
The experiments described have been concerned with active immunity to virus infection of the upper respiratory tract of sheep, but, in addition, we have evidence that the colostrum-fed offspring of ewes having serum antibodies to P13 virus are protected against challenge infection (Smith, 1975b). Passively acquired IgG antibody was protective in these lambs, and it was found that, after the feeding of colostrum to newborn lambs and the absorption of IgG into the serum, IgG was transferred to the secretions of the upper respiratory tract (Smith et al., 1976a). No immunoglobulins were detected in nasal-secretion samples collected before suckling, but IgG was present in all samples obtained approximately 24 h after first suckling, from which time the concentration of IgG declined over the first 3 weeks of life. A similar transfer of IgG to lacrimal secretions was observed. We consider that this transfer of maternal immunoglobulin to the mucosal surfaces of the newborn may constitute an important protective mechanism and that it plays a valuable role in providing transient protection against infection before active production of local IgA and IgM begins at 2–3 weeks of age.

In conclusion, we suggest that IgG antibodies in the nasal secretions constitute a humoral defence mechanism operating on the mucosal surfaces of the sheep respiratory tract. This IgG-antibody system is additional to that due to locally produced IgA antibodies, and is present in newborn suckled lambs and in immunized sheep in which there are high concentrations of circulating serum IgG antibody.


The Clearance of MOPC-315-Tumour Immunoglobulin A from the Serum of BALB/c Mice

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A standard procedure for the determination of catabolic rates of serum proteins involves the intravenous injection of radioactively labelled purified proteins and following their rates of decline in serum or whole body over a period of time. This approach has been used to determined that the half-life (t½) of IgA (immunoglobulin A) in serum of mice is of the order of 12 h (Bazin & Malet, 1970). Previously, Fahey & Sell (1965) had shown a t½ of 1.2 days when the whole-body radioactivity was measured. This discrepancy may have been due to either the different counting procedures or problems associated with the purification and labelling of the proteins. To circumvent the latter we chose to follow the fate of a natural label, that of an idiotype-specific determinant of IgA. This technique has been successfully used by Tada et al. (1975) in the determination of t½ of IgE in rats. Our source of IgA was serum from BALB/c mice bearing the MOPC-315 tumour.

An anti-idiotype serum was prepared in a goat immunized with a purified IgA fraction from MOPC-315-tumour serum and made specific for the idiotypic determinant by immunoabsorption on a column of milk-IgA-Sepharose.
To measure amounts of the MOPC-315-tumour IgA idiotype (idiotype MI) in serum we have used an automated latex-agglutination technique that is highly sensitive and reproducible (Cambiaso et al., 1977). Briefly, polystyrene particles (latex) were sensitized with a small amount of the IgG fraction of the anti-idiotypic serum. These (25 μl of a 0.1% suspension) were made to react with 25 μl portions of sera dilutions containing idiotype MI for 20 min, diluted in 5 ml of 0.27 M-glycine buffer (pH 9.0), and the numbers of particles counted on a Technicon auto-counter. By comparison with the numbers of particles present in the absence of serum, the degree of agglutination was calculated. All titres were determined for 50% agglutination. In this assay, whole MOPC-315-tumour serum gives a 50% end point of the order of 10^{-6} depending on the batch of serum, whereas normal mouse serum has a background titre of 2 × 10^{-2}-10^{-2}. This low background value may represent both a non-specific interaction of the latex with other serum proteins (Cambiaso et al., 1977) and interaction with natural antibodies expressing the MOPC-315-tumour idiotype.

In the first experiment, 6-8-week-old normal BALB/c mice were injected intravenously with 0.2 ml of a pool of MOPC-315-tumour serum. At various times, mice were killed by exsanguination, and sera assayed for the presence of the idiotype. The idiotype present at 1 h was arbitrarily chosen as the 100% level. The results presented in Fig. 1 show two principal features. First, there is a rapid elimination of IgA; some 80% of the original is removed from the serum in 10 h. Secondly, after 24 h the rate of clearance slows considerably and it was calculated that the t1/2 for IgA is of the order of 2.2 days. This experiment was repeated with one group of mice (6) that, after injection with IgA, were bled from the retro-orbital plexus over a 48-h period. An identical initial fast clearance rate was again observed. This initial rapid loss is also evident from the results obtained by Bazin & Malet (1970). These authors did not observe the second phase of the elimination, as clearance was followed for only 15 h. The biphasic nature of the clearance may be due to the heterogeneity of the IgA molecules in MOPC-315-tumour serum. It is known that the IgA produced by the

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Fig. 1. Clearance of MOPC-315-tumour IgA in Balb/c mice

Each point represents the mean of values from at least three mice. Bars represent 1 s.d. from the mean. Experimental details are given in the text.
MOPC-315 tumours consists of both monomeric and polymeric forms (Della Corte & Parkhouse, 1973) and it may be that each component is cleared at a different rate.

That the clearance of IgA from serum is an active process was tested by giving two intravenous injections of MOPC-315 serum spaced by 24h. Fig 2 shows that the fast clearance of the second dose is similar to that of the first injection, suggestive of an active mechanism and not of a simple diffusion of IgA to extravascular sites.

It was shown by Fahey & Sell (1965) that the concentration of IgA in serum does not influence its rate of clearance. This was confirmed in our study by injection of a tenfold-lower dose of MOPC-315-tumour serum into mice and observing that the rate of clearance was identical with that of the higher dose. Normal mouse serum is known to contain only low concentration of IgA (see Vaerman, 1973), and this demonstration of a rapid removal from serum may represent one facet of this. The following three possibilities may be proposed to explain these results. (a) Mouse IgA is indeed rapidly catabolized, although the above experiments tend to argue against this. (b) IgA, in one form or another, is rapidly stored in some site(s) in the body before catabolism and/or excretion. (c) IgA is rapidly removed at some site(s) in the body and actively transferred to regions with high concentrations of IgA, namely mucosal secretions.

The present study shows the existence of a rapid and active mechanism for the removal of IgA from the serum of mice.

The Relationship Between Secretory Immunoglobulin A and Mucus

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Little is known of any relationship that might exist between immunoglobulins on the one hand and mucous membranes and exocrine secretions on the other. Exocrine secretions vary widely in complexity depending on the source. Even uncomplicated seromucous secretions arise from different cell types and glands, and contain, in addition to the major mucus glycoprotein fractions and IgA (immunoglobulin A), a large number of other constituents including most of the serum proteins.

The most important constituent of mucus is a high-molecular-weight glycoprotein, and this is responsible for the physicochemical properties of the material. It has a characteristic amino acid and carbohydrate composition. Thus it contains relatively large amounts of proline and the hydroxy amino acids, serine and threonine, but is deficient in aromatic and sulphur-containing amino acids. The native glycoprotein has a molecular weight of several million, and more than one-half of this is contributed by carbohydrate. As the oligosaccharide units have an average size of only eight to ten monosaccharide residues, this means that the glycoprotein contains many thousands of oligosaccharide units closely packed along the polypeptide chain. Such an arrangement renders the material resistant to denaturation and to proteolysis, ideal properties to fulfil the role of mucosal protection and lubrication, particularly in the gastrointestinal tract.

The oligosaccharide units are O-glycosidically linked from N-acetylglalactosamine to the hydroxyl groups of either serine or threonine. In addition to the linkage sugar, the average oligosaccharide unit contains one or two residues of fucose, three or four of galactose, three or four of N-acetylglucosamine and none or one residue of N-acetylneuraminic acid.

The most likely ways in which secretory IgA could be bound to mucus glycoproteins are by hydrogen-bonding or by disulphide linkages. There is some evidence that IgA, in common with certain other serum proteins, may be covalently linked to the mucus glycoprotein molecule (Roberts, 1974, 1976). If this finding is confirmed, it will have important implications for the role and function of antibodies in mucus secretions.

The evidence for non-covalent association between immunoglobulins and mucus is more difficult to obtain. There is no doubt that in most sputum samples extensive washing does not remove all the associated protein. This 'trapped' protein is likely to be non-covalently bonded because it is released only by disrupting the gel structure with, for example, 6M-urea (Roberts, 1976). In some sputum samples the released protein is almost pure IgA (J. M. Creeth, personal communication).

It is also of considerable theoretical interest that the hinge region of IgA1 (Fig. 1) contains a sequence that is rich in serine, threonine and proline (Frangione & Wolfenstein-Todel, 1972; Liu et al., 1976). In addition, this stretch possesses a number of O-glycosidically linked oligosaccharide units. Although all immunoglobulin classes contain covalently attached carbohydrate, IgA1 is unusual in possessing this stretch, although possibly IgD may be similar in this respect. The other classes, i.e. IgG, IgM and IgE, contain other types of oligosaccharide units as shown in Fig. 2. These units are N-glycosidically linked through asparagine and are of two types, 'simple' and 'complex'. The simple unit contains just mannose and N-acetylglucosamine,