INTRODUCTION

The theory of mucosal immunology is now well advanced and supported by experimental data. It is clear that mucosal immune responses can be manipulated and that individuals who can be defined as having a deficit in mucosal immune competence appear to be prone to chronic conditions such as recurrent infection, atopy and clinical asthma.

A deficiency in secretory IgA (S-IgA) at mucosal surfaces may facilitate the entry of allergens and pathogens through the gastrointestinal or respiratory mucosa. Mucosal S-IgA deficiency occurs in the neonatal period and the length of deficiency varies. The incidence of allergic disease is much higher in IgA-deficient individuals and in retrospective studies of children with atopy or asthma the salivary IgA levels have been reported to be lower than in control subjects. Transient serum IgA deficiency was reported to be associated with the development of infantile atopy and a prospective study of children with a family history of atopy demonstrated significantly lower levels of salivary IgA in children at 4 and 8 months who subsequently developed atopy. The data on whether respiratory infections in the first year of life predisposed to the development of asthma or atopy is conflicting. Several studies have reported a significant association between respiratory viral infection and the subsequent development of asthma or atopy, while other studies failed to show a difference with control groups.

Over the past decade we have conducted studies to assess the ontogeny of the mucosal immune system. In a longitudinal programme, 263 healthy full term children were studied from birth to 5 years of age. The mucosal immune status of the children was assessed using saliva collection at regular intervals. Two cross-sectional studies have also been conducted: a study of normal school children aged 5 to 13 years; and a study of Papua New Guinea highland children aged from birth to 5 years. Patterns of mucosal immune ontogeny have been established, factors which affect the ontogeny pattern investigated and markers of mucosal immunocompetence identified.
Salivary IgA was not detected at birth and in the first week of life was present in only 14% of samples. Salivary IgA levels increased rapidly from the first week of life to peak at 6 weeks of age (median = 19 mg/l; 95% confidence interval (CI), [1.0, 87.6] mg/l). The concentration decreased to lower levels at 12 weeks (median = 13.5 mg/l; 95% CI, [2.7, 51.0] mg/l) and several infants (2-6% of cohort) had consistently low levels and transient absences of salivary IgA during the first 4 years of life (unpublished observations).

Up to 4 years of age the geometric mean of total salivary IgA remained below 20 mg/l. At 5 years of age the concentration of salivary IgA significantly increased (p<0.05; mean = 27.0 mg/l; 95% CI [20.2, 36.3] mg/l). In an independent cross-sectional study of school aged children the mean salivary IgA level was 100.7 mg/l (95% CI, [81.5, 124.4] mg/l) at 5 years of age. The IgA levels in the school children decreased between 5 years and 7 years (mean = 49.3 mg/l; 95% CI [38.0, 64.0] mg/l). The IgA levels remained relatively constant after 7 years of age and were similar to the levels observed in adults (mean = 53.2 mg/l; 95% CI [38.9, 72.8] mg/l).

IgA antibody specific against *Escherichia coli* O antigen was measured to assess the pattern of development of specific immunity in the mucosal system to a common antigen. *E. coli* has been shown to be an almost universal inhabitant of the intestinal tract of man and to colonize the gut soon after birth. Low levels of IgA antibodies were detected during the first 4 years of life. The levels increased 2-3 fold when children attended school (mean = 2.00 ELISA Units [EU/ml]; 95% CI [1.31, 3.03] EU/ml) and remained relatively constant to 8 years of age after which the levels increased towards adult levels (mean = 8.20 EU/ml; 95% CI, [5.33, 12.63] EU/ml).

### FACTORS WHICH AFFECT THE PATTERN OF IgA ONTOGENY

Our studies have identified 5 factors which modify the pattern of IgA ontogeny, namely: the mucosal IgM response, mucosal permeability, feeding, environmental exposure and nutritional status.

#### The Mucosal IgM Response

The ontogeny pattern for total IgM was similar to that described for IgA. IgM was absent in saliva at birth. It was detected in 15-20% of infants between 4 and 26 weeks of age and was observed in approximately 10% of children older than 26 weeks. The presence of IgM was significantly associated with IgA. The level of salivary IgA was significantly higher in infants with positive IgM measurements than for those with no IgM detected at almost all ages studied up to 4 years. This suggests that the appearance of both IgA and IgM in mucosal secretions is stimulated by exposure to "novel" antigens or to polyclonal mitogens and that in neonates mucosal IgA deficiency is not compensated for by IgM antibodies as is the case in congenital IgA deficiency in adults and children. The strong association between salivary IgA and IgM levels also supports the concept of local plasma cell secretion rather than serum transudation.