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Postnatal human lung growth

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ABSTRACT Standard morphometric methods were applied to the lungs of 36 boys and 20 girls aged from 6 weeks to 14 years, dying as a result of trauma or after short illnesses. Individual lung units, alveolar dimensions, and number of alveoli per unit area and volume did not differ between boys and girls, but boys had bigger lungs than girls for the same stature. This resulted in a larger total number of alveoli and a larger aveolar surface area in boys than in girls for a given age and stature. There may be more respiratory bronchioles in boys than girls. There was rapid alveolar multiplication during the first two years of life and alveolar dimensions and number of alveoli per unit area and volume did not change much during this period. There was little or no increase in the total number of alveoli after the age of 2 years but the data are hard to interpret. There is a wide scatter of the total number of alveoli in the growing lung, in keeping with the observation that the total number of alveoli is very variable in adults. Prediction data are given for the various morphometric variables studied.

In 1962 Dunnill[1] applied the morphometric technique developed by Weibel[2] to postnatal lung development in 10 children of unstated sex between birth and 8 years. He found that there were 20 million alveoli at birth and that alveolar multiplication was rapid in the first few years of life. He reasoned, from the then available data in adults, that alveolar multiplication slowed after the age of 4 years and stopped at 8 years He found a very precise linear relationship between alveolar surface area and body surface area and a correlation coefficient of +0·999 can be calculated from his data. Davies and Reid,[3] although more interested in the growth of the pulmonary arteries, studied alveolar growth in five children between birth and 11 years (three boys and two children of unstated sex) and found similar results for total alveolar number, their figures being about 10% higher than Dunnill's. Thurlbeck and Angus[4] studied lungs from 14 subjects of unstated sex from birth to 19 years and likewise found a rapid increase in total number of alveoli in the first four years of life. Their report, however, differed from the two previous ones in that their data showed a much greater scatter of total alveolar number. Dunnill[1] and Davies and Reid[3] suggested that alveolar dimensions changed little in the first few years of life. Dunnill's data, however, show an increase in alveolar diameter that can be calculated to be significant.

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Reid and Davies showed a fall in alveoli per unit volume in their cases; Dunnill by contrast found no change between birth and the age of 4. In three of the cases of Davies and Reid death was from trauma; one child died after surgery; and one was stillborn. The age of the last is uncertain but the lung volume was about one-quarter that of a full-term infant.[1] The cases in the other two series were derived from hospital necropsies on children dying from non-respiratory causes.

Thus the number of cases studied so far is relatively small: sex differences have not been allowed for; the normality of some of the cases is uncertain; and the results are to some degree conflicting. It thus seemed appropriate to examine lung growth in a larger and better-defined group of cases.

Methods

One or both lungs were obtained from 36 boys and 20 girls between 6 weeks and 14 years of age. Trauma and physical causes were the commonest cause of death (31 cases), followed by infections (20 cases). Five deaths were due to other causes. The children dying of non-traumatic causes had been previously well and died of acute illnesses of less than two weeks' duration. None of the children had previous respiratory or other illnesses requiring hospitalisation. The lungs and heart were removed together and the pulmonary vessels ligated. The heart was removed and static pressure-volume curves were performed on the majority of the lungs.

The lungs were then degassed and distended with 10% formalin and then maintained at a transpulmonary pressure of 25 cm of formalin for at least 24 hours. Lung volume was measured by weighing the lungs in water and in air.[5] When only one lung was available the left lung was considered to form 47·5% of total lung volume and the right 52·5%.[6] The lungs were cut into sagittal slices and these were sampled as previously described.[7] These blocks of tissue were photographed while immersed in water and shrinkage during processing was determined by comparing the size of the blocks to the size of the tissue as seen on the histological slides. Both of these were measured by projecting the images on to a computer-controlled digitiser. With slides 5 μm thick, stained with haematoxylin and eosin, standard morphometric techniques were used to obtain and calculate the following data: average between-intercept distance (Lm), alveolar surface area, volume proportion of alveolar duct air, volume proportion of alveolar air, number of alveoli per unit area, number of alveoli per unit volume, and total number of alveoli. "Alveolar duct air" refers to the core of air lying internal to alveoli in alveolar ducts, alveolar sacs, and respiratory bronchioles. The average transection length of alveoli and alveolar ducts is their volume proportion multiplied by Lm. Average alveolar volume was calculated by dividing lung volume by the total number of alveoli. All measurements are referred back to formalin-fixed lungs distended at a transpulmonary pressure of 25 cm of formalin, which corresponds closely to radiologically determined total lung capacity.[6] Body surface area was calculated from the formula $S = 0{\cdot}007184\ W^{0{\cdot}425} \times H^{0{\cdot}725}$, where S is body surface area, W is weight in kilograms, and H is height in metres.

The morphometric variables were compared with chronological age, body length, and body weight fitting linear ($y = ax + b$), exponential ($y = ae^{bx}$), and logarithmic ($y = a + b.\ln(x)$) regressions. Regression equations were calculated for girls and boys separately and together. A linear regression only was calculated for comparison of body surface area with alveolar surface area. The relation between age and body length and the morphometric variables was about equal and was better than the relationship between body weight and the morphometric variables. For the sake of simplicity, age is used as the independent variable. The cases were also grouped by age and the means compared. The age groupings were: greater than 1 month to 6 months (seven boys, four girls); greater than 6 months to 1 year (three boys, 1 girl); greater than 1 year to 2 years (four boys, four girls); greater than 2 years to 4 years (five boys, four girls), greater than 4 years to 7 years (four boys, three girls), greater than 7 years to 8 years (4 boys, 1 girl), greater than 11 years to 12 years (four boys, one girl), greater than 12 years to 14 years (five boys). Analysis of variance was performed and, when statistically significant, individual groups were compared with t tests, corrected for multiple use.

The number of alveoli per unit volume is calculated from the equation

$$N_V = \frac{N^{3/2}}{B.\ V_{\mathrm{Valv}}{}^{1/2}}\ D,$$

where N_V = number of alveoli per unit volume, N_A = number of alveoli per unit area, B = shape constant describing alveolar shape, V_{Valv} = the volume proportion of alveoli, and D is a distribution variable of the characteristic linear dimension of the alveoli. The total number of alveoli is calculated by multiplying lung volume by the number of alveoli per cm^3. I have used 1·55 as the alveolar shape constant[2] and have assumed that it does not change with age. The distribution variable, D, is assumed to be 1.

Results

SOURCES OF ERROR AND PROBLEMS IN INTERPRETATION

The assumption that alveolar shape does not change with age may be unlikely, but changes in alveolar shape are not likely to change the alveolar shape constant, B, by more than 20%.[8] The assumption that the distribution variable, D, should be 1 is also unlikely, since during alveolar multiplication a wide variation of alveolar size would be anticipated because of the simultaneous presence of developing and developed alveoli. In these circumstances the distribution curve would be skewed to the left. Even wide variations in standard deviation, however, increase D by only about 10%.[2] Thus values for the number of alveoli per unit volume and the total number of alveoli have to be regarded as having potentially significant errors. Values for the number of alveoli per unit area have the same limits. The number seen per unit area is a function of the number per unit volume (the number that is really required), the alveolar shape constant, and the distribution variable.

The nature of the relation between the morphological variables and growth parameters (age, length, weight) is sometimes hard to predict. For example, alveolar dimensions may not change with age in early life, then they may increase but may again remain constant when somatic growth ceases. Thus a sigmoid curve may be the most useful description of growth. In other instances it is clear that certain relations cannot exist—for example, a

Correlation between age (years) and morphometric variables (the first number is* a *in the equations and the second* b*—see under "Methods")*

	Boys	Girls	Boys and Girls
Surface area (m^2)	log*** 21·90, 10·70	*** 18·51, 7·695	—
Between-intercept distance (μm)	lin*** 3·450, 164·7	*** 5·305, 161·1	** 3·786, 164·4
V_{Vduct}	log** 0·1697, 0·01516	NS	—
V_{Valv}	log*** 0·5039, 0·02061	NS	—
V_{Vduct}xLm (μm)	NS	NS	NS
V_{Valv}xLm (μm)	lin*** 2·924, 80·54	*** 3·065, 82·76	*** 2·904, 81·63
V_L (l)	log*** 0·9736, 0·5719	*** 0·7944, 0·4528	—
N_A ($cm^{-2} \times 10^{-1}$)	exp*** 564·2, −0·05107	*** 533·9, −0·04732	*** 551·8, −0·04951
N_V ($cm^{-3} \times 10^{-3}$)	exp*** 433·7, −0·08239	*** 389·2, −0·07093	*** 416·5, −0·07874
N_{AT} ($\times 10^{-6}$)	log*** 311·2, 62·79	** 269·4, 55·49	
V_{alv} ($\mu m^3 \times 10^6$)	lin** 0·2157, 1·055	*** 0·1477, 1·355	*** 0·2003, 1·143

*For abbreviations see legends to figures.
Log (logarithmic), lin (linear), and exp (exponential) indicate the nature of the regression equation.
*** = $p < 0·001$ ** = $p < 0·01$ NS = $p > 0·05$

linear relation between surface area or total number of alveoli and age. In most instances relationships are not very close and there is no great difference between the various types of regression. In general, the regression equation most likely to fit that variable has been given.

The oldest girl in the study was 12 years old and the oldest boy 14. Thus the pubertal growth spurt and its effect on lung growth could not be assessed. (This was the reason for excluding the one 17-year-old whose lungs were collected in this study.) The effect of pubertal growth and the growth spurt is significant. For example, the projected surface area for adults from the given equation derived from children in this study is too small when compared with data on adults.[9–11]

GENERAL CHARACTERISTICS

Six cases were above the 95th percentile or below the 5th percentile for age both for body length and for body weight. Thirteen cases were above the 90th percentile or below the 10th percentile for age for length and 12 for weight. There was no difference in length between boys and girls within the age group studied. This is the anticipated result. They are the same size until girls reach puberty and then girls become taller than boys. Boys then reach puberty and outgrow girls and continue to do so until somatic growth ceases.

SPECIFIC VARIABLES

The table lists the correlations with the regression equations.

Total lung volume, number of alveoli, and surface area

Of all variables, lung volume showed the best correlation and was marginally better related to body length than to age. Figure 1 shows the regression equation and shows that, for age, boys have larger lungs than girls, a difference which becomes significant at about the age of 2 years. Figure 2 compares body length with lung volume and shows that boys have larger lungs, a difference that becomes significant at a height of 110 cm. Another way of

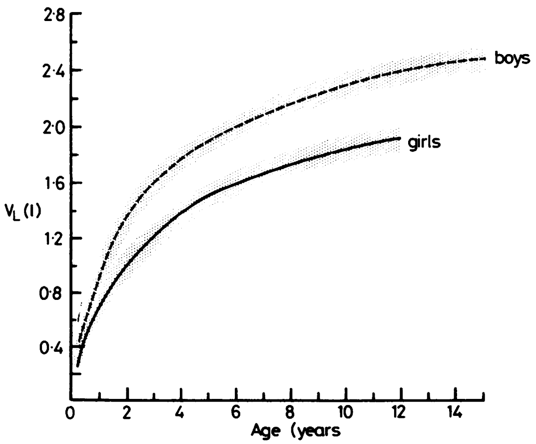


Fig 1 *Regression equations for lung volume against age plotted for boys and girls: mean ± one standard error shown. V_L = lung volume at a transpulmonary pressure of 25 cm formalin.*

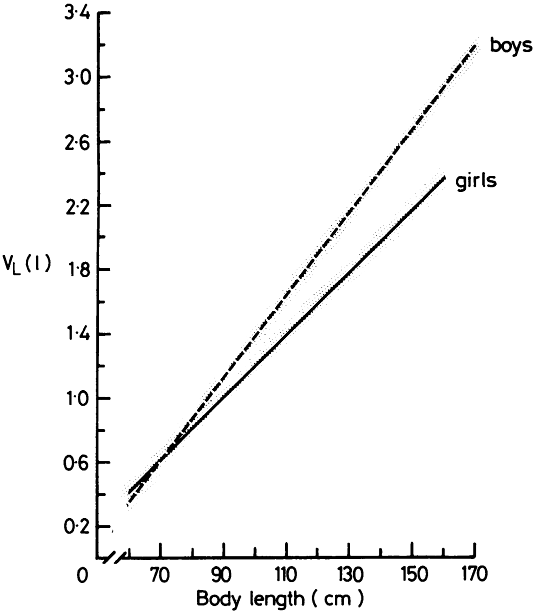


Fig 2 *Linear regression equations for lung volume and body length plotted for boys and girls; V_L as in figure 1 (mean ± 1 SE).*

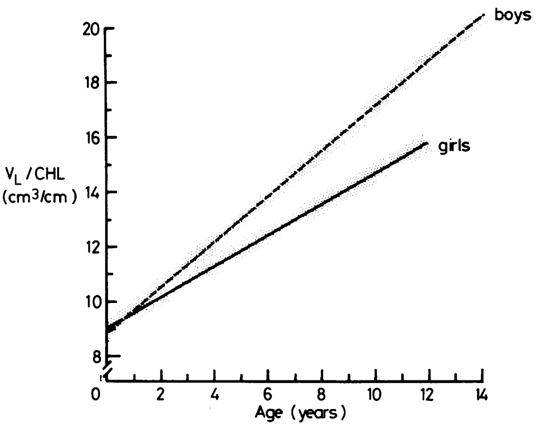


Fig 3 *Linear regression lines for lung volume (V_L) divided by body length (CHL) against age for boys and girls (mean ± 1 SE).*

expressing this is shown in figure 3, which plots lung volume divided by body length against age and shows that with increasing age boys tend to have larger lungs per unit of stature. This has several consequences. The average between-intercept distance (Lm) is the same in boys as in girls and thus alveolar surface area, which is directly related to lung volume and reciprocally related to Lm, is larger in boys than girls (fig 4). The number of alveoli per unit volume and area is identical in boys and girls, and the total

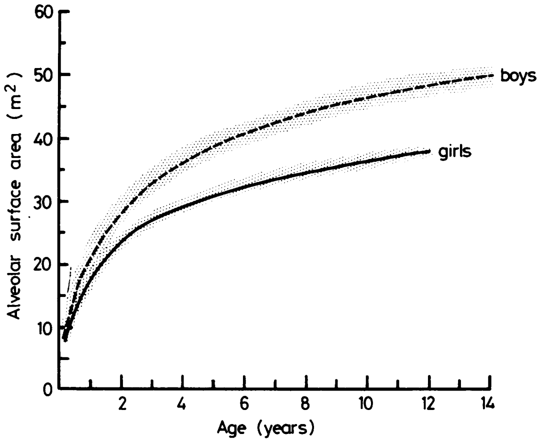


Fig 4 *Logarithmic regression line for alveolar surface area against age for boys and girls (mean ± 1 SE).*

number of alveoli is larger in boys than girls as a consequence of the larger lung volume in boys.

Variables reflecting the way the lung grows

There is a rapid change in the volume proportion of alveoli and alveolar ducts in the first two to three years of life (fig 5). This is significant for all growth parameters and regression equations in boys but only for body weight (alveolar duct air) and height (alveolar air) in girls. In both sexes there is no significant change in the average transection distance of alveolar duct air, but the mean alveolar transection distance and average alveolar volume increase with age. The number of alveoli per unit

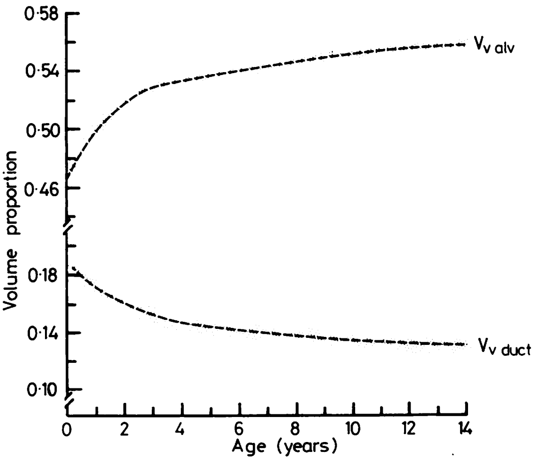
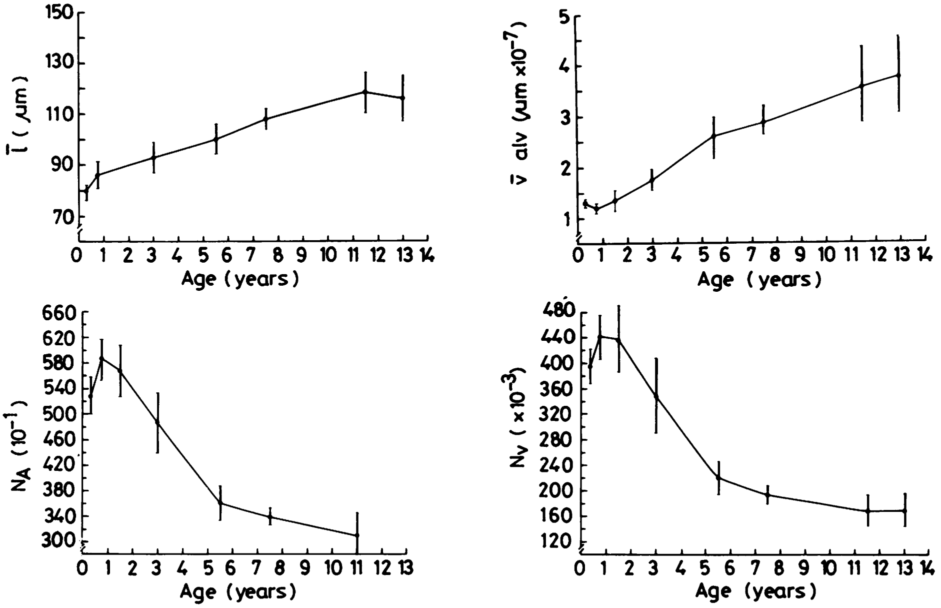


Fig 5 *Exponential regression equations for the volume proportion of alveolar duct air ($V_{V duct}$) and volume proportion of alveolar air ($V_{V alv}$) drawn for boys (mean ± 1 SE).*



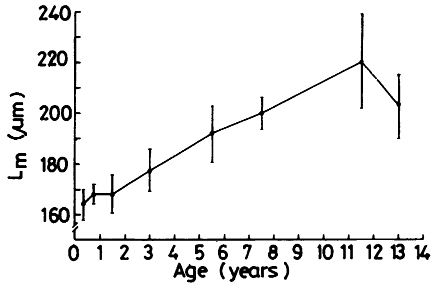


Fig 6 *Top left: Average alveolar transect distance (l); top right: average alveolar volume; middle left: number of alveoli per unit area (N_A), middle right: number of alveoli per unit volume (N_V) and (bottom) between-intercept distance (L_m) are shown in children grouped by age (see text).*

volume and area falls in both boys and girls and the regression lines for these four variables were virtually superimposable.

Grouping cases by age and then comparing the means of these groups may be a more useful method of examining the details of lung growth. It is also possible to group boys and girls together when the variables do not differ significantly between the sexes. The average alveolar transection distance, average alveolar volume, number of alveoli per unit volume, number of alveoli per unit area, and the average intercept distance are shown in figure 6. These data suggest that up to age 2, and perhaps up to 3 on average, alveoli remain about the same size and the number of alveoli per unit volume remains constant. After this age there is an apparent steady increase in linear dimension of about 30% to the age of 14 and about a doubling of alveolar volume during this time. The number of alveoli per unit volume approximately halves.

The total number of alveoli is grouped by age in figure 7. The number of cases is small in each group to that interpretation of the data is difficult. In both sexes (fig 7*a*) there is a rapid increase in the total number of alveoli in the first two years of life and there may be no further increase after that. Boys and girls are grouped together up to 10 years in figure 7*b*. (The proportion of boys and girls is not significantly different in the groups in the ages shown). The resultant curve is smoother, but with large standard errors. Once again there is a rapid increase in the first two years of life, with perhaps no further increase thereafter.

Body surface area and alveolar surface are closely correlated in both boys (r = 0·82, alveolar surface area = body surface area × 37·47 + 4·123) and girls (r = 0·87, alveolar surface area = body surface area × 36·62 + 2·18) and in the two sexes (r = 0·84, alveolar surface area = body surface area × 37·98 + 3·00). From the equation it is apparent that boys

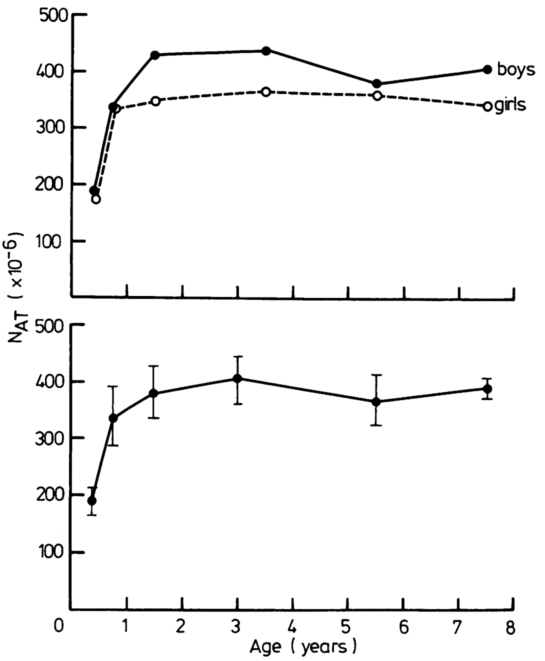


Fig 7 *(a) Total number of alveoli (N_{AT}) shown for (a) boys and girls grouped for age; (b) boys and girls grouped together (means ± 1 SE).*

have a larger alveolar surface area for a given body surface area and this becomes significant when the body surface area is 0·95 m².

Discussion

These data document lung growth more completely than previously, with a larger group of cases that are more nearly normal than those in our previous study[4] or the cases reported by Dunnill.[3]

Of interest was the difference between boys and girls. The difference was primarily in lung volume, which, although well documented in adults, is less well recognised in children. As in adults, the lungs of males are larger than the lungs of females of identical stature.[12] The increase in lung size, however, is brought about not by having larger alveoli but by there being more of them. Elsewhere I have argued that lungs have the same number of airways and that large lungs differ from small lungs in that they have more alveoli per unit peripheral airway.[13] This may not be the case. The radial alveolar count[14] does not differ between males and females (see accompanying papers, pp 572 and 580). The radial alveolar count is a function of the number of alveoli between respiratory bronchioles and the end of the acinus. If males have more alveoli than females, but have the same radial count, this suggests that males have more respiratory bronchioles.

The rapid increase in alveolar air and decrease in alveolar duct air corresponds to the phase of rapid alveolar multiplication. In animals alveolar multiplication is entirely a postnatal event and is brought about by subdivision of primary saccules by secondary crests.[15 16] Primary saccules are simple, tubular structures that do not have an adult counterpart. It has been suggested that alveolar multiplication is controlled by the elastin-collagen network, which acts as though it is an anchoring fishnet through which alveoli protrude.[17] In mice the distance between elastic fibres in the wall of primary saccules does not differ from the distance between elastic fibres around the mouths of alveoli in alveolar ducts in older animals.[16] This suggests that primary saccules form the counterpart of "alveolar duct air," as used in this paper. Thus from this analogy we might anticipate that the decrease in alveolar duct air proportion with age reflects an increase in lung volume (brought about mostly by formation of alveoli), the amount of alveolar duct air remaining relatively constant. This idea is given credence by the fact that the mean alveolar duct transection distance remains constant. Lung volume increases about 10-fold, however, so that the absolute amount of alveolar duct air must increase. If the alveolar duct transection distance does not increase, this indicates that more alveolar ducts must be formed.

These results are similar in some ways, but differ in others, from previously reported results. The following variables are given in, or can be calculated from, Dunnill's paper[1] — average between — intercept distance, number of alveoli per unit area, alveolar surface area, lung volume, number of alveoli per unit volume, total number of alveoli, and average alveolar volume. All variables, except average alveolar volume in one case, fall within two standard deviations of the mean of the data presented here. Dunnill's average between-intercept distance and number of alveoli per unit area are close to the mean values presented here; lung volume and surface area are generally lower than the mean; numbers of alveoli per unit volume are all below the mean; and average alveolar volumes are all above the mean reported here. In the data presented by Davies and Reid[3] the number of alveoli per unit volume is greater than two standard deviations above the mean in the present data and the average alveolar volume is more than two standard deviations below the mean. The linear regression lines for lung volume and between-intercept distance reported by Thurlbeck and Angus[4] are about 10% lower than those calculated from the present data and the number of alveoli per unit volume is

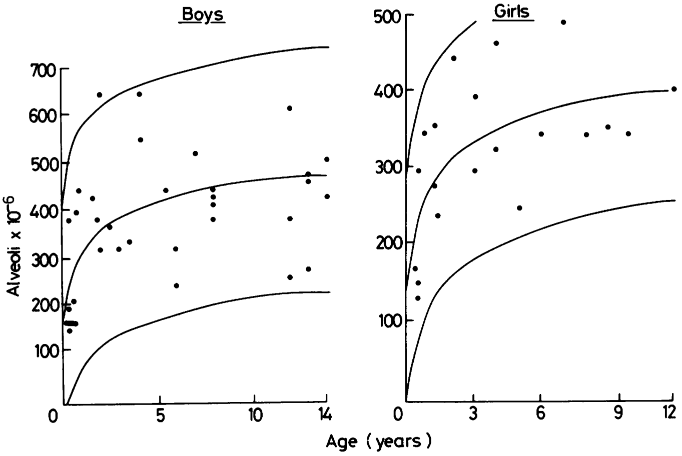


Fig 8 *Total number of alveoli, with the regression lines, compared with age in boys and girls.*

almost precisely the same. Although alveolar surface area and body surface area are closely correlated the precise correlation found by Dunnill did not occur in this study.

A major difference in results is in the total number of alveoli in the lung. Our data indicate a higher total alveolar number than those of Dunnill[1] and Davies and Reid[3] but it is not clear why this is the case. Inter-observer variation may account for this in part, although in our laboratory this variation between workers is acceptably small. Our definition of "alveolar ducts" is different from that of others and it is not clear whether other authors have included alveoli that are found in alveolar ducts and respiratory bronchioles in their number of alveoli per unit area and volume. If not, then this would account for our high total number of alveoli. Another reason for the greater total number of alveoli is that, while total alveoli per unit area was about the same in Dunnill's study as in this one, our lungs had larger lung volumes. Why this should occur is not clear.

Our present data also show a wide scatter rather than the close fit reported by Dunnill[1] and Davies and Reid[3] between total alveolar number and age. This is true even when boys or girls are considered alone (fig 8). A wide scatter is perhaps to be anticipated. Elsewhere we have shown that the total number of alveoli in adult human lungs may vary from 212 $\times 10^6$ to 605 $\times$ 10^6 and that the total number of alveoli is directly related to stature.[18] This wide variation means that there should be a wide variation in total alveolar number in developing lungs.

The wide variation in alveolar number has another consequence. In his classical paper Dunnill[1] argued that alveolar multiplication was slow after the age of 4 and stopped by 8 years. He based this on his observations that the 4-year-old child in his study had 257 $\times$ 10^6 alveoli and the 8-year-old child 280 $\times$ 10^6 alveoli. He claimed that the former number was significantly different from the adult number of 296 $\times$ 10^6 but the latter was not. Because of the wide variation in adults, however, the conclusion is not necessarily correct. For example, the 4-year-old child falls within the wide normal range and we could argue that alveolar multiplication ceases at this age. Alternatively, the 8-year-old child may have been destined to have a total number of alveoli in the high normal range and thus perhaps half of the alveoli appear after the age of 8. The present data are not very helpful. The wide scatter of data presented here makes conclusions from regression lines tenuous. The logarithmic regression for both boys and girls (fig 8) has a shape very similar to the curve found by Dunnill.[1] This indicates a similarity to his results—that is, a slow increment in alveolar number between the ages of 4 and 8 years, and little increase thereafter. Grouping the data did not clarify the issue and, indeed, suggested a different conclusion. The total number of alveoli did not increase significantly in statistical terms after the group aged 6 months to 1 year and this reflects the large standard errors resulting from small numbers in the groups. The way the cases are grouped is arbitrary and other groupings can be used. For example, if we group cases under the age of 1 year and compare this group to cases over 6 years, then there is a statistically significant difference. Descriptively, there appears to be an increase in total alveolar number up to the age of 2 in boys and an increase up to 4 years in girls, and also in boys and girls grouped together. These data, with the data on alveolar dimensions (fig 6), suggest that the great bulk of alveoli are present by the age of 2 years and limited, or no, alveolar multiplication occurs subsequently.

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