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Postnatal decline of maternally acquired viral antibodies of different specificities

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SUMMARY

The rates of decline (half-lives) of maternally acquired antibodies of two different specificities in a group of infants were found to be highly variable, ranging from 18 to 192 days for parainfluenza type 3 antibody (54 infants) and from 15 to 251 days for influenza A 2 antibody (nine infants). For antibodies of both specificities approximately 75% of the half-lives were between 15 and 60 days. With parainfluenza type 3 antibody, and possibly with influenza A 2 antibody, the half-lives were inversely proportional to the initial antibody titre of the babies' sera. This relationship could be described by a rectangular hyperbola. Babies with high antibody titres at birth lost this antibody rapidly whereas in babies with low initial titres antibody declined over a longer period.

The half-lives of parainfluenza type 3 antibody and influenza A 2 antibody were compared with that of rubella antibody in the same group of infants (previously published). Maternally acquired viral antibodies of different specificities did not necessarily decline at similar rates in any given child. In nine infants, maternally acquired antibodies of two different specificities (rubella and parainfluenza type 3) declined at significantly different rates in the same child. It is suggested that although the half-life of antibody of a given specificity is related to its concentration in the serum, it is independent of the level of serum antibodies of other specificities.

INTRODUCTION

In a previous study we have shown that the rate of postnatal decline (half-life) of maternally acquired rubella antibody in a large group of infants was highly variable, with half-lives in different children ranging between 14 and 70 days (Cloonan, Hawkes & Stevens, 1970). A significant relationship was found between the half-life and the rubella antibody titre at or near birth ('initial titre') which could be described by a rectangular hyperbola, such that babies having high titres at birth lost their antibody rapidly, whereas in those with low initial titres antibody declined at a slower rate.

The unexpected nature of these findings prompted further investigations of the decline of maternally acquired viral antibodies of other specificities present in the sera of the same group of infants. These studies have considered, in particular,

(i) whether antibodies of different specificities decline at a similar rate in a given child, (ii) whether the half-lives are independent and related only to the initial level of specific antibody in the serum or whether they are influenced by levels of antibodies of other specificities which might also be present in the serum.

To facilitate comparison with the previous study in which rubella antibody was measured by the haemagglutination-inhibition test, two haemagglutinating viruses, influenza A 2 and parainfluenza type 3 were used as test antigens. This study reports the postnatal decline of maternally acquired antibodies to these viruses, and describes the relationship between the rates of antibody decline and initial antibody titres for both antibodies. The results are discussed in relation to those obtained previously with rubella antibody.

MATERIALS AND METHODS

Study group and sera for the study

The babies in this study and the collection of test sera have been described previously (Cloonan *et al.* 1970). Although there were 120 babies in the original group, sufficient serum was left from only 102 babies for the influenza A 2 tests and from only 70 babies for the parainfluenza type 3 tests. Previous tests on mothers' sera had indicated that, though only nine babies could be expected to have influenza A 2 antibody of maternal origin in their sera at birth, parainfluenza type 3 antibody could be expected in the sera of 54 babies.

Viral antigens

The influenza A 2 strain (A 2/NSW/61) was obtained from Dr M. F. Warburton of the Commonwealth Serum Laboratories, Melbourne. The parainfluenza type 3 (Crowe) strain was isolated in our laboratory during September 1969.

Serological techniques

Influenza A 2 antibody was determined by the haemagglutination-inhibition (HI) test (Fazekas de St Groth & Webster, 1966), modified by removing non-specific inhibitors from the sera by treatment with trypsin and potassium periodate (Davenport & Minuse, 1964) and by testing the sera in a micro-system. Antibody to parainfluenza type 3 virus was also determined by the HI test (Chanock & Johnson, 1964). Many of the sera contained agglutinins for guinea-pig red cells; these were removed by prior absorption of the sera with guinea-pig red cells (final concentration 20 %) for 2 hr. at 4° C. Non-specific inhibitors were removed by the trypsin and periodate method. A micro-system was also used for the titration of this antibody.

The babies whose sera were to be tested on a given day were selected by an appropriate ranking procedure in order to minimize bias, and all sera from a given baby were tested at the same time. The influenza A 2 and parainfluenza type 3 tests were performed separately and, for both, ten samples of a standard positive serum were included in each test as a check on the within-test and between-test

variability. Negative control sera were included in each test as a check on the removal of non-specific inhibitors from the sera.

Determinations of antibody half-lives were made only on those babies possessing antibody in at least three but usually four to five sequential sera. The antibody titres were punched onto data cards and were analysed in an IBM 360 Model 50 computer. Using these antibody titres, a linear regression of log. titre against time (days from birth) was computed; the print out included the rate of antibody decline (half-life) for each baby. The computer program used previously (Cloonan *et al.* 1970) was modified in that: (i) it contained the rubella data (half-lives and initial antibody titres) and the input was a second set of data (in this case influenza A2 or parainfluenza type 3 titres) on which half-life calculations were performed; (ii) it carried out a test of significance of regression on all sets of data using the linear equivalent of the model proposed by Brambell, Hemmings & Morris (1964); (iii) it permitted a test of the relationship between the initial titre of either influenza A2 or parainfluenza type 3 antibody and the half-life of rubella antibody, after allowing for the effect of the initial titre of rubella antibody on the half-life of rubella antibody.

RESULTS

Antibody status of babies

Fifty-four babies possessed parainfluenza type 3 antibody and nine had antibodies to influenza A2. Of the 54 babies having parainfluenza type 3 antibody, 43 also possessed rubella antibody, thus permitting comparisons between these two groups. Although the small size of the influenza A2 group limited its usefulness, there were five babies in which antibodies of all three specificities (rubella, parainfluenza type 3 and influenza A2) were detected.

Rate of antibody decline (half-life)

Frequency distributions of the half-life values obtained with both antigens are shown in Fig. 1. In both cases half-life values were spread over a wide and similar range. In the larger parainfluenza type 3 group there was a range of half-life values from 18 to 192 days, with a mean of 58 days, and 75% of the values lay between 15 and 60 days. In most cases the straight line obtained from the regression equation was a good fit to the observed values (Fig. 2). However, during the first month of life, four babies had a fourfold rise, and one baby had a stationary titre, of parainfluenza type 3 antibody. After this, antibody declined in an exponential manner. These five babies were not members of the group of ten babies in which similar variations in rubella antibody titre occurred early in life (Cloonan, *et al.* 1970).

Antibody status in twins

Both members of each of four pairs of twins possessed parainfluenza type 3 antibody. In these pairs both the initial titre at birth and the half-life of parainfluenza type 3 antibody were similar.

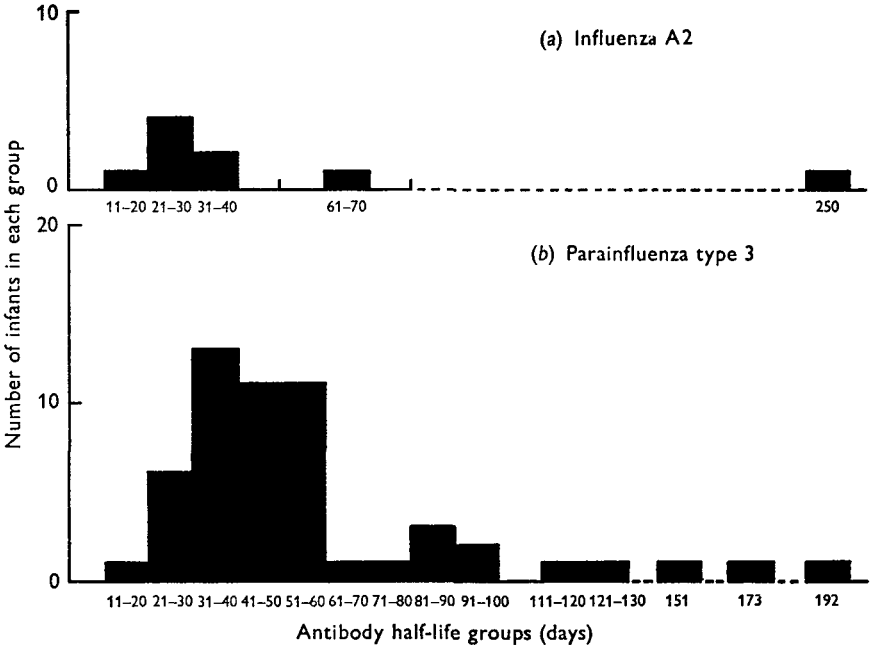

Fig. 1. Frequency distribution of half-life values. (*a*) Influenza A2 antibody, (*b*) parainfluenza type 3 antibody.

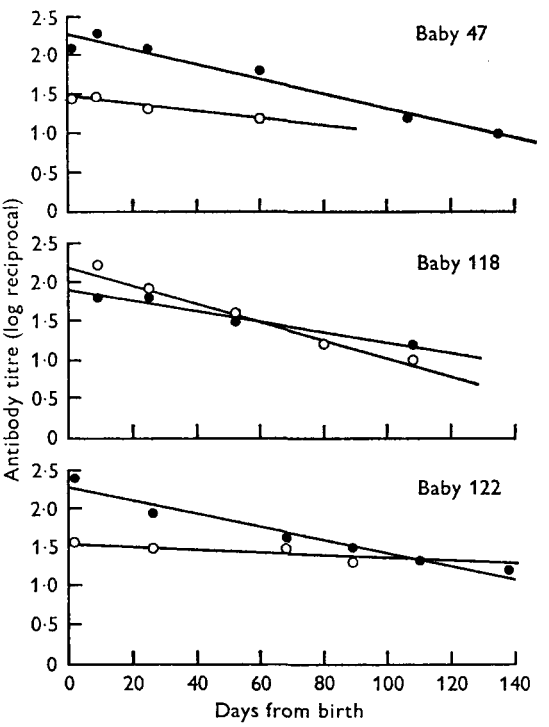

Fig. 2. Examples of postnatal decline of maternally acquired viral antibodies in three infants. ●, Rubella antibody; ○, parainfluenza type 3 antibody.

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Sex of the babies

There was no statistically significant difference between the mean parainfluenza type 3 antibody half-lives of the sexes, and the frequency distributions of the half-lives in the sexes were also similar.

Relationships between initial antibody titre, birth weight and gestational age

There was no statistically significant relationship between initial parainfluenza type 3 antibody titre and birth weight, nor between initial antibody titre and gestational age. Though a linear trend in these relationships was evident, the scatter of points was considerable.

Relationship between antibody titres of infants at birth and those of their mothers

A significant linear correlation between the baby's initial parainfluenza type 3 antibody titre and that of its mother was found ($r = 0{\cdot}30$, $P < 0{\cdot}05$). Eleven (21 %) of the babies had a titre at least twofold greater (7) or lower (4) than that of their mothers; these differences were never greater than sixfold.

Duration of detectable maternally acquired antibody

From the regression equation for each baby it was possible to determine the time for the antibody titre to fall to 1/10 (the limit of detectability of both antibody

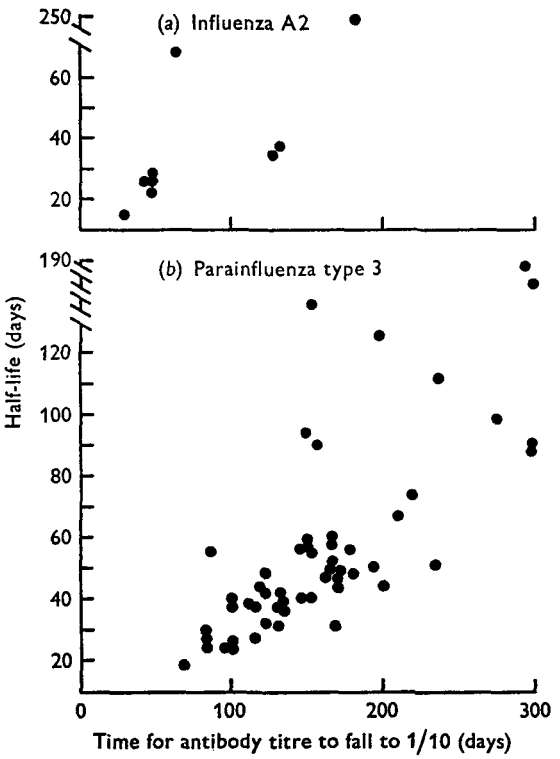

Fig. 3. Relationship between half-life and time calculated for antibody to decline to a titre of 1/10. (*a*) Influenza A2 antibody, (*b*) parainfluenza type 3 antibody.

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tests). The relationship between half-life and the number of days for the titre to reach 1/10 for both antigens is shown in Fig. 3. It can be seen that, in both instances, there is a positive relationship between half-life and the duration of detectable antibody. From the experimental results it was observed that, with parainfluenza type 3 antibody, 13% of the babies had detectable antibody at 6 months of age and 5% had antibody at nine months.

Relationship between half-life and initial antibody titre

Using the linear equivalent of the model proposed by Brambell *et al.* (1964) to describe the relationship between the catabolism of IgG and its concentration in the serum, it was found that, in the parainfluenza type 3 group, there was a significant relationship between the antibody half-life and the initial titre ($r = 0{\cdot}43$, $P < 0{\cdot}001$). This took the form of a rectangular hyperbola (Fig. 4) such that the higher the initial titre of parainfluenza type 3 antibody, the greater the rate of decline of this antibody. In the smaller influenza A2 group the relationship between the half-life and initial titre was similar but was not significant (Fig. 4).

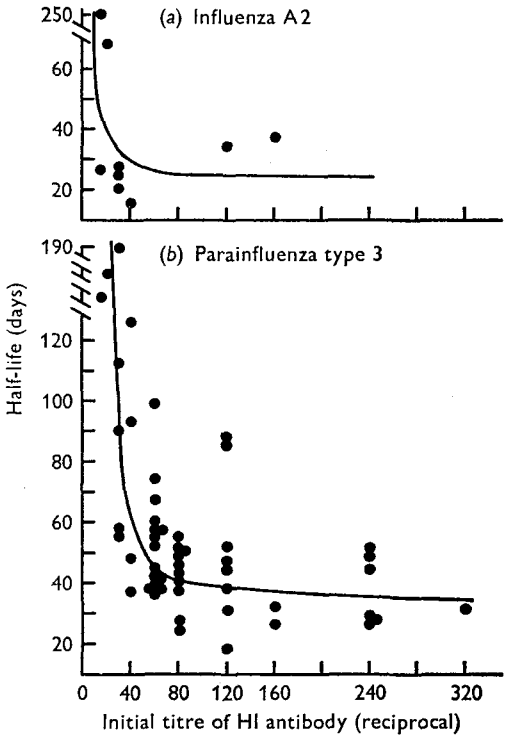

Fig. 4. Relationship between half-life and initial antibody titre in infants. (*a*) Influenza A2 antibody, (*b*) parainfluenza type 3 antibody. The curves (Brambell *et al.* 1964) are:

$$(a)\ \text{half-life} = \frac{\text{initial titre ln 2}}{0{\cdot}03\ (\text{initial titre} - 8{\cdot}35)} \qquad (b)\ \text{half-life} = \frac{\text{initial titre ln 2}}{0{\cdot}02\ (\text{initial titre} - 20{\cdot}71)}$$

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Comparison between half-lives within a given baby

Since the computer print-out for each baby included the half-life and its variance, it was possible to compare the half-lives, for a particular infant, of parainfluenza type 3 antibody and of rubella antibody (as reported previously – Cloonan *et al.* 1970) using the *t* test. It was found that in 21 % of the babies having both antibodies, the half-lives were significantly different (*t* test, $P < 0{\cdot}05$). It should

Table 1. *Decline of antibodies in infants whose rubella and parainfluenza type 3 half-lives were significantly different*

	Antibody half-life (days)	
Baby no.	Rubella	Parainfluenza type 3
8	24·6	56·2
16	42·9	27·3
23	33·9	59·6
30	33·3	18·4
36	31·7	99·0
47	32·8	55·5
101	58·4	27·1
118	46·3	25·8
122	36·2	191·7

Table 2. *Decline of antibodies in infants who possessed antibodies of all three specificities (rubella, parainfluenza type 3 and influenza A 2) at birth*

	Antibody half-life (days)		
Baby no.	Rubella	Parainfluenza type 3	Influenza A 2
45	33·0	31·1	21·5
46	27·1	39·6	26·1
62	36·4	30·9	33·9
74	30·2	40·1	14·9
118	46·3	25·8	68·2

be noted that in the repeated application of the *t* test to all 43 babies a significant difference in half-lives would be expected to occur by chance in two or three babies. However, in this study significant differences were obtained in nine babies, and these results are summarized in Table 1. In five babies the half-life of parainfluenza type 3 antibody exceeded that of rubella, whereas in the remaining four the reverse occurred. The actual results with three of these babies are presented graphically in Fig. 2.

There were five babies for whom the half-lives of antibodies of all three specificities (rubella, influenza A 2 and parainfluenza type 3) were determined. Whereas three of the babies had similar half-lives for all three antibodies, two babies had markedly different values (Table 2). Because of the small size of this group, statistical tests to assess the significance of the differences were not applied.

Relationship between initial titre of parainfluenza type 3 antibody and half-life of rubella

Using the results from those babies having both rubella and parainfluenza type 3 antibodies, and an appropriate regression analysis, no significant relationship was found between the initial titre of parainfluenza type 3 antibody and the half-life of rubella antibody, after allowing for the effect of the initial rubella titre on the rubella half-life.

DISCUSSION

We have previously reported a high degree of variability in the rate of decline of maternally acquired rubella antibody in the babies used in the present study (Cloonan *et al.* 1970). For that antibody the range of half-lives was between 14 and 70 days, with the exception of three babies whose values were between 74 and 259 days. A similar degree of variability has now been demonstrated with two other viral antibodies. In the case of influenza A 2 antibody the half-lives ranged from 15 to 251 days, and for parainfluenza type 3 antibody from 18 to 192 days (Fig. 1). This study therefore confirms our previous suggestion that the range of half-life values for maternally acquired antibody must be extended beyond the generally accepted range of 20–30 days (Brambell, 1970).

This study has also shown that with parainfluenza type 3 antibody, and possibly with influenza A2 antibody, the half-life is inversely proportional to the initial antibody titre of the baby's serum. A relationship of this type has previously been demonstrated between the level of passively acquired IgG in the serum and its half-life both in animals (Brambell *et al.* 1964; Brambell, 1966) and in man (Waldmann & Strober, 1969). These results confirm our earlier finding with rubella antibody, and indicate that, for an antibody of a given specificity, babies having high antibody titres at birth lose this antibody rapidly whereas in babies with low initial titres antibody declines over a longer period of time. Since maternally acquired antibody in the infant may provide protection against virus infection, it would seem that children with moderate to low initial antibody titres may possess effective congenital immunity for longer periods than those having comparatively high antibody titres at birth.

It has been tacitly assumed that maternally acquired antibodies of different specificities decline at the same rate in a given infant, and that this rate is the same as that of total maternally acquired IgG. This study has shown, however, that for some of the infants maternally acquired antibodies of two different specificities (rubella and parainfluenza type 3) declined at significantly different rates in the same child (Table 1). In addition, there were two babies (Table 2) who had very different rates of decline for all three antibodies (rubella, influenza A 2 and parainfluenza type 3). It would seem that antibody of a given specificity declines at a rate which is proportional to its initial titre in the serum and which is independent of the titre of other serum antibodies. This independence is supported by two other observations. In the present study, no relationship was found to exist between the initial titre of antibody of one specificity (parainfluenza type 3) and the rate of decline of another antibody (rubella). In associated studies on the same

group of infants, the IgG concentrations were determined in the initial serum (Wells, 1969). There was no correlation between the half-lives of either of these viral antibodies and the initial IgG concentration.

A feature of these results was that, for each antibody, there was considerable variability in the half-lives for each initial antibody titre (Fig. 4). This also occurred in the previous study with rubella antibody (Cloonan *et al.* 1970). The postnatal decline of maternally acquired antibodies is due partly to the catabolism of the antibodies (Schultze & Heremans, 1966) and partly to dilution of antibodies as a result of expansion of the volume occupied by the plasma and extravascular protein pools as a result of the infants' growth (Trevorrow, 1959; Trevorrow & Washburn, 1970). The latter factor may well account for some of the observed variability in half-lives of antibody of a single specificity, since it is most likely that the rate of growth in the months following birth varied considerably from infant to infant.

In view of the unforeseen nature of these findings, it should be emphasized that all possible care was taken both with the serological tests (conduct of the tests, incorporation of negative and positive control sera) and with the statistical aspects of the study (selection of babies, recording and processing of results). It has been assumed in this study that the influenza A 2 and parainfluenza type 3 antibody in the infants' initial sera is entirely maternally acquired IgG. It could be argued that babies with long antibody half-lives might have experienced a postnatal infection with one of the viruses used in this study or one which was serologically related. This does not appear likely. In both babies having an influenza A 2 half-life of 60 days or longer, the antibody titre fell to less than 1/10, while in 9 of the 14 babies with a parainfluenza type 3 antibody half-life of 60 days or more, the titres also fell to less than 1/10. In the remaining five cases, sera had not been collected for a sufficiently long period to enable observation of such a decline.

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