

Pathogenesis of Respiratory Syncytial Virus Diseases in Infancy

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Ross, C. A. C., Pinkerton, I. W., and Assaad, F. A. (1971). *Archives of Disease in Childhood*, 46, 702. **Pathogenesis of respiratory syncytial virus diseases in infancy.** In a series of 54 children under 1 year old with respiratory syncytial virus infection, the highest proportion of severe illnesses (bronchiolitis and pneumonia), and the highest proportion of 'slow' antibody responses, were found in children under 6 months. Severe illness may therefore be related to immunological immaturity and to lack of protection by maternal antibody, rather than to an allergic response as has been suggested. A high male to female ratio (approximately 2 : 1) was found both in the present series, and in two larger series of respiratory syncytial virus infection in infants.

Two different hypotheses, both based on an allergic response, have been advanced to explain the pathogenesis of respiratory syncytial (RS) virus infection and its severity in the first 6 months of life. Chanock *et al.* (1970) explained severe disease in early infancy by postulating interaction of maternal serum antibody and RS viral antigen in lungs of subjects who have deficient respiratory tract secretory antibody. They postulated that both bronchiolitis and pneumonia were explained by a Type 3 allergic reaction (Gell and Coombs, 1968) between excess virus antigen and persisting maternal antibody. Gardner, McQuillin, and Court (1970), on the basis of their finding that RS virus could be easily isolated from lungs in infants with pneumonia but with difficulty in those with bronchiolitis, suggested that bronchiolitis might be the result of a Type 1 allergic response dependent on a previous sensitizing infection with RS virus. They also considered from their evidence that RS virus pneumonia represents a primary widespread infection with RS virus in the absence of local antibody to inhibit its growth.

It seemed that a study of the clinical presentation of RS virus infection in children under 1 year in relation to the rapidity of the serological response might provide evidence in favour of one or other of these hypotheses.

Materials and Methods

The patients comprised all children under 1 year old admitted to Ruchill Hospital from 1965-1970 with acute respiratory illnesses from whom paired sera were received and who yielded virological evidence of RS virus infection by serological findings and/or virus isolation, by techniques described elsewhere (Ross *et al.*, 1964; Grist *et al.*, 1966). For estimation of RS antibodies, complement fixation (CF) tests were employed as they are as reliable as and more convenient than neutralization tests for diagnosis of acute respiratory infections due to RS virus (Suto *et al.*, 1965). Assessment of clinical diagnosis (upper respiratory infection, acute bronchitis, bronchiolitis, or pneumonia) was made by observers (F.A. and I.P.) independently from the observer (C.R.) who assessed the type of serological antibody response as 'slow' or 'rapid'.

Serological assessment. For the purpose of this study a 'rapid' CF antibody response was as follows: a fourfold or greater rise in titre in sera with 7 to 13 days interval, an eightfold or greater rise with 14 to 21 days interval, a sixteenfold or greater rise with 21 days to 8 weeks interval; paired sera at these intervals showing lower or no rising titres were classified as 'slow' responses.

Clinical assessment. At the end of the illness each child was assigned to one of the following four clinical categories.

A: Upper respiratory infections. These were patients who exhibited rhinitis and pharyngitis, but who had no signs, either clinical or radiological, of involvement of the respiratory tract below the larynx.

- B: *Acute bronchitis.* This group comprised patients with lower respiratory features such as rhonchi and crepitations, who lacked the specific clinical and radiological features of bronchiolitis or radiological shadows indicating pneumonia.
- C: *Bronchiolitis.* These patients showed marked evidence of lower respiratory obstruction with high pitched rhonchi, subcostal indrawing, and in some cases radiological evidence of pulmonary over-distension.
- D: *Pneumonia.* Patients in this category all had radiological evidence of pneumonic consolidation.

Results

Clinical diagnosis and age (Table I). None of the children had been previously admitted to hospital with respiratory infections. Of the total 54 infants, the largest proportion, 18 (33%), was

TABLE I

Distribution of RS Virus Infections by Age, Clinical Diagnosis and Serological Response

Age (mth)	Upper Resp. Disease	Acute Bronchitis	Bronchiolitis	Pneumonia	Total
<3	1	—	6	6	13
3-5	—	3 (1)	6 (2)	9 (4)	18 (7)
6-8	—	7 (6)	3 (2)	4 (4)	14 (12)
9-11	1 (1)	4 (4)	1 (1)	3 (3)	9 (9)
Total	2 (1)	14 (11)	16 (5)	22 (11)	54 (28)

() Rapid serological response.

in the age group 3 to 5 months and the smallest, 9 (17%), in the age group 9 to 11 months. Of the 31 infants under 6 months of age, 27 (87%) had either bronchiolitis or pneumonia compared with

11 (49%) of 23 infants over 6 months old. The proportion of children with bronchiolitis or with pneumonia in the age group under 3 months was not significantly different from the corresponding figures in the group 3 to 5 months.

Antibody response. The CF titre in the first sera was <8 in all but 4 children aged from 6 to 11 months. The proportion of children with a 'rapid' antibody response showed a progressive increase with age, namely, none of 13 infants under 3 months old, 7 (39%) of the 3 to 5 months group, 12 (85%) of those 6 to 8 months, and 9 (100%) of those over 9 months.

Sex, clinical diagnosis, and serological response (Table II). There were 34 males and 20 females in the total series; the male preponderance was observed in each age group except in those under 3 months. Correlation of sex with clinical diagnosis showed that there was no appreciable difference in the number of males and females with bronchiolitis or with pneumonia, and though there were more males than females with mild illnesses, namely upper respiratory disease and acute bronchitis, the difference was not statistically significant ($\chi^2, 0.20 > P > 0.10$).

Discussion

The present study had the inherent limitation that it was concerned with infants who showed disease as a result of infection with RS virus, and the relative infection rate of different age groups in the community was not known. However, our findings lend no support to the suggestion by Gardner *et al.* (1970) that bronchiolitis is the reaction produced by a previous sensitizing infection, since in the present series bronchiolitis

TABLE II

Distribution of RS Virus Infections by Age, Sex, Clinical Diagnosis, and Serological Response

Age (mth)	Upper Resp. Disease		Acute Bronchitis		Bronchiolitis		Pneumonia		Total	
	M	F	M	F	M	F	M	F	M	F
<3	1	—	—	—	2	4	3	3	6	7
3-5	—	—	2 (1)	1	4 (2)	2	5 (3)	4 (1)	11 (6)	7 (1)
6-8	—	—	5 (4)	2 (2)	2 (1)	1 (1)	4 (4)	—	11 (9)	3 (3)
9-11	1 (1)	—	4 (4)	—	—	1 (1)	1 (1)	2 (2)	6 (6)	3 (3)
Total	2 (1)	—	11 (9)	3 (2)	8 (3)	8 (2)	13 (8)	9 (3)	34 (21)	20 (7)

() Rapid serological response.

seemed to be as frequent in the infants under 3 months as those between 3 and 6 months. Moreover the majority of those under 6 months with bronchiolitis showed a slow antibody response which is also against a secondary stimulus.

Our finding supports the earlier suggestion by Gardner, Elderkin, and Wall (1964) that infants under 6 months of age became severely ill with RS infection because of immunological immaturity and because maternal antibody confers little or no protection. It also seems possible that a slow antibody response may be paralleled by slow production of secretory IgA by the respiratory mucosa, and it may be, as suggested by Gardner *et al.* (1970), that an important element in the pathogenesis of bronchiolitis is a failure to produce sufficient surface-protecting antibody in the small bronchii and bronchioles. The difference in pathogenesis between bronchiolitis and pneumonia may be related to excess infective antigen over antibody, this excess being greater in pneumonia than in bronchiolitis. Though our findings do not support or conflict with the hypothesis of Chanock *et al.* (1970), it seems unnecessary to postulate that residual maternal antibody is related to severe disease. Moreover the finding that RS virus infection of the newborn may be a mild illness (Neligan *et al.*, 1970) suggests that if maternal antibody is concerned in the pathogenesis, it is probably residual and difficult to measure.

Another factor associated with the pathogenesis of RS disease is sex. The higher male to female ratio in children under 1 year in the present series was also found in the total RS virus infections diagnosed by our laboratory in patients with respiratory disease during the same five-year period: of 213 children under 1 year old with RS virus

infections, 139 (65%) were male and 74 (35%) female. A male preponderance was also found in RS virus infections in children under 1 year reported in Communicable Diseases Scotland during 1969–1970: of 123 infections, 73 (60%) were in males and 50 (40%) in females. The possible relation of male-associated clinical respiratory disease in infancy to male-associated clinical respiratory diseases of adults, such as chronic bronchitis and bronchial carcinoma, requires further investigation.

We wish to thank Dr. D. Reid, Epidemiologist, Communicable Diseases Scotland, for 1969–1970 data.

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