Letters to the Editor

The study of Kendeel and Ferris in your May 1977 issue reports no significant increase of muscle in the pulmonary arterioles and arteries of victims of the sudden infant death syndrome (SIDS). This is counter to a previous study from our laboratory which found an increase of such muscle in the SIDS victims (New England Journal of Medicine, 1973, 289, 1167). The methods used by Kendeel and Ferris would not likely demonstrate the vascular abnormality. Our original study found that pulmonary arterioles were dilated in SIDS victims. Kendeel and Ferris will have excluded the largest arterioles in SIDS victims from their analyses, those with the most muscle, because dilatation gave these largest arterioles a diameter greater than the 100 micron limit established for arterioles. Dilatation would have had a similar effect on measurements from arteries which were limited to 101-200 microns diameter and on the number of medial nuclei in both arterioles and arteries. If the arterioles and arteries dilated over their normal size limits had been included in the analyses, the SIDS victims would almost certainly have had more muscle in these vessels than the non-hypoxic and acute hypoxic controls.

The relative size of arteriolar and arterial muscle cells is less affected by vessel dilatation, and the data of Kendeel and Ferris show the SIDS victims with somewhat larger muscle cells in their pulmonary arterioles than the acute hypoxia controls (p < 0.01). This difference between the SIDS victims and the controls would have been substantially greater if the comparison had used cytoplasm/muscle cell rather than total cell size. It has been shown repeatedly that the size of muscle cell nuclei in pulmonary arterioles and arteries is not affected by chronic hypoxia.

The acute hypoxic controls used by Kendeel and Ferris are suspect, because they died with respiratory tract infections. Children who have repeated episodes of sleep apnoea have recently been found to have an excessive death rate in early life from respiratory tract infections. Monitoring has shown that many children with repeated episodes of sleep apnoea have chronic hypoxaemia between apnoeic episodes. Thus children who die with acute respiratory infections in the early months of life cannot be assumed to have been free of chronic hypoxia during sleep before the onset of the fatal illness.

Victims of accidents and homicide used as non-hypoxic controls by Kendeel and Ferris cannot be used uncritically for this purpose. We have found that a high proportion of homicides and a smaller proportion of accident victims have evidences of brain damage incurred before the final traumatic event. There is no way to be certain that such brain damage does not influence alveolar ventilation and therefore a very thorough postmortem study of such brains must be undertaken before such cases can be used as non-hypoxic controls. In our original study of pulmonary vessels in SIDS victims, more than half of the homicide and accident victims considered as possible controls were excluded from the analyses because of brain abnormalities, often subtle.

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The authors have commented as follows:

Thank you for allowing us the opportunity to reply to Dr Naeye's comments on our paper in the Journal of Clinical Pathology, 30, 487, 1977.

It was not the purpose of our study to investigate vessels of all sizes in the lungs of our cases. This study was stimulated by the findings of Dr Naeye (the New England Journal of Medicine, 1973, 298:1165). However, unlike his reported results, which were restricted to vessels of less than 100 microns, we expanded our investigations to include arteries and arterioles of up to 200 microns.

We agree that the problem of vascular dilatation or contraction renders the quantitative assessment of arterial muscle tissue difficult, and our studies showed that dilatation of pulmonary arterioles was not a constant finding in all cases of sudden infant death syndrome (SIDS). In addition, various degrees of dilatation, and sometimes contraction, were found in cases from all groups under study. As we reported, the problem is largely compensated by dividing the medial muscular area by the number of medial muscle
nuclei, which presumably remains a constant number. The relative proportion of nuclear size to quantity of cytoplast will not have any significant effect upon the total thickness of a vessel wall.

It seems that one major area of disagreement is with regard to an interpretation of the term ‘chronic hypoxia’ and the term must be defined separately for each study. In our cases we considered that children who were the subject of acute respiratory illness of less than seven days’ duration were not chronically hypoxic. Using this as our basis, we have clearly shown that with regard to the amount of muscle tissue in pulmonary vessels of less than 200 microns, SIDS, sudden deaths from trauma, and children dying with acute respiratory infections of less than one week’s duration all are statistically comparable, and the amount of muscle present is significantly less than that in neonatal deaths and congenital heart disease. We chose our cases after careful clinical and postmortem studies, which led to the exclusion of about two out of three possible control cases.

Our findings do not exclude the possibility that cases of SIDS are subjected to repeated episodes of hypoxia, as suggested by Steinschneider (Pediatrics, 1972, 50: 646), but simply that by using pulmonary vessel muscle thickness as an indicator, SIDS cannot be readily distinguished from most other rapid infant deaths of whatever cause and that they are significantly different from neonates and children with chronic respiratory embarrassment.

We think that the evidence for hypoxia being an essential part of the sudden infant death syndrome is overwhelming, and we have reported elsewhere that repeated episodes of hypoxia could account for a significant difference in the amount of fibrous remoulding of the conducting tissue in such cases (Journal of Pathology, 1975, 117:123). However, it is our unrepentant view that a study of the amount of muscle in pulmonary vessels of less than 200 microns in SIDS as a means of determining evidence of chronic hypoxia will be unrewarding.

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Alpha-1-antitrypsin globules in the liver and PiM phenotype

The case of α₁-antitrypsin phenotype PiM with intrahepatic globules recorded recently in the journal (Bradfield and Blenkinsopp, 1977) is almost certainly a carrier of the variant allele M₉duarte, described by Lieberman et al. (1976), which has PiM electrophoretic mobility, intrahepatic globules, and a serum α₁-antitrypsin level approximately the same as the Z allele. The PiM phenotype (Cox, 1976) and the ‘M-like’ phenotype (Kueppers et al., 1977) may also be identical with the PiM phenotype. The serum level of 2.3 g/l at 24 hours after major surgery is perfectly consistent with heterozygosity for the deficiency allele M₉duarte. The case of Bradfield and Blenkinsopp (1977) would therefore be more aptly said to have an ‘apparent M phenotype’ or an ‘M-like phenotype’. Their conclusion that the identification of characteristic globules can no longer be regarded as conclusive evidence of an abnormal α₁-antitrypsin phenotype is ill-founded when based on their evidence.

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References


The authors have asked Dr Cook to comment on their behalf.

Dr Kelly points out that the patient described as Pi type M by Bradfield and Blenkinsopp (1977) is ‘almost certainly’ a carrier of the variant allele PiM (sometimes known as M₉duarte). We must admit that anyone of the apparent phenotype M might be a carrier of this variant allele unless it could be excluded by family studies (which were not possible in this case). We considered the possibility of the genotype PiM⁻PiM (but thought it most unlikely for two reasons. The intensity of the Pi M bands was greater than we have ever seen in any Pi M heterozygote, even after surgery. Secondly, the PiM phenotype must be rare in the United Kingdom. We have studied 177 unrelated Pi Z individuals but have seen no examples of PiM⁻PiM homozygotes. Moreover, we have typed samples from 812 other unrelated individuals of various variant phenotypes such as Pi MS, where we would expect to detect the product of the PiM phenotype, yet have noticed it only once. We suspect that our patient was almost certainly not a carrier of the PiM phenotype.

Our case would have been stronger if the patient had been of a Pi phenotype such as S or MS, when a more positive exclusion could have been made. By chance, Fisher et al. (1976) have now described a Pi MS patient with globules in the liver. We admit that if our patient was of the common Pi phenotype M, he could not easily be explained on the current established genetic hypotheses about the Pi system. But this was one motive for publication.

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References
