Pulmonary aplasia—a quantitative analysis of the development of the single lung

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Quantitative studies have, for the first time, been carried out on the single lung in a case of unilateral pulmonary aplasia, in which the other lung was represented by a rudimentary bronchial stump. The patient died at the age of 3 months. The lung was enlarged to almost twice the normal volume, filling the intrathoracic cavity. The bronchial generations were reduced in number. Pulmonary artery branches were also too few, the supernumerary being more reduced than the conventional; muscle had extended abnormally far into peripheral arteries. The alveolar number was twice the normal for one lung, that is, it represented the normal total for age; alveolar size was rather less than normal.

The hypoplasia of airways and blood vessels represents an early intrauterine disturbance in lung growth, caused perhaps by the same factor that inhibited the development of the second lung; the increased alveolar multiplication probably reflects increase in available space during fetal life.

Over 200 cases of underdevelopment of the lung have been described, the earliest recorded being those of de Pozzis (1673), Morgagni (1761), and Haberlein (1787). Most recent articles describe a small number of cases, often only one, and the most exhaustive reviews are those of Oyamada, Gasul, and Holinger (1953), Valle (1955), and Maltz and Nadas (1968). Only four cases of absence of both lungs have been described (Devi and More, 1966). In 1909 Schneider proposed a classification of the degree of underdevelopment that has been adopted by most authors since:

- Class I Agenesis—total absence of bronchus and lung
- Class II Aplasia—rudimentary bronchus without lung tissue
- Class III Hypoplasia—bronchial hypoplasia and variable but reduced amount of lung tissue.

Recently, for the first time, a quantitative analysis has been made of the degree of development of airways, alveoli, and arteries in a hypoplastic lung—an example of class III—and of the contralateral lung (Henderson, Hislop, and Reid, 1971). The present paper reports the first detailed study of the state of a single lung as is present in class I or II: the present case falls in class II.

In all cases of pulmonary agenesis (class I) the pulmonary artery to the affected side is absent and it is usually so in aplasia (class II). Although the anatomical features of the remaining lung have not been previously described, many authors have noted complete or partial failure of lobation. Structural detail is given in the following reports. Killingsworth and Hibbs (1939) described 'moderate emphysema' in the upper lobe of the single lung with alveolar walls 'moderately thickened and hyperaemic': blood vessels and small bronchi were normal. The lower lobe showed the appearance of 'fetal atelectasis', and since some airways included no muscle or cartilage the antenatal development of this lobe seems to have been incomplete.

In another case, Pruys, Veen, and Zuimeda (1939) described saccular bronchiectasis in the single lung. Ferguson and Neuhauser (1944), Garber (1945), and Finner (1932) reported emphysema, patchily distributed. Knott (1934) and Mitchell (1936) described 'hypertrophy' of the lung. Muhamed (1923), Hepner (1934), Heemstra (1939), and Olcott and Dooley (1943) considered it as 'enlarged'.

In 1937 Rienhoff, in one of the more detailed reports, described a man who had survived to the age of 50 with one lung before succumbing to a non-pulmonary disease. The single lung

showed enlargement of all lobes and had spread across the midline to occupy part of the contralateral hemithorax but on microscopic examination was 'entirely normal, there being not the slightest suggestion of fragillation of elastic tissue or emphysema'.

Ten years later Smart (1946) reported two cases of 'agenesis of the lung' in living patients. Since, after maximal inspiration, respiratory function tests showed a rapid return to the original lung volume, he inferred that there was no emphysema. Certainly emphysema with air trapping would seem not to have been present (Reid, 1967).

PRESENT CASE (CLASS II—SCHNEIDER, 1909)

The patient was a boy with aplasia of the right lung who died at the age of 3 months. He was the second child of a 39-year-old woman who had borne a normal child 20 years previously during an earlier

marriage. The pregnancy and delivery were normal and the child left hospital without any abnormality having been detected. At the age of 1 month he was re-admitted for investigation of persistent tachypnoea and episodes of cyanosis lasting a few minutes at a time. The diagnosis was made of pulmonary agenesis. From this time until his death two months later, he suffered repeated attacks of pneumonia which responded poorly to treatment.

INVESTIGATION Clinical examination revealed an apex beat below the right scapula and dullness to percussion at the right base; the radiograph showed the cardiac opacity in the right hemithorax and no right lung markings were visible. An electrocardiogram indicated normal heart rate, rhythm, and intraventricular conduction but, because of the extreme rotation and displacement of the heart, no assessment of right or left ventricular hypertrophy could be made.

NECROPSY No external abnormality was noted. A tension pneumothorax was found when the chest was

FIG. 1. Thoracic block (A) anterior view, and (B) posterior view (Ao=aorta; H=heart; LUL and LLL=left upper and lower lobe; RB=rudimentary right main bronchus; Tg=tongue; Tr=trachea). The left upper lobe is greatly enlarged.

opened but this was probably a terminal event as it was not detected clinically or on the radiograph during life. The heart lay in the right hemithorax with its apex pointing to the left, the pericardium being loosely anchored to the chest wall in the right mid-axillary line. The anterior mediastinum was absent and there was a single pleural cavity and single lung, the left (Fig. 1A, B). The aortic arch was normal, but the pulmonary artery ran directly to the hilum of the left lung without giving off any branch to the right. The right lung was absent, being represented only by a small, blindly ending bronchial stump arising from the trachea. This vestigial bronchus was 1.3 cm long with an internal lumen 3 mm in diameter. Four or five plates of cartilage were found in the bronchial wall, indicating that development had ceased before the lobar bronchi had formed. The distal end of the bronchus was covered by a nubbin of lung tissue showing the microscopic appearances of the 'glandular phase' (Dubreuil, Lacoste, and Raymond, 1936). The left lung was larger than normal and its upper lobe extended across the midline, filling part of the right hemithorax.

The only other developmental abnormalities were the presence of 13 ribs on each side and the absence of any muscle in the medial half of the left diaphragm. This was composed of a thin translucent layer of connective tissue; there was no diaphragmatic hernia.

EXAMINATION OF SPECIMEN The lungs were inflated and fixed by tracheal infusion of formol saline, at a head of pressure of 60 cm maintained for 48 hr. It was not possible subsequently to inject contrast medium into the fixed vascular tree but as many as possible of the investigations described by Hislop and Reid (1970) were carried out and results of the following are reported for the single lung (the left) present in this patient:

the volume of the left lung and of the right lung rudiment as determined by displacement of water;

the number of branches (this analysis included the use of serial sections) from an axial airway in the posterior basal segment of the lower lobe, and in the anterior segment of the upper lobe; the thickness of the bronchial submucosal gland layer in the left lung, as well as in the rudimentary right bronchus, estimated as a gland to wall ratio (Reid, 1960);

the total alveolar number and the number of alveoli per millilitre, calculated after macroscopic and microscopic quantification of lung tissue elements (Dunnill, 1962; Weibel and Gomez, 1962; Weibel, 1963); radial alveolar counts (Emery and Mithal, 1960);

the branching pattern of the pulmonary artery accompanying each of the two airways mentioned above: the muscularity of the pulmonary artery at different levels in the lung, assessed in relation to their accompanying airways—

respiratory bronchioli, alveolar ducts, and alveoli—and by classifying the small arteries as muscular, partially muscular, and non-muscular (Elliott, 1964);

the ventricular preponderance determined by weighing the left ventricle and septum separately from the right ventricle (Fulton, Hutchinson, and Jones, 1952).

RESULTS

LUNG VOLUME (upper lobe enlarged)

The volume of the vestigial right lung was 3–4 ml, of the left 133 ml, a value considerably above normal since the left lung of a 4-month-old child prepared similarly was 108 ml (Davies and Reid, 1970). This increase in volume was due to enlargement of the upper lobe. In the present case the upper and lower lobes were 74 and 59 ml respectively, in the normal 4-month-old 37 and 71 ml. At all ages the upper lobe usually comprises less than half the lung volume.

Macroscopic and microscopic examination revealed a small area of congestion in the base of the lung but otherwise no pathological change was seen.

BRONCHIAL BRANCHES (reduced)

Along the longest axial pathway in each of the two lobes of the left lung, airway branching patterns were determined by dissection, combined with cutting serial sections of the periphery. In both, fewer bronchial branches than normal were found (Table I). In the upper lobe the bronchus divided 12 times between the hilum and the respiratory bronchiolar region where normally 17 to 20 branches would be found. In the lower lobe airway, 17 bronchial generations were present, the normal range being 19 to 26. Both airways

TABLE I
AIRWAY AND PULMONARY ARTERY BRANCHES

	Upper Lobe		Lower Lobe	
	Normal ¹	Present Case	Normal	Present Case
Airway branches	17–20	12	20–28	17
Pulmonary artery branches				
Conventional	17–20	12	19–26	17
Supernumerary	39–62 ²	19	43–76	24
Total	56–82	31	62–102	41
Ratio—supernumerary to conventional arteries	2.3–3.1	1.6	2.3–3.1	1.4

¹ Normal values (Hislop, personal communication).

² Normal values calculated from lower lobe ratio.

terminated in three generations of respiratory bronchioli. Five non-axial bronchioli were also followed, each giving off between two and five generations of respiratory bronchioli before terminating in alveolar ducts. Boyden and Tompsett (1965) reported four generations of respiratory bronchioli in a 2-month-old infant lung, but added that at this age the distal respiratory bronchioli are rapidly being transformed into alveolar ducts. It seems that in the present case there is a relative increase in the number of respiratory bronchioli between the hypoplastic bronchi on one hand and the excessively numerous alveoli on the other. The impression from examination of sections was that the alveolar ducts were more elongated and narrower than is normal.

BRONCHIAL GLAND THICKNESS (increased)

Both in the rudimentary right bronchus and in the airways of the left lung the submucosal gland layer was thicker than normal, the gland/wall ratio (Reid, 1960) being 0.52 in the left lung and 0.58 in the right rudimentary bronchus.

In the newborn and fetal lung the glands are relatively larger than in the adult, but these glands are even larger than those described by Field, Davey, Reid, and Roe (1966), who reported a group of 40 patients under the age of 4 years. Only two had gland/wall ratios of more than 0.5. Reid and de Haller (1967) found ratios of 0.37 and 0.40 in small groups of fetuses and newborn infants respectively. Since Field (1968) reported that the glands of babies dying with pulmonary infection were even larger for age, the gland hypertrophy of the present case could be due to repeated lung infection rather than to maldevelopment.

ALVEOLAR NUMBER AND SIZE (number increased ; size reduced)

Tissue elements, judged macroscopically (as parenchyma, bronchi, connective tissue, and blood vessels) and microscopically (as alveolar lumen, alveolar walls and alveolar duct lumen), were all present in normal proportions. The alveoli seemed more numerous and smaller than usual, this impression being confirmed when total alveolar number and the number of alveoli per millilitre were calculated (Table II and Fig. 2). Thus the present case has a single lung, whose volume lies between that of one and two normal lungs, and yet has developed 73.75×10^6 alveoli, twice its normal complement. This total alveolar

number is appropriate for the age of the patient. The alveoli are accommodated in only one lung and thus alveolar size is smaller than is normal at this age (Fig. 2).

TABLE II
ALVEOLAR NUMBER AND SIZE

	Total Alveoli ($\times 10^6$)	Alveoli/ml ($\times 10^5$)
Present case—3 mth (1 lung)	73.75	9.2
Stillborn ¹ —38 wk (2 lungs) ²	17.5	10.1
Normal —4 mth (2 lungs)	76.6	7.85

¹ Davies and Reid (1970).

² Calculated from value for left lung.

FIG. 2. The single left lung contains nearly twice its normal complement of alveoli but, because of its large volume, the alveoli are only slightly decreased in size (alveoli/ml).

MEDIAL ALVEOLAR COUNTS (reduced)

Emery and Mithal (1960) gave 4.4 (S.E. 0.17) as the more normal value of the 'radial alveoli count' at birth and 5.5 (S.E. 0.21) for lungs aged between 1 week and 4½ months. In the present case the results were 4.8 (S.E. 0.552) for the upper lobe and 4.95 for the lower lobe, both somewhat lower than is normal for age, being more appropriate to the lung of a newborn. Certainly they are much less than expected from the total alveolar number. An explanation for this is offered below.

PULMONARY ARTERY (number of branches reduced)

The number of branches of the pulmonary arteries accompanying the two axial airways was counted. Fewer than normal branches of the pulmonary artery were found, even taking into account the reduction that would follow the decreased number of bronchi (Table I). Conventional arteries are defined as vessels running with a bronchus and, since bronchial branches are reduced in number, so are the conventional arteries. The supernumerary arteries were also fewer, both absolutely and relatively, the ratio of supernumerary to conventional artery branches in the lower lobe being 1.4:1. The average during fetal life is 2.7:1 (Hislop, personal communication), similar to that found in the adult (Elliott, 1964). The reduction affected the whole length of the vessel, the pre-acinar as well as the intra-acinar region.

PULMONARY ARTERIAL MUSCULATURE (abnormal extension into acinus)

By identifying the structure of 350 arteries running with respiratory bronchioli, alveolar ducts or alveoli, the proportion of muscular, partially muscular or non-muscular arteries running with each type of airway was assessed (Fig. 3). The intra-acinar arteries are more muscular than those present in a normal lung of 3 days or 10

months (Hislop, personal communication): the significance of this is uncertain since Hislop also found that in her case of 4 months these arteries were more muscular.

VENTRICULAR WEIGHTS (right ventricular preponderance)

The heart was dissected and revealed no abnormality apart from a patent foramen ovale (3 mm in diameter). The left ventricle and the septum (LV+S) weighed 16.51 g; the right ventricle (RV) 9.598 g, giving a total of 26.1 g and the ratio of LV+S/RV of 1.72. This indicated mild right ventricular preponderance, the normal left preponderance being represented by a ratio of 2.3 or more (Fulton *et al.*, 1952). This result is probably within the normal limits for the age of the subject. In normal children, according to Arias-Stella and Recavarren (1962), the left ventricle becomes dominant by the age of 6 months. Although he and his colleagues used a slightly different method of dissection of the ventricles, similar findings were reported by Davies and Reid (1970) in a small series investigated by the technique of Fulton and his colleagues (1952).

DISCUSSION

A case of aplasia of the right lung (Schneider, class II) with absent pulmonary artery is presented in which the single lung nearly filled the thoracic cavity. There were no other gross congenital abnormalities and the diaphragm, although abnormally thin on the left, was complete. The single left lung had a large volume of space in which to develop.

The presence of four to five plates of cartilage in the vestigial bronchus suggests that development on that side was arrested before segmental bronchi developed, that is, before the fifth week of intrauterine life. The reduction of branches in the bronchi of the left lung indicates that those airways achieved a degree of maturation equivalent to 12 to 14 weeks of intrauterine life—certainly less than 16 weeks, at which age the bronchial tree is complete (Bucher and Reid, 1961a). The pulmonary artery seems even less developed since, in the preacinar region, its branches are reduced relative to airway number. It may be that an intrinsic abnormality had affected the two lung buds unequally.

The most unexpected finding was the alveolar number. It seems that, despite a poorly developed bronchial and vascular tree, the single lung

FIG. 3. Muscularity of arteries at different levels in the acinus. At this age the vessels would be expected to have less muscle than this.

achieved an alveolar population appropriate for two normal lungs at this age. The alveolar density (alveoli/ml) is higher than normal, indicating that the alveoli are rather smaller than is normal at this age. Contrary to expectation, the radial alveolar count (Emery and Mithal, 1960) was not raised: two factors may have contributed to this. Firstly, the intercept count is an index of the number of alveoli in each 'terminal pulmonary unit'. In the single lung of the present case the number of respiratory bronchiolar generations seems increased and, as a result, the number of alveoli beyond the ultimate respiratory bronchiolus may not be. Secondly, the alveolar intercept count is made in the plane of a line drawn between the lumen of the respiratory bronchiolus and a nearby connective tissue septum, that is, from the centre to the periphery of an acinus. For counts in different lungs to be comparable the acinar shape must be similar; if the impression of lengthening and attenuation of the alveolar ducts in the present case is correct, it follows that the acinus as a whole has become elongated. Alveolar intercept counts would then be taken more often at right angles to the direction of the alveolar duct than down its length; more often across the cylinder of the acinus than from one end to its other. In these circumstances a reduced intercept count could be compatible with an increase in the total number of alveoli. Such an explanation would also be in accordance with Boyden and Tompsett's (1965) finding that alveoli of adult form develop first along the walls of respiratory bronchioli and transitional ducts.

The pulmonary artery was less developed in its number of branches than were the airways. A reduction in conventional branches is expected as these are defined by their association with branches of the airway, but paucity of the supernumerary arteries was greater than of the conventional ones, indicating an intrinsic vascular hypoplasia. Yet the single lung had to accommodate the entire cardiac output, for there were no clinical signs of intracardiac shunt, the foramen ovale being too small to have allowed significant right to left flow. It was unfortunate that formalin fixation of the specimen precluded injection of contrast medium into the pulmonary artery and more detailed study of the vascular tree.

The thickness of the bronchial gland layer is in accord with previous work (Bucher and Reid, 1961b; Reid and de Haller, 1967; Field *et al.*, 1966) describing relatively thicker glands in the

newborn and the child than in the adult. In this case the rudimentary right lung had a thicker gland layer than the left lung, so that bronchial gland size was proportional to the degree of bronchial hypoplasia. It is possible that the gland size, large for age, is a response to the repeated lung infections during the last two months of the child's life.

In the case of hypoplasia of a lung reported by Henderson *et al.* (1971), airway and artery number, as well as alveolar number, were reduced. The number of alveoli per acinus was relatively less reduced, however, and total alveolar number might seem to follow the airway number. There was no mechanical cause for failure of development in this case although the changes were similar to those seen in the case of congenital diaphragmatic hernia described by Kitagawa, Hislop, Boyden, and Reid (1971) in which airway, alveolar, and blood vessel number were all reduced, doubtless due to encroachment upon the thoracic cavity by abdominal viscera.

In the case here reported, bronchial reduction evidently represents an intrinsic fault in the developing airways and yet the alveoli have increased strikingly, which suggests that alveolar and airway development may be stimulated by different factors. It seems likely that the increase in alveolar number began before birth. The only other case in which an increase in alveolar number has been reported is that of the 'polyalveolar' lobe (Hislop and Reid, 1970) found in a newborn, and hence representing antenatal overgrowth. In the contralateral lung of the case of hypoplasia referred to above, Henderson *et al.* (1971) showed that compensatory emphysema, even if occurring soon after birth, is not associated with an increase in alveolar number. In the present case the stimulus to alveolar multiplication was probably the increase in available space; it is probable that to be effective in producing excessive alveolar growth the stimulus must be antenatal.

The findings in such cases have some bearing on the behaviour of the remaining lung after surgical resection. While, after resection, the weight of the ensanguinated residual lung increases rapidly (Cohn, 1939), it is not clear whether airway or alveolar multiplication occurs. Airway multiplication normally occurs only before birth, and numbers above the normal have never been described. Longacre and Johansmann (1940) considered that, if resection is carried out before growth is complete, increased alveolar multiplication occurs: but these and other studies that have been reported (Reid, 1967) would not seem to

justify any general conclusion. The cases discussed above suggest that alveolar multiplication beyond the normal does not occur after birth.

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