THE POSTNATAL DEVELOPMENT OF ALVEOLI IN PREMATURE INFANTS

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The general gross features of development of the alveoli of the lung in the foetus are well known and are described in the textbooks on paediatric pathology (Morison, 1952; Potter, 1952). The classical description of the development of the lung divides its growth into three phases, bronchial, tubular and alveolar, of which the latter takes place last and chiefly after birth. This late alveolar growth was thought to be due largely to the stimulus of breathing (Dubreuil, Lacoste and Raymond, 1936). However, Laumonier (1952) and Lelong and Laumonier (1953) from subjective assessment of the lungs of infants born prematurely, found no evidence of prococious development of the lungs in 'prem' infants and suggested that the growth of the lung was determined by maturity alone.

In order to elucidate some of these problems we have attempted to put some aspects of lung development on an objective and measurable basis (Emery and Mithal, 1960) and have shown that the peri-

pheral respiratory unit has a radial count of about two alveoli at 28 weeks and up to four at 40 weeks gestation age. The present study uses this measurement to compare the alveolar count in children born prematurely who survived for varying lengths of time over 17 days, with the alveolar counts that the same children would have had, had growth continued *in utero*.

Material and Methods

Lung sections from babies born at less than 38 weeks' gestation were surveyed. All those in which there were congenital anomalies of any system and those with gross pulmonary pathology were excluded.

Ten radial counts were made from each case, using the same method as used for establishing normal counts (Emery and Mithal, 1960). To make assessment less biased, lung sections from full-term infants were also included when counting was done. At the time of counting, only the serial autopsy number was known, and no clinical data were available.

From those data, only those cases were selected that had lived for at least one week after birth as only these could be expected to show any maturation changes. Twenty-five such prematurely born infants were thus found suitable for analysis.

The average radial alveolar count from each case was then plotted and related to the gestation age at the time of death. Thus an infant born at 30 weeks gestation age who had lived for six weeks after birth was plotted at 36 weeks gestation age. The graph so obtained was analysed statistically and then superimposed on the chart showing the $2\frac{1}{2}$ and $97\frac{1}{2}$ percentile ranges of stillborns studied previously (Fig. 1).

Statistical analysis was done to test the difference between the means of the liveborn and stillborn groups (Student's 't' test). The formula for 't' tests is:

SURVIVING PREMATURES COMPARED WITH STILLBORNS

FIG. 1.—A chart showing the radial alveolar counts related to gestation age. The mean line and shaded area and the $2\frac{1}{2}$ percentile and $97\frac{1}{2}$ percentile are from normal stillborns. The black spots represent the counts from children born prematurely and surviving for varying periods beyond seven days.

Difference between means/Standard error of difference between means.

The standard error of difference between means is calculated by the formula $\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}$.

The 't' value obtained was compared with the 't' value for the number of cases $(n_1 - 1) + (n_2 - 1)$ that is, 59 cases.

Results

The 36 stillborns showed a mean radial alveolar count of 4.211 ($\sigma = 0.522$) and the 25 premature born of similar gestation a mean radial alveolar count of 3.264 ($\sigma = 0.874$). The difference between the means was 0.947 and the 't' value obtained 4.85, the 't' ratio for tables from 59 cases at 0.001 level being 3.551.

Thus, as shown statistically, the number of alveoli in radial counts from a terminal bronchiole is significantly lower in children born and living over a week after birth than in stillborns of comparable gestational ages.

Discussion

Contrary to the view that birth itself stimulates the growth of alveoli (Dubreuil *et al.*, 1936) we have conclusive evidence that premature birth is associated with a diminished rate of proliferation of alveoli. The diminishing growth may, however, be part of a general diminution in growth associated with factors causing death in these infants. We have reason to believe that this is not entirely the case. The technique applied here, that of comparing measurements of organs of equal gestation age born at different times was used on the growth of the ventricles of the heart. That study showed (in the same cases as were used in the present investigation) no diminution in growth of the right ventricle and actual hypertrophy of the left ventricle after premature birth (Mithal and Emery, 1961). Thus we feel that the relative as well as absolute diminution in growth rate of the lung alveoli found in the present study is valid.

The literature on the lungs of the newborn has largely been concerned with hyaline membrane, atelectasis and infection, but recently Wilson and Mikity (1960) described the post-mortem appearance

of lungs of premature infants who showed late respiratory distress, and found instances of thickened inter-alveolar septa which they thought similar to Hamman-Rich syndrome (Hamman and Rich, 1944). Those (Wilson and Mikity, 1960) lungs are a little like the lungs that MacMahon (1948) described as alveolar dysplasia. That lung picture, however, is one that many of us see not infrequently, and we agree with Potter (Potter, 1948) that it does not represent a specific disease. It seems likely that these lungs (Wilson and Mikity, 1960) could well be the result of a diminished alveolar proliferation in immature infants.

Summary

Radial alveolar counts of the terminal respiratory units from 25 infants born prematurely and surviving for over a week were compared with the counts from stillborns of the same gestation age.

After premature birth, there is a significant diminution in alveolar proliferation of the terminal respiratory unit.

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