PAPERS AND ORIGINALS

Role of Respiratory Viruses in Childhood Mortality

M. A. P. S. DOWNHAM, P. S. GARDNER, J. McQUILLIN, J. A. J. FERRIS

British Medical Journal, 1975, 1, 235-239

Summary

Respiratory viruses have been identified at necropsy in the lungs of 13 out of 24 children who died with observed acute respiratory illness. The histological appearances of the lungs supported the association between virus and death in each of these 13 children and suggested an unidentified virus aetiology in a further five cases. Histological appearances compatible with bacterial infection were found in the lungs of only two of the 24 children.

Similar virus and histological findings have been reported in about one-third of victims of the sudden infant death syndrome (cot deaths), indicating a rapid unobserved respiratory virus infection as the most likely mode of death in this group. Evidence that respiratory viruses may be involved in a larger proportion of sudden unexpected deaths, perhaps as antigens in a hypersensitivity reaction, is discussed.

Respiratory viruses seem the major identifiable agents contributing to the maintenance of the postneonatal mortality rate since acute respiratory illness and the sudden infant death syndrome together account for about two-thirds of deaths at this age.

Introduction

Most deaths in childhood after the first month of life occur during the first year (table I). The mortality rate for this postneonatal age group over the past 20 years has not shared the improvement shown by the perinatal mortality rate (Department of Health and Social Security, 1970). The postneonatal and perinatal mortality rates over the past 20 years for England and Wales are shown in fig. 1. The rates for Newcastle upon Tyne are shown also, indicating that the trends on Tyneside are broadly representative of the country as a whole.

TABLE I—*Numbers of Childhood Deaths by Age in Newcastle 1967-71*

	1967	1968	1969	1970	1971	Yearly Average
Perinatal Deaths						
Stillborn	71	49	48	39	54	52
<1 week	49	30	24	30	30	33
1-3 weeks	13	7	9	12	5	9
Postneonatal Deaths						
4 weeks-1 year	31	39	21	26	35	30
1-4 years	14	10	9	7	15	11
5-14 years	10	13	11	10	13	11

Respiratory infection and congenital anomalies have long been recognized as two major causes of death during the postneonatal period (*Registrar General's Statistical Reviews of England and Wales 1948-71, 19[illegible]-73*). More recently, however, the concept of grouping together children dying suddenly and unexpectedly as victims of sudden infant death syndrome (S.I.D.S.; Bergman *et al.*, 1970) has introduced a third major category. In England and Wales the study of the incidence of this syndrome has been hindered by the inability until recently of pathologists and coroners to enter it as a cause of death on death certificates. In 1971 S.I.D.S. became recognized by the Registrar General as a registrable cause of death, but it has not yet gained a place in the International Classification of Diseases. Studies of incidence in Northern Ireland (Froggatt, 1970; Marshall, 1970), however, agree with local studies in England and Scotland (Richards and McIntosh, 1972; Fedrick, 1973; Milligan, 1974) in assessing the incidence of S.I.D.S. at between 2 and 3 per 1000 live births.

A retrospective analysis of postneonatal death certificates in Newcastle upon Tyne (total population 274 000) for 1967-71 showed that S.I.D.S. and acute respiratory infection together seemed to be responsible for about 63% of the total (table II). We could not distinguish between S.I.D.S. and respiratory deaths because sudden unexpected deaths had often been labelled as acute bronchiolitis or pneumonia and retrospective clinical and necropsy details were incomplete.

It seems, therefore, that respiratory infection and S.I.D.S. each contribute about one-third of postneonatal deaths, while congenital anomalies may be responsible for about one-fifth.

Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

M. A. P. S. DOWNHAM, M.R.C.P., D.C.H., First Assistant, Child Health
P. S. GARDNER, M.D., DIP.BACT., Professor of Clinical Virology
J. McQUILLIN, F.I.M.L.T., B.SC., Principal Scientific Officer, Department of Virology
J. A. J. FERRIS, M.D., D.M.J., Senior Lecturer in Pathology, Department of Pathology

TABLE II—*Causes of Postneonatal Deaths for Newcastle 1967-71 as Indicated by Death Certificates*

	1967	1968	1969	1970	1971	Total (%)
Respiratory infection + S.I.D.S.	20	18	17	17	24	96 (63)
Congenital anomalies	9	13	1	4	7	34 (22)
Other	2	8	3	5	4	22 (14)
Total	31	39	21	26	35	152

These figures may underestimate the parts played by both respiratory infection and S.I.D.S. in two ways. Firstly, children with congenital anomalies often have a terminal respiratory infection and, secondly, some children are excluded from the category of S.I.D.S. by the necropsy finding of congenital anomalies, which may not of themselves constitute an adequate explanation for their sudden death.

The major part played by viruses in the aetiology of respiratory illness in the first year of life is well established and their association with fatal respiratory illness has been reported though not in a consecutive series (Aherne *et al.*, 1970).

The association between viruses and S.I.D.S. has been examined by many workers (Gold *et al.*, 1961; Ray, 1970; Brandt, 1970), but virological techniques, the selection of material for investigation, and the special interest of the investigators have all varied widely so that studies have produce inconsistent results. The recent application of the immunofluorescent antibody technique to necropsy material (Gardner *et al.*, 1970) has enabled a more reliable demonstration and localization of virus antigen in the respiratory tracts of some children with S.I.D.S. to be made, and this association has been strengthened by the demonstration of histological changes compatible with virus infection in the lungs of the same children (Ferris *et al.*, 1973).

In this paper we describe the viruses found and the histological appearances of the lungs in an unselected series of 24 children who died with acute respiratory illnesses. As well as indicating the frequency of the involvement of viruses in respiratory deaths we draw attention to the similarities—clinical, virological, and histological—between these deaths and those of victims of S.I.D.S.

Methods

VIROLOGY

For several years necropsy material from the lower respiratory tract of children dying after the first week of life with respiratory illnesses in Tyneside hospitals has whenever possible been investigated for the presence of viruses by methods previously described, including immunofluorescence (Ferris *et al.*, 1973).

The quantity of fluorescent virus antigen in lung sections was assessed on a three-point scoring system (+ to +++) without knowledge of the histological appearances.

LUNG HISTOLOGY

The histological changes in the lungs of the 24 children were assessed without knowledge of the virus findings. Three categories of lung histological changes have been described in cases of S.I.D.S. (Ferris *et al.*, 1973): type 1, varying degrees of congestion, increased cellularity and oedema of alveolar walls, and intra-alveolar haemorrhage; no peribronchiolar lymphocyte infiltration and no infiltration with polymorphs; type 2, varying degrees of peribronchiolar lymphocytic infiltration, and necrosis of bronchiolar epithelium; small bronchioles often plugged with mucus and cell debris; and type 3, polymorphonuclear leucocytes have infiltrated bronchi and bronchioles, and packed alveolar spaces; inflammation principally lobular in distribution.

When the histological appearances of the lungs of the 24 children were examined we found it necessary to describe a fourth category: type 4, easily identifiable lymphocytic infiltration of alveolar walls and interstitial lung tissue, sometimes associated with a minor degree of peribronchiolar lymphocytic infiltration. Examples of these types of lung histology are shown in figs. 2-5.

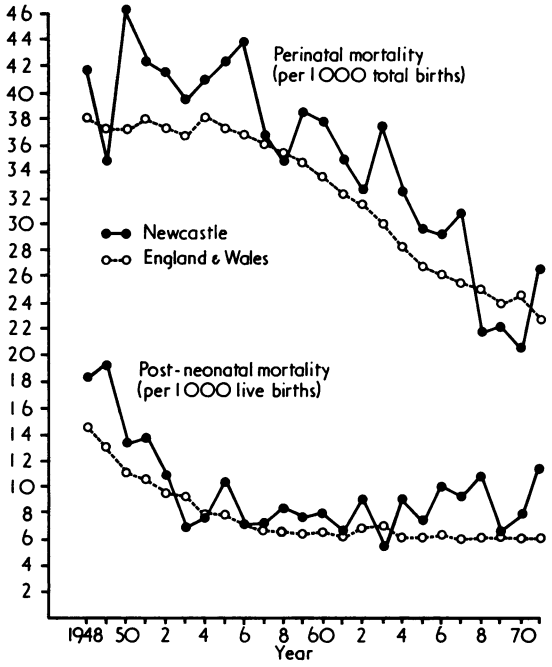

FIG. 1—Perinatal and postneonatal mortality rates 1948-71 for England and Wales (*Registrar Generals' Statistical Reviews of England and Wales 1948-71, 1950-73*) and for Newcastle upon Tyne (Newcastle upon Tyne Medical Officer of Health, 1949-72)

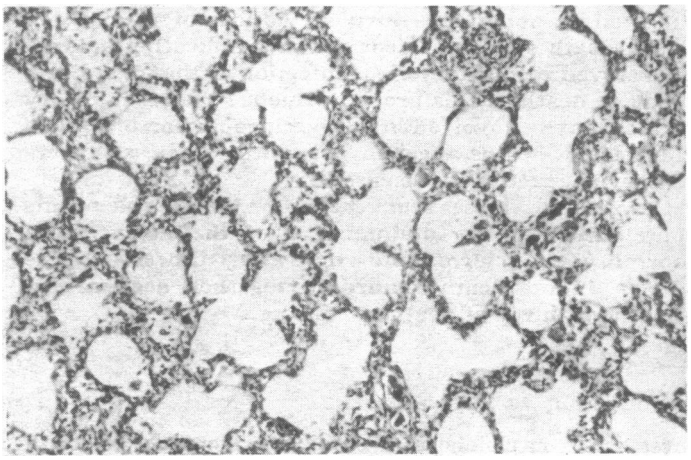

FIG. 2—Type 1 histological appearances of lung. (× 84.)

Results

Between October 1968 and January 1973 the lungs of 24 children who died with acute respiratory illnesses were histologically examined and investigated for the presence of viruses. In one further child whose parents did not give permission for a full necropsy percutaneous needle aspiration of lung tissue was carried out after death for virus investigation.

Surveillance of respiratory deaths was not complete throughout this period; altogether 54 children died with

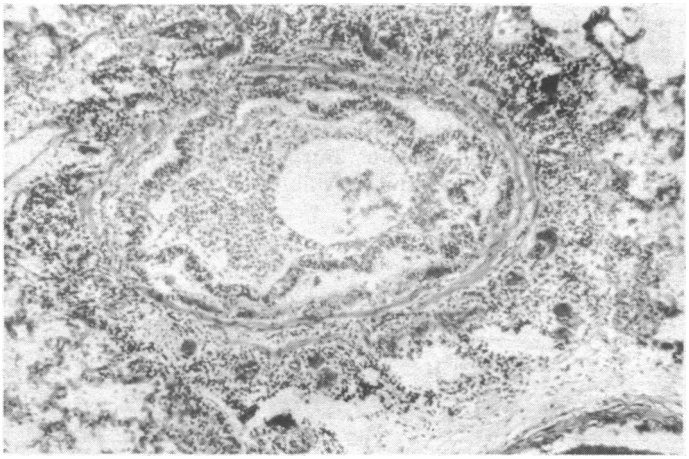

FIG. 3—Type 2 histological appearances of lung. (× 112.)

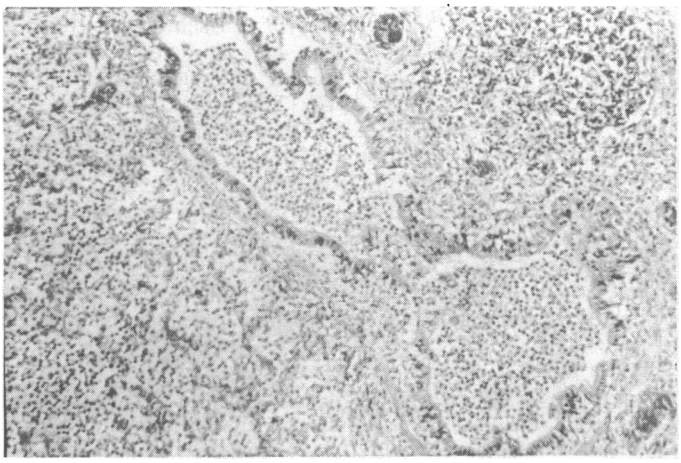

FIG. 4—Type 3 histological appearances of lung. (× 112.)

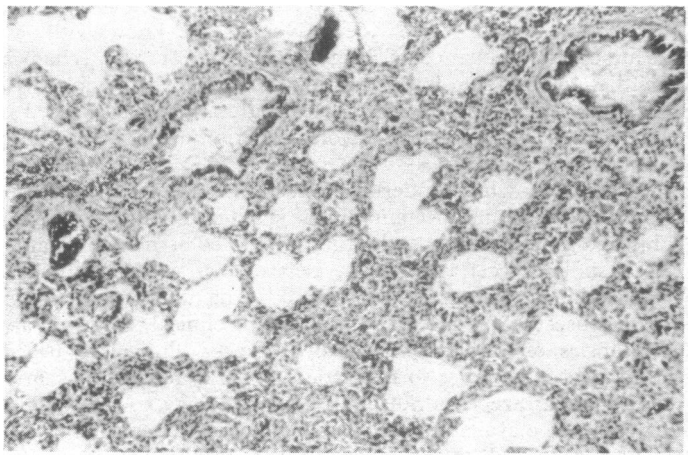

FIG. 5—Type 4 histological appearances of lung. (× 84.)

respiratory illnesses in hospital. For 12 of these permission for necropsy was not given, and most of the remaining 18 who missed virus investigation died during the first two years of the period, when not all paediatricians and pathologists in the area were fully aware of the interest in virus investigation of necropsy material. It is unlikely that the group studied was biased in favour of virus identification.

CLINICAL FEATURES

The ages of the children ranged from 22 days to 2 years 11 months; 13 of the 24 were under six months and 17 under 12 months.

The clinical and radiological diagnosis was bronchiolitis in 11 children and pneumonia in 10 according to the definitions which are used in Newcastle (Gardner *et al.*, 1960). The remaining three children were diagnosed as having asthma, acute epiglottitis and febrile convulsions complicating an upper respiratory tract infection. Eight of the 24 children had severe congenital abnormalities: one had transposition, tricuspid atresia, and ventricular septal defect; Down's syndrome, cystic fibrosis, interstitial pulmonary fibrosis, biliary atresia, cretinism, orofacial-digital syndrome, and combined immunodeficiency were each present in one child. The child who died with asthma, aged 2 years 11 months, had a history of many previous attacks of severe bronchospasm. One child aged 10 weeks with bronchiolitis had been born at 32 weeks' gestation and had a history of respiratory distress syndrome. The previous history of the remaining 14 children was unremarkable.

VIRUS FINDINGS

The viruses identified at necropsy in the lower respiratory tracts of the 24 children who died with acute respiratory illness and also the previously reported virus findings in 51 children with S.I.D.S. are shown in table III (Ferris *et al.*, 1973). A virus was identified in 13 out of the 24 children. Ten of these viruses were types which could be identified by immunofluorescence.

In addition respiratory syncytial virus was identified in the lung tissue obtained by percutaneous needle aspiration from a child aged 27 months with bronchiolitis and Down's syndrome who did not have a full necropsy.

TABLE III—*Virus Findings in Series of Acute Respiratory Deaths and Series of Victims of Sudden Infant Death Syndrome*

Virus	No. of Acute Respiratory Deaths in Hospital	No. of Sudden Infant Deaths†
Respiratory syncytial virus	5	6
Influenza A	3*	2
Parainfluenza 1	2*	—
Parainfluenza 3	1	1
Parainfluenza 4B	1	—
Rhinovirus	1	1
Echovirus type 11	1	—
Adenovirus types 1 and 5	—	3
No virus identified	11	38
Total	24*	51

*Includes one dual identification of parainfluenza 1 and influenza A.
†Ferris *et al.*, 1973.

LUNG HISTOLOGY

All 13 children in whom viruses were identified showed lymphocytic infiltration on histological examination of their lungs (table IV)—six primarily peribronchiolar in distribution (type 2) and seven primarily into their alveolar walls (type 4). These changes are compatible with virus infection of the lung and therefore strengthen the association between virus and death. In five other children similar histological changes (type 2 in two and type 4 in three) suggested that virus may have been present,

TABLE IV—*Relationship between Lung Histology and Virus Findings in 24 Children who Died with Acute Respiratory Illnesses. Results are Numbers of Children*

Histological type:	1	2	3	4	Congenital Interstitial Fibrosis	Normal
Virus identified		6		7		
No virus identified	2	2	2	3	1	1

but identification was unsuccessful. It may be relevant that in two of these children the history of respiratory illness before death was long (two weeks, as compared with a mean of seven days for the virus-positive group). Another was treated by bronchial lavage terminally, and a fourth showed evidence at necropsy of extensive aspiraton of gastric contents. All these factors could have an adverse influence on virus identification.

Only two children showed typical polymorphonuclear infiltration suggesting bacterial infection. One had cystic fibrosis and the other child's respiratory illness had begun three weeks before death. In three other children with lymphocytic infiltration occasional foci of polymorphonuclear infiltration were also found. Two of these had severe congenital abnormalities (Down's syndrome, orofacial-digital syndrome), and the third had been on a ventilator. A type "0 86" *Escherichia coli* was grown from both faeces and laryngeal swab in this last child before death. This was the only antemortem bacteriological finding of possible significance, and bacteriological investigation at necropsy was inadequately standardized and not performed soon enough to yield reliable results.

Two children had histological appearances of the lung which could not be assigned to any of the four categories. One of these was a child who died with acute epiglottitis whose lungs were assessed as being histologically normal. The other was a child who had had respiratory difficulty after birth and then died with clinical bronchiolitis at the age of nine weeks. Her lungs showed a generalized interstitial fibrosis, which was probably congenital rather than infective in origin.

There was no correlation between the clinical and histological diagnoses of bronchiolitis and pneumonia. Both the child with asthma and the child diagnosed clinically as having an upper respiratory infection with febrile convulsions had type 2 lung histology.

QUANTITY OF VIRUS IN LUNG SECTIONS

The relationship between lung histology and the quantity of fluorescent virus antigen in lung sections, assessed independently, in the 10 children with virus types which could be identified by the immunofluorescent method is shown in table V.

TABLE V—*Quantification of Virus and Histological Category in Lungs of Children who Died with Acute Respiratory Illness*

Case No.	Virus Type	Virus Quantity in Lung Sections*	HistologicalType
1	R.S. virus	+	2
2	R.S. virus	+	2
3	R.S. virus	+	2
4	R.S. virus	+ (left lung) + + (right lung)	2†
5	R.S. virus	+ + +	4
6	Influenza A	+	2
7	Influenza A	0	4
8	Influenza A	0	
	Parainfluenza type 1	+	2
9	Parainfluenza type 1	0	4
10	Parainfluenza type 3	+ + +	4

*0 = Virus identified in lower respiratory tract secretions but not in lung sections. + = Scanty amount of virus localized in bronchioles. + + = Moderate amount of virus associated with bronchioles and occasional alveolar cells. + + + = Widespread virus invasion of lung tissue.
†Also some areas of type 4. See discussion.
R.S. virus = Respiratory syncytial virus.

COMPARISONS WITH S.I.D.S.

The viruses found in this series of respiratory deaths are compared with those found by the same methods in 51 children with S.I.D.S. in table III. Though viruses were identified in a smaller proportion of the children with S.I.D.S. the range of virus types was similar. The amount of virus antigen found in lung sections by immunofluorescence in the series of children with S.I.D.S. was always scanty and localized to bronchioles or alveolar ducts.

The numbers in each of the four categories of lung histology for the two series of deaths are shown in table VI. The main point of interest here is that there were two children among the respiratory deaths with type 1 histology, which is the picture most commonly described in S.I.D.S. and which was found in 33 out of the 51 cases in our recent series. In neither of these two children was a virus identified, just as no viruses were identified amongst the 33 sudden deaths. Furthermore, both children died after very short severe respiratory illnesses lasting four hours and 10 hours.

TABLE VI—*Comparison of Lung Histology in Acute Respiratory Deaths with that found in Deaths due to Sudden Infant Death Syndrome (S.I.D.S.)*

Histological type:	1	2	3	4
No. of Respiratory Deaths	2	8	2	10
No. of Deaths due to S.I.D.S.	33	16	2	

Discussion

The identification of a virus in the lower respiratory tract of 13 of the 24 children in this series and the presence of histological appearances in each case compatible with acute virus infection support the concept that viruses play a major role in fatal respiratory disease in young children. The relationship between lymphocytic lung histology (types 2 and 4) and positive virus identification is statistically significant ($P < 0.01$). In a further five children lung histology suggested that viruses may have been the cause of death though they were not identified. Several factors might be responsible for failure to identify a virus, including the period of delay between death and necropsy, which was often about 48 hours and on four occasions was longer than this. In addition, viruses not readily amenable to current virological techniques may be involved. We hope in future to be able to show a higher rate of virus identification by expediting necropsy, but in cases where delay is unavoidable or permission for full necropsy is not obtained percutaneous needle aspiration of lung tissue as soon as possible after death offers an alternative diagnostic method.

We recognize that there are many problems associated with the histological interpretation of the lungs of these children. Different areas of lung may show different changes and the extent of any change—for example, increased cellularity of the alveolar wall—can vary widely. Nor do we know with any accuracy the influence of length of illness or of mechanical ventilation on the lung histology of children dying with respiratory illnesses. We are increasingly aware of the need to further define and quantify histological criteria and are currently studying this problem.

A difficulty which underlies both the identification of viruses and histological interpretation is the small number of children in this age group whose deaths can be defined as non-respiratory with sufficient certainty to be regarded as controls. We are attempting to overcome this problem by maintaining a thorough and consecutive surveillance, through clinical histories and necropsies, of children dying from all causes. There is an urgent need for such studies to be carried out in a number of centres with standardized multidiscipline methodology so that enough cases become available to allow adequate interpretation.

Bacteriological investigation of the respiratory tract after death presents even greater difficulties. The presence of a wide variety of bacteria in the healthy respiratory tract obscures their pathogenic implications and probably means that delay between death and necropsy introduces an even greater distortion than for viruses. The histological findings in this series, with only two children showing the picture typical of bacterial pneumonia, suggest that bacteria are a relatively rare cause of respiratory death, which accords with the established major role of viruses in non-fatal respiratory illnesses in children (Gardner, 1975). Possibly, however, there is a greater risk of bacterial infection in

children with severe congenital abnormalities and in those treated by mechanical ventilation.

According to our findings viruses seem to play a dominant part in the aetiology of respiratory deaths in young children. But what of their role in sudden unexpected deaths? Recent reviews have given scant recognition to the possible role of viruses in S.I.D.S. (Camps and Carpenter, 1972; *British Medical Journal*, 1974). We have shown a close similarity as regards both lung histology and virus types between children dying with frank respiratory illness and some of those with S.I.D.S. This seems to point clearly to virus involvement in some of these sudden unexpected deaths—about 30% in our hands. It must be emphasized that S.I.D.S. is not a pathological entity but probably embraces many aetiological pathways to death, including respiratory virus infection.

As has been pointed out before (Froggatt, 1970; Marshall, 1970) there is much epidemiological evidence to support the hypothesis that respiratory infection plays a part in S.I.D.S.—in particular, the increased incidence during winter months, the higher rate of upper respiratory tract symptoms in the week before death compared with controls, and the similar age distribution of children with S.I.D.S. and those with acute bronchiolitis. This similarity in age distribution is shown in fig. 6, which takes the point one step further by making the comparison with a group of children clearly defined, clinically and virologically, as having bronchiolitis caused by respiratory syncytial virus.

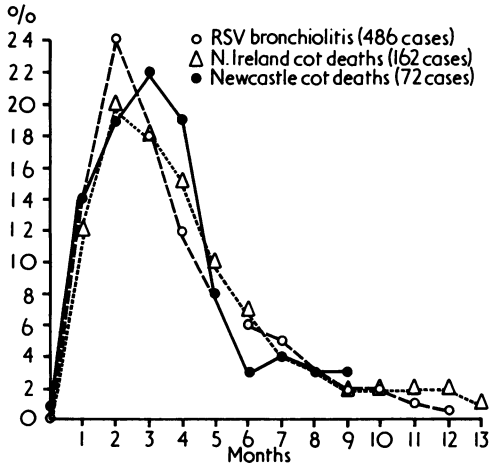

FIG. 6—Age distribution of children with respiratory syncytial virus (R.S.V.) bronchiolitis (Public Health Laboratory Service, 1972, 1973) compared with that of victims of sudden infant death syndrome. (Data for Northern Ireland come from Bergman *et al.* (1970).)

The closeness of these epidemiological comparisons raises the possibility that respiratory viruses may be involved in more than the 30% of sudden unexpected deaths in which there is firm evidence of such involvement. Type 1 lung histology—the type found in most children with S.I.D.S.—was shown in two of the children with frank respiratory illnesses, and both these children died only a few hours after the onset of symptoms. Could some at least of those S.I.D.S. children with this type of lung histology (33 out of 51 in our series) have died after rapid respiratory illnesses which were not observed? Evidence is accumulating that there is wide variation in the observation of symptoms by parents and in their readiness to seek medical advice (Watson, 1974). No viruses were identified in these two children with rapid respiratory deaths nor in the 33 children with S.I.D.S. A possible explanation for these negative virus findings is that death in some of these children might be due to an acute hypersensitivity reaction to amounts of virus antigen in the lung which are too small to be identified by current techniques. Possibly other non-viral antigens, such as those contained in cows' milk (Parish *et al.*, 1964), act in a similar way in some cases of sudden death. The hypothesis that an allergic mechanism involving a range of antigens may be a factor common to many cases of S.I.D.S. is supported by the increased numbers of lymphoreticular aggregates and discharged mast cells found in the lungs of such children (Emery and Dinsdale, 1974; Emery and Carpenter, 1975).

The role of viruses as sensitizing agents in some cases of S.I.D.S. accords with the accumulating body of evidence for an allergic mechanism in the pathogenesis of respiratory syncytial virus bronchiolitis (Gardner *et al.*, 1970) and, in particular, the scanty distribution of virus antigen in the lungs of children dying with this condition, as previously reported (Aherne *et al.*, 1970). Our blind comparison of quantity of virus with histological changes (table V) showed a statistically significant correlation for respiratory syncytial virus between a scanty amount of virus and the histological diagnosis of bronchiolitis (type 2), while in the one case of histological pneumonia (type 4) there was a large amount of virus present. In case 4 the histology was predominantly type 2 but there were also some areas of type 4. Though it was not possible to establish exact anatomical relationships between the presence of fluorescent virus antigen and lung histology it seems likely that these type 4 areas may have coincided with the areas in the right lung in which quantity of virus was in excess of that usually found in bronchiolitis (++). The little evidence available from acute respiratory deaths and S.I.D.S. suggests that parainfluenza virus type 3 may have a similar pathogenesis to that of respiratory syncytial virus. The correlation for the small numbers of other virus types is so far poor, which may indicate different mechanisms of pathogenesis. For respiratory syncytial virus, however, the small quantity of virus found in both bronchiolitis and in some children who die suddenly and unexpectedly points to a relationship in which the common element may be hypersensitivity to virus antigen.

References

Aherne, W. A., *et al.* (1970). *Journal of Clinical Pathology*, **23**, 7.

Bergman, A. B., Beckwith, J. B., and Ray, C. G. (editors) (1970). *Sudden Infant Death Syndrome: Proceedings of the Second International Conference on Causes of Sudden Death in Infants*. Seattle, University of Washington Press.

Brandt, C. D. (1970). In *Sudden Infant Death Syndrome: Proceedings of the Second International Conference on Causes of Sudden Death in Infants*. ed. A. B. Bergman, J. B. Beckwith, and C. G. Ray, p. 161. Seattle, Univeristy of Washington Press.

British Medical Journal, (1974). **1**, 341.

Camps, F. E., and Carpenter, R. G. (editors) (1972). *Sudden and Unexpected Deaths in Infants (Cot Deaths)*. Bristol, Wright.

Department of Health and Social Security (1970). *Confidential Report on Post-Neonatal Mortality, 1964-1966*. London, H.M.S.O.

Emery, J. L., and Carpenter, R. G. (1975). *Proceedings of the Francis E. Camps International Symposium on Sudden and Unexpected Deaths in Infancy*. In press.

Emery, J. L., and Dinsdale, F. (1974). *Archives of Disease in Childhood*, **49**, 107.

Fedrick, J. (1973). *British Journal of Preventive and Social Medicine*, **27**, 217.

Ferris, J. A. J., *et al.* (1973). *British Medical Journal*, **2**, 439.

Froggatt, P. (1970). In *Sudden Infant Death Syndrome: Proceedings of the Second International Conference on Causes of Sudden Death in Infants*, ed. A. B. Bergman, J. B. Beckwith, and C. G. Ray, pp. 32, 38. Seattle, Washington University Press.

Gardner, P. S. (1975). *Hospital Medicine*. In press.

Gardner, P. S., McQuillin, J., and Court, S. D. M. (1970). *British Medical Journal*, **1**, 327.

Gardner, P. S., *et al.* (1960). *British Medical Journal*, **1**, 1077.

Gold, E., *et al.* (1961). *New England Journal of Medicine*, **264**, 53.

Marshall, T. K. (1970). In *Sudden Infant Death Syndrome: Proceedings of the Second International Conference on Causes of Sudden Death in Infants*, ed. A. B. Bergman, J. B. Beckwith, and C. G. Ray, p. 108. Seattle, University of Washington Press.

Milligan, H. C. (1974). *Public Health (London)*, **88**, 49.

Newcastle upon Tyne Medical Officer of Health (1949-72). *Annual Reports* 1948-71. Newcastle upon Tyne, M.O.H.

Parish, W. E., *et al.* (1964). *International Archives of Allergy*, **24**, 215.

Public Health Laboratory Service (1972). *British Medical Journal*, **3**, 482.

Public Health Laboratory Service (1973). *British Medical Journal*, **2**, 788.

Ray, C. C. (1970). In *Sudden Infant Death Syndrome: Proceedings of the Second International Conference on Causes of Sudden Death in Infants*, ed. A. B. Bergman, J. B. Beckwith, and C. G. Ray, p. 145. Seattle, University of Washington Press.

Registrar General's Statistical Reviews of England and Wales 1948-1971. (1950-73). London, H.M.S.O.

Richards, I. D. G., and McIntosh, H. T. (1972). *Archives of Disease in Childhood*, **47**, 697.

Watson, E. (1974). "An Analysis of the Findings of the Inner North London Sudden Death in Infancy Project." Presented to The Society of Community Medicine.