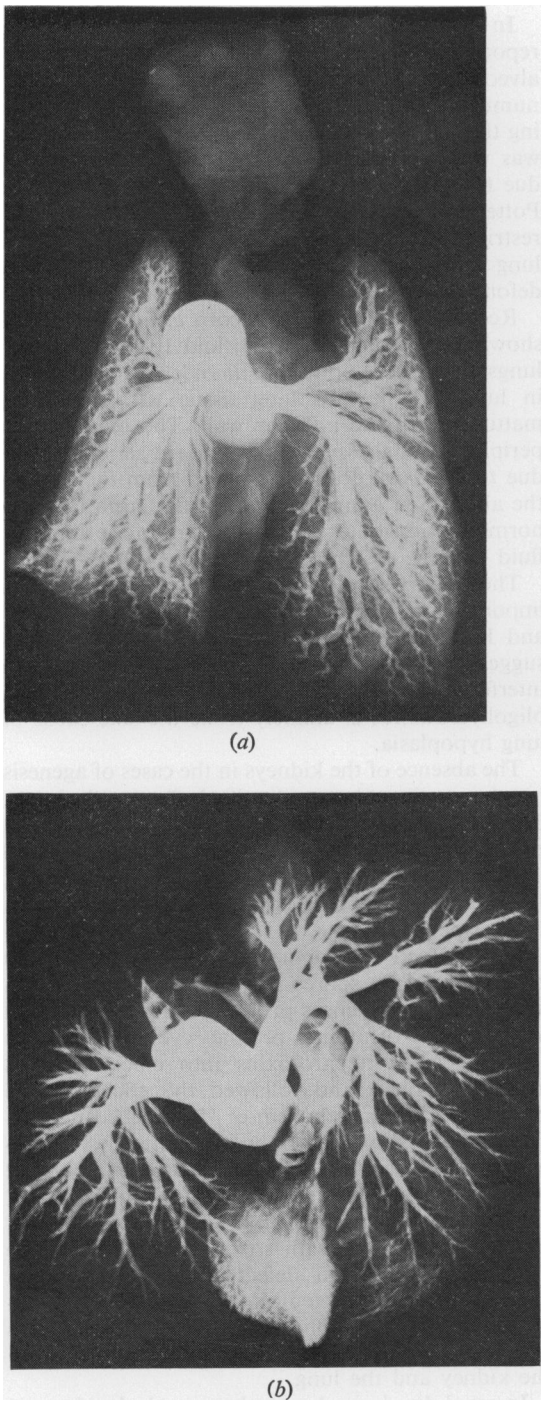

Figure. *Arteriogram of the lung of (a) Case 2 (renal agenesis) and (b) Case 8 (renal dysplasia) (× 1). The arteries have been injected with a radio-opaque medium.*

In two cases of dysplasia (Cases 6 and 8) wall thickness was at normal fetal level and in the 3rd it was thicker than normal. This case also had an increase in pulmonary vein wall muscle while in all others vein walls were normal.

Muscularity was also assessed by estimating the size of vessels with muscular walls and also the level within the lung to which muscular arteries extended. The pattern of muscularity did not correlate with renal diagnosis nor did it correlate with alveolar development. In 4 patients with agenesis and 2 with dysplasia, the muscle extended into smaller and more peripheral vessels than normal. One patient with agenesis and one with dysplasia had normal muscle distribution by size but less muscle within the acinus, and one patient with agenesis had less arterial muscle, both by size and position, than normal.

Heart weight. The ventricles of the heart were dissected and weighed and the ratio between weight of left ventricle plus septum and right ventricle estimated. In all patients the ratio was in the normal fetal range, between 1 and 2 (Hislop and Reid, 1972a). Total heart weight was less than expected for gestational age in 3 of the 5 patients with renal agenesis and in 2 of these it was reduced even for the reduced body weight. Of the 3 infants with renal dysplasia, heart weight was normal in 2 and reduced in the 3rd but this infant was small, being a twin, and the heart to body weight ratio was normal.

Discussion

These cases with renal agenesis or dysplasia are further illustrations of Potter's observation that the lungs from infants with bilateral renal agenesis are hypoplastic (Potter, 1946). Precise morphometric techniques have now made it possible to analyse separately the several structural constituents of the lung and to detect the presence and define the degree of hypoplasia in each. The abnormality can be interpreted according to the schedule of normal fetal development previously described (Bucher and Reid, 1961; Hislop and Reid, 1972b). Although many of the changes in the lungs were similar in patients with either agenesis or dysplasia, there were features sufficiently different to suggest that in these two conditions the severity or timing of interference may have been different or even that a different factor may have operated.

Pathological changes. Total lung volume was reduced in all cases but particularly so in patients with renal agenesis. Reale and Esterly (1973) found that cases with bilateral renal agenesis had the lowest lung

weight/body weight ratio when compared with other types of kidney anomalies. In the present series however, lung volume/body weight ratio was similar in both groups.

Airways and alveoli. The reduction in number of airway generations suggested an arrest in development at between 12 and 16 weeks' gestation because only the broncholi were affected (Bucher and Reid, 1961). It may be that the precise time of effect or the degree of sensitivity at this time explains the greater reduction in renal agenesis. In both groups the drop in airway number must lead to a reduction in number of acini. In the babies with renal agenesis, growth within the acinar region as well as of airways was thought to be reduced because microscopically the respiratory region was small even for the reduced airway number, and the cartilage plates and airways were disproprortionately large when related to lung volume. A relatively greater reduction in the respiratory region has also been reported in one case of thoracic dystrophy by Finegold *et al.* (1971) and in congenital diaphragmatic hernia by Kitagawa *et al.* (1971). The disproportion was not seen in the dysplastic patients. In all lungs the reduced respiratory region was due partly to fewer acini because of fewer airway generations and partly to the small size of alveoli; in 5 cases, in addition, the number of alveoli per acinus was clearly reduced.

In infants with renal agenesis, Potter (1965) described in uninflated lungs, immaturity of the alveolar region, some lungs apparently having no alveoli at all. In the present series there was normal maturity of alveoli.

Arteries. In both renal agenesis and dysplasia, arterial number was reduced and probably followed the reduction in number of airways. In agenesis the arteries were also disproportionately large. In renal agenesis pulmonary arterial wall thickness was less than normal fetal levels. This could reflect a difference in haemodynamic behaviour before birth or an effect on arterial growth other than that associated with size.

Pathogenesis of lung hypoplasia. In the past it has only been possible to discuss the nature and severity of the lung hypoplasia associated with renal disease in terms of the role of amniotic fluid, lung fluid, and urine production; and the explanations were not entirely satisfactory.

In a retrospective study of 31 cases with renal anomalies Perlman and Levin (1974) found that 21 of these had oligohydramnios associated with hypoplastic lungs; the remainder with normal lungs had normal amniotic fluid.

In 2 cases of prolonged leakage of amniotic fluid reported by Perlman *et al.* (1976) the number of alveoli present at birth was the normal expected number at the time of onset of the leakage, suggesting that no further development occurred after fluid was withdrawn. It is pressure of the uterine wall, due to lack of fluid, which is likely to produce the Potter facies and the limb malformations but restriction of the thoracic cavity is unlikely to cause lung hypoplasia as the chest wall is never badly deformed in renal agenesis.

Recent experiments by Alcorn *et al.* (1977) have shown that drainage of the fluid from fetal lamb lungs during development *in utero* leads to a decrease in lung volume and lung tissue with abnormal maturation of the alveolar wall. The reduction in peripheral lung tissue in the present series may be due to excessive drainage of fluid from the lung in the absence of amniotic fluid. In the lamb the lung normally contributes about one-third of the amniotic fluid (Strang, 1977).

The contribution of the kidney to the liquor is important only relatively late in pregnancy (Saunders and Rhodes, 1973). Findings in the present series suggest that because the airway number implied an interference with growth before 16 weeks' gestation, oligohydramnios is unlikely to be the sole cause of lung hypoplasia.

The absence of the kidneys in the cases of agenesis may have a direct but unidentified effect on the lungs. Experimental nephrectomy in fetal lambs has an effect on subsequent fetal growth with a reduction in the glycogen reserves of the liver (Thorburn, 1974). Unfortunately, the lungs were not studied in these experiments.

During fetal development the kidney appears to be an important source of proline: it contains an arginase that influences proline production through an arginine ornithine proline cycle. Clemmons (1977) injected nephrotoxins into chick embryos at various times and followed the effect on the production and metabolism of ^{14}C labelled proline. Decreased ability to metabolise proline was associated with decreased collagen formation. Because it grows actively during the times chosen, he studied the morphological state of the lung, and found it became hypoplastic with sparse mesenchyme. The association of a renal defect and lung hypoplasia can now be interpreted in the language of biochemical and metabolic processes and this offers new ways of investigating the interaction between the kidney and the lung.

In renal dysplasia, lung volume and alveolar and airway size and number are reduced but the cases vary in their severity. In renal agenesis these changes are more pronounced and are associated in addition

with disproportionately larger airways and arteries, the latter also having thinner walls. The fact that more severe hypoplasia is seen with renal agenesis than with dysplasia may reflect either a greater reduction in available proline or a difference in the time-table of interference.

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