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Increased incidence of lymphoreticular aggregates in lungs of children found unexpectedly dead

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Emery, J. L., and Dinsdale, F. (1974). *Archives of Disease in Childhood*, **49**, 107. **Increased incidence of lymphoreticular aggregates in lungs of children found unexpectedly dead.** A quantitative study was carried out of the number of lymphoreticular aggregates in standard sections of the lungs of 316 children. Of these, 128 showed no recognizable lung disease, 104 of whom presented as sudden unexpected death. The number of lymphoreticular aggregates was higher in the unexpected than in the expected child deaths.

As lymphoreticular aggregates are nonspecific indicators of previous antigenic stimulation, it follows that many of the children in the unexpected death group had been subject to a greater amount of such stimulation.

As part of a general study of the development of the lymphatic tissue in the lungs of children (Emery and Dinsdale, 1973), the lungs from children found unexpectedly dead ('cot deaths') were analysed as a group. This paper is concerned with the findings in lungs that appear to be histologically normal in children found dead, as compared with children dying under hospital circumstances.

Material and methods

Our method involved taking standard cross-sections across the middle right lobe of all lungs at necropsy, and a quantitative assessment was made of the number and location of lymphoreticular aggregates and lymph nodes within such sections. Details of the method used are described elsewhere (Emery and Dinsdale, 1973).

The right middle lobes of 316 children were studied and the scoring of the lymphatic tissues of the lungs was carried out with no knowledge of the age or type of death of the child. The lung sections of this lobe were independently reassessed together with sections from all other lobes of the lung. All lungs showing any pathological feature were eliminated, thus excluding any mild tracheitis, bronchitis, or other inflammatory reaction within the respiratory tract but not the presence of lymphoreticular aggregates within the lung field. The presence of a small amount of oedema in the alveoli or of a few apparently free cells lying within partially collapsed alveoli were not considered indications for eliminating lungs, as these can be found at every necropsy.

In this way 105 lungs were eliminated. In addition, 68 children were either stillborn or died within 2 weeks of birth, and 15 were more than 1-year-old. This left 128 presumably normal lungs from children aged 2 weeks to 1 year, of which 104 were sudden unexpected deaths.

We subdivided the children found unexpectedly dead into four categories as listed below.

Group A. Children found to be suffering from some long-standing disease such as congenital heart disease or mongolism, and in whom death was likely, or probably inevitable at some point.

Group B. Children dying from known relatively acute diseases such as pneumonia, pyelonephritis, meningitis, or acute tracheobronchitis.

Group C. Children dying with histories of minor illness and in whom minor pathological features were found, such as minimal tracheitis, minute areas of pneumonia, or skin sepsis, or laryngitis, i.e. pathological findings that would be likely to be found and are indeed frequently found in children killed by motor accidents. Such findings thus represent normal recoverable and treatable disease.

Group D. Children in whom no definite recognizable disease-producing or symptom-producing pathological features were found. This group is subdivided into those cases in which there was indirect evidence of preceding disease, such as the presence of fatty changes in the liver, discharge of thymus, or growth arrest of the rib, and those children in whom no lesions whatever were found.

Using the criteria put forward at the Second Seattle Conference (Bergman, Beckwith, and Ray, 1970), groups

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C and D were children who would be accepted in the 'Unexpected Death in Infancy Syndrome'. For the purposes of general comparison, these groups were combined. Children of group B were almost wholly eliminated due to the presence of definite pathology, but in group A there were a few cases in which no immediate cause of death could be discovered.

The lymphoreticular aggregates in the lung were divided into two groups: those lying in intimate relation with the alveoli and those lying in the connective tissue or within the walls of the bronchi and bronchioles. This distinction is made since the peripheral alveolar aggregates appear unquestionably to be acquired lesions, whereas lymphoreticular aggregates lying within the connective tissue and in association with lymphatics within the lung could, in some instances, represent an early stage in the development of lymph nodes.

Results

In the Table the average number of aggregates among sudden deaths and among other deaths is compared in each of three age groups within the range 2 to 30 weeks. Total lymphoreticular and peripheral alveolar aggregates are tabulated separately and are also shown in Fig. 1 and 2, respectively.

TABLE

Number of children in different age groups found suddenly unexpectedly dead (SUD) and others; and average number of lymphoreticular aggregates in the standard sections of right middle lobes of lungs

Age group (wk)	Category	No. of cases	Average no. of aggregates in lung section	
			Total	Peripheral
2–6	SUD	15	2·26	0·07
	Others	9	0·70	0
7–15	SUD	50	6·00	1·58
	Others	6	1·00	0·17
16–30	SUD	33	6·48	2·00
	Others	4	4·00	0·25

These figures suggest a trend of increasing numbers of aggregates with increasing age at death and higher values for sudden death than for the others. Statistical analysis of the data is given at the end of the article.

This analysis showed that the mean number of total aggregates per necropsy was significantly higher among the sudden deaths than among other deaths (allowing for differences between age groups). Allowing for this difference between the two types of death, the number of total aggregates was also found to differ significantly from one age group to another. There was no evidence to show that the *difference* between the sudden and other deaths varied from one age group to another. For peripheral aggregate counts there was no evidence of significant age differences or that such differences had been masked by differences between the types of death.

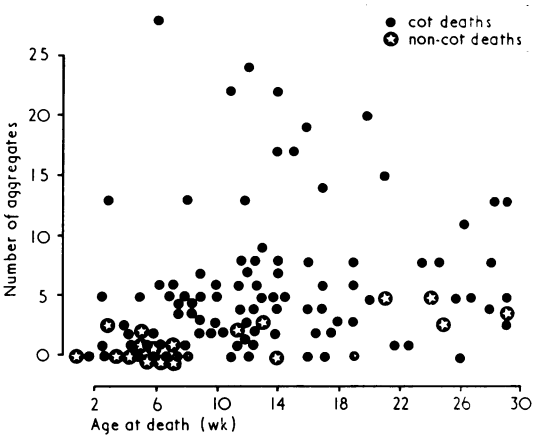

FIG. 1.—*Total aggregate score for right middle lobe standard sections. Scores from children found unexpectedly dead and in whom no lung pathology was found are shown as black dots, and those of children dying in ordinary hospital circumstances are indicated by stars in circles.*

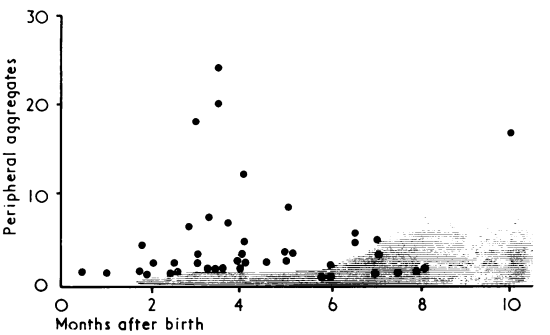

FIG. 2.—*Peripheral aggregate scores for the right middle lobe standard sections. Scores from children found unexpectedly dead and in whom no lung pathology was found are shown as black dots set against the total range of children dying in ordinary hospital circumstances (hatched area). Lungs from cot deaths scoring no aggregates are not marked on this chart.*

Discussion

Lymphoreticular aggregates (Fig. 3) consist predominantly of lymphocytes but include a few plasma cells, eosinophils, macrophages, and an occasional polymorphonuclear cell within a loose

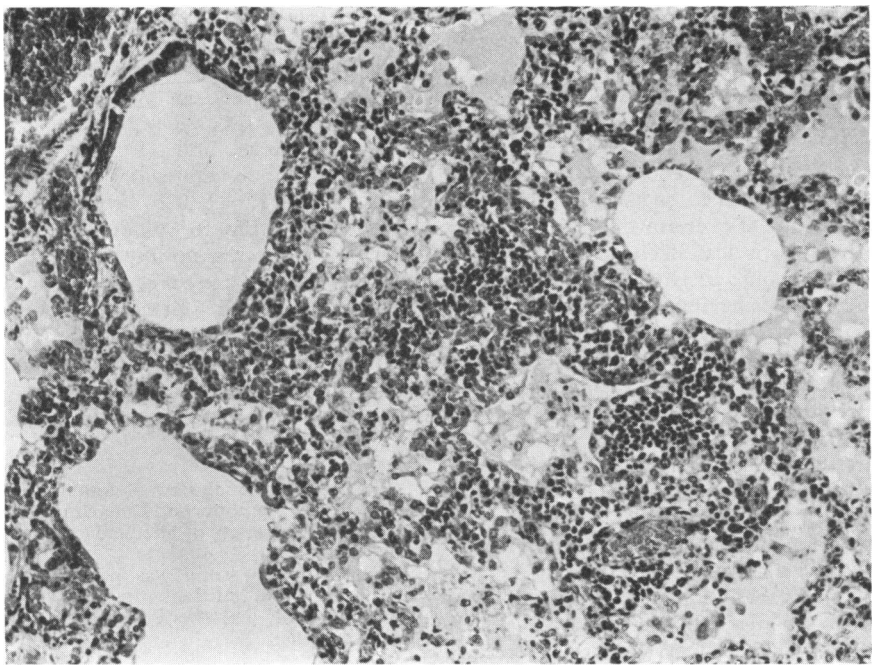

FIG. 3.—*Lung from a child showing a lymphoreticular aggregate.* (×160.)

irregular reticulin network (Jelinek and Jelinkova, 1957). Such lesions occur at the site where the cellular immunological reactions take place. Aggregates develop within a week of the antigenic stimulus and can persist for varying lengths of time, but are not necessarily permanent structures (Ward, Johnson, and Abell, 1963; Movat and Fernando, 1965; Green and Kass, 1964; Horowitz *et al.*, 1964). The importance of these structures in infant lungs was drawn to our attention by the work of Jericho (Jericho, 1968, 1970) on the formation of such aggregates in the lungs of newborn pigs delivered by caesarean section under sterile conditions and maintained in a germ-free state. Such pigs did not develop lymphoreticular aggregates in the lungs and the lungs remained free of such aggregates up to an age that would be equivalent to at least 3 years in a human child. When they were allowed to breathe air containing bacteria, viruses, or live or dead parasites, lymphoreticular aggregates developed in virtually direct dose-related quantities (Jericho, Derbyshire, and Jones, 1971b). When similar pigs were subjected to inorganic material such as carbon (i.e. nonantigenic substances), aggregates were not found (Jericho *et al.*, 1971a). Jericho (1970) also found that he could relate the number of aggregates in domestic pig's lungs to the general condition under which the pigs were raised, the highest count being found in pigs bred where hygienic conditions were poor and where regular cleaning of litter was not carried out. The implication from Jericho's work is that the presence of peripheral lymphoreticular aggregates in lungs is a direct indication of the amount of biologically active airborne material in the local environment.

Our work on lymphoreticular aggregates in children's lungs indicates that the normal newborn human lung is free of aggregates, that they increase progressively in number after birth, and that the significance of the aggregates is the same in the human as it is in the pig. Our present findings that over half of the children found unexpectedly dead, and in whom no specific lung disease was found, have a level of peripheral reticular aggregates outside those of apparent normals, suggest that this group contains children having enhanced environmental antigenic stimulation. In the absence of identifiable parasites, lymphoreticular aggregates are non-specific, and the precise antigenic stimulus in any child is not at present assessable. It could be bacteria, viruses, parasites, or antigenic proteins, and thus the stimulus could be provided by inhaled milk or by home contacts with open respiratory tract infections. There is no evidence to suggest that the presence of peripheral lymphoreticular aggregates in the lungs are themselves a cause of

death, or even cause any disability. They appear to be respiratory antigenic markers—they indicate experience.

The socioeconomic groupings of children found unexpectedly dead are known to be largely orientated within Social Classes III, IV, and V (Froggatt, Lynas, and Mackenzie, 1971; Richards and McIntosh, 1972), i.e. social groups where environmental factors of overcrowding are increased and general hygiene is less likely to be observed. We know little about air hygiene in domestic situations, such studies having been largely confined to hospitals, naval establishments, and factories.

Among the theories of the cause of cot deaths, that of cow's milk allergy has recently been popular. If a child had previously inhaled some foreign protein, it would be likely to produce lymphoreticular aggregates in the lung. Our own material from children who have been unconscious and convulsing shows that such lungs frequently show a great increase in the number of lymphoreticular aggregates.

There is no doubt that virus infections are in some way related to many unexpected child deaths (Gardner, 1968), and Gardner and his co-workers (1967) have incriminated respiratory syncytial virus in certain deaths. Gardner has suggested that the lethal effect of the virus may be in its second rather than its first invasion, and it could well be that the high aggregate counts in some of our cot deaths support such a thesis.

About a quarter of the children dying unexpectedly in our present group had no increase in lymphoreticular aggregates in the lungs and thus, apparently, came from a clean antigenic environment. It is unlikely that sudden unexpected death in infants is due to a single pathological process.

Assessing the number of peripheral lymphoreticular aggregates in the lungs of 'cot deaths' should enable us to separate out those in which death may be determined by respiratory antigen as against those that are biochemically determined or of nervous origin. Our findings indicate that within the category of unexplained child deaths there is a case for detailed study and measurement of the antigenic state in the environment of a particular group of these children, and that the significance of those found to be reacting needs further examination.

Statistical analysis

To compare the mean number of aggregates for the two types of death (sudden unexpected and other) the two-way analysis of variance technique for unequal sized cells was used.

The mean number of aggregates per necropsy was significantly higher ($P = 0 \cdot 025$) among the sudden deaths than among other deaths (allowing for differences between age groups).

Using the three age groups (1·5–6·4 weeks, 6·5–15·4 weeks, and 15·5 to 30·4 weeks) the number of total aggregates was found to differ significantly ($P = 0 \cdot 025$) from one age group to another (allowing for differences due to type of death). There was no interaction, i.e. no evidence that the effect of age *per se* was any different for the sudden than for the other deaths.

For peripheral aggregate counts, differences between the three age groups, between the types of death, and the age/death-type interaction were not significant.

The statistical analysis was done by Dr. R. A. Dixon and Mr. A. Lambourne, Department of Community Medicine, University of Sheffield. Photographs by Mr. Alan Tunstill.

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