Immunopathology of Measles

Professor P J Lachmann
(Department of Immunology, Royal Postgraduate Medical School, Ducane Road, London W12 0HS)

Introduction

The roots of immunology are to be found in the study of immunity to infectious disease and particularly to viruses. Long before an antibody – not to mention complement or a cytotoxic T cell – had ever been heard of, it was recognized that prior exposure to smallpox virus, or subsequently to vaccinia virus, gave immunity to subsequent smallpox infection. From these beginnings grew the study of prophylactic immunization against virus infection which probably remains medicine's major single achievement. Dr Beale (p 1116) has already discussed the vaccines that have recently been developed for the prophylaxis of measles. There can be no doubt, therefore, that the allergic response to viruses is a 'good thing'. Nevertheless, it must be recognized that the very allergic responses that prevent virus infection can also play a major part in the pathogenesis of virus disease. This is by no means a new idea. In 1902 von Behring suggested that many of the manifestations of acute infectious disease – the incubation period, the fever, the exanthem – could be explained on an allergic basis. In this, as in so many other things, von Behring showed great insight, as much subsequent work has demonstrated (*see* Coombs *et al.* 1974).

This involvement of immunological processes in the manifestations of the acute virus infection makes a convenient first heading under which to discuss the immunopathology of measles. The involvement of immunological processes in the complications of measles form a second heading and the involvement of immunological responses to measles virus in diseases that are not obviously caused by measles infection at all provides the third.

The Role of Allergic Factors in Acute Measles

The evidence on this point is derived largely from observations on the occurrence and course of acute measles in children with specific immunity deficiency states. Thus, children with antibody deficiency syndromes (specific deficiencies of the B cell system) have quite unremarkable attacks of measles with the characteristic rash and normal recovery. Furthermore, they are not unduly prone to reinfection. It therefore seems that serum antibody, at any rate in any quantity, is not required for the production of the measles rash; nor for the normal recovery from the disease; nor to prevent reinfection. Nevertheless, as has already been discussed, there is no doubt that antibody given passively can provide a perfectly adequate protection against measles infection. Anti-measles antibody thus provides a sufficient but not a necessary mechanism for anti-measles immunity.

On the other hand, children with severe combined immunity deficiency and children with leukæmia treated with cortisone whose T cell function is believed to be particularly depressed get atypical attacks of measles complicated by giant cell pneumonia, frequently leading to death. Characteristically, there is no measles rash seen in such children. It would therefore seem that the measles rash is a T cell mediated phenomenon and the supposition that the measles rash may be a general Type IV reaction is strengthened by the close resemblance to the measles rash of the rash seen in generalized graft versus host reactions in children. Further, it seems that T cell function is needed to terminate the measles infection. It does not seem to be established what the mechanism here is: whether the T cells mediate killing of measles-infected cells displaying measles antigens on their surface; or whether the production of interferon from activated T lymphocytes is important.

The Immunopathology of the Complications of Measles

Bacterial infection following measles: It was originally observed by von Pirquet that during attacks of acute measles the delayed hypersensitivity response to tuberculin was lost. It has subsequently been confirmed that this loss of cell-mediated reaction during acute measles is found to a variety of antigens and is not restricted to the loss of the skin reaction but can be demonstrated by a number of *in vitro* tests for T cell function as well. This loss of delayed hypersensitivity is often given the name 'anergy'. The mechanism of anergy in acute measles infection is not certainly known but may be the result of direct infection of the T cell system by measles virus – a subject on which Dr Valdimarsson (p 1125) has more to say. It is clearly plausible that a generalized failure of cell-mediated immunity may facilitate the growth of other organisms and may play a part in the frequent occurrence of bacterial infection following upon measles. It should also be borne in mind that T cells function in antibody formation, not only in the well-known cooperative role but also in certain circumstances by modulating B cell

activity in the negative sense, i.e. in suppressing antibody formation. It is therefore possible that one of the consequences of T cell failure may be the production of unusually large amounts of antibody; a possibility which may have some relevance in the pathogenesis of SSPE (*see below*).

Post-measles encephalomyelitis: It seems likely from clinical data on EEG changes in acute measles that the measles virus may commonly enter the brain during measles infection. However, acute encephalomyelitis is an infrequent complication of the disease and the possibility arises that this is not due to direct measles damage to the brain but that this disease is analogous to allergic encephalomyelitis and that a delayed hypersensitivity reaction to the virus in the brain is causing the damage. The model for this is lymphocytic choriomeningitis infection in the mouse where the infection of adult mice with this virus leads to an encephalomyelitis which is dependent on the existence of normal delayed hypersensitivity reactions. If mice with deficient delayed hypersensitivity reactions, for example neonatal mice, are infected with the virus they show no neurological disease but may develop a chronic indolent infection with virus which eventually gives rise to a generalized immune-complex disease as discussed further below.

Post-vaccinal syndromes: Children immunized with killed measles vaccine who subsequently contract measles infection have in some cases developed an unusual form of the disease complicated by a bronchiolitis (Fulginiti *et al.* 1967) which is believed to represent an acute immune-complex disease occurring in the lung. A similar syndrome has been described in children given killed RSV vaccine who subsequently became infected with RSV (Parrott *et al.* 1967). There is also a similar naturally occurring situation in the case of dengue virus. Here children who have been infected with one serotype of dengue and are infected within about two years by a different serotype may develop the dengue shock syndrome. The pathogenesis of this condition has been studied in some detail and it has been shown that there is formation of substantial amounts of immune complex with massive complement activation and that this is likely to be responsible for the syndrome produced (Bokisch *et al.* 1974).

These conditions epitomize the paradoxical situation of having an allergic response without immunity. This is a general problem of great importance in the immunopathology of infectious disease – how it is that an allergic response may fail to eliminate the infectious organism. A number of factors may be involved:

(1) There may be a failure of cell-mediated reaction to the antigen. This is the situation known as immune deviation and, as has already been mentioned above, in some circumstances the failure of cell-mediated immunity may actually lead to the formation of excessive amounts of antibody rather than the reverse. Whereas in the case of measles the failure of delayed hypersensitivity may be a result of measles infection, it is now also known that capacity to develop cell-mediated responses to particular antigens is under genetic control. In mice and guinea-pigs it has been found that there is a set of dominant or co-dominant genes transmitted as single mendelian characters which control the capacity to give a cell-mediated response to particular antigens. These so-called 'immune response' or Ir genes have been found in most cases to be linked to the principal transplantation locus. In man, direct measurements of immune response genes are still few but a good deal of effort has been devoted to showing linkage between the H-LA locus, the principal transplantation locus in man, and particular diseases, especially those with immunological overtones (*see* McDevitt & Bodmer 1974). Such studies have so far given one overwhelmingly convincing association: that of the antigen W27 with ankylosing spondylitis and a number of related diseases. There are also a number of significant but rather weaker associations. One of these, the association of multiple sclerosis with LD 7a and with the failure of cell-mediated immunity to paramyxoviruses, is discussed in detail by Dr Platz (p 1133).

(2) Antibodies may be formed to the wrong antigen, i.e. to antigens which are not directly involved in the entry of virus into the cell, and therefore are not 'immunogenic' in its true rather than its usual sense. As has already been discussed, this may well be the reason why hitherto available killed measles vaccine is so poor at producing immunity. Such antibodies to, for example, the nucleocapsid of measles virus may nevertheless be perfectly good at producing immune-complex disease so that a child immunized with an inappropriate vaccine may well be worse off than one not immunized at all. There may be indeed a further twist to this story. Halstead *et al.* (1974) have suggested in the case of dengue that the allergic response to the initial serotype of the dengue virus may allow, on subsequent infection, the rapid growing up of a line of transformed lymphocytes which are themselves a particularly good culture medium for the growth of the second strain of virus. In this way, an inappropriate allergic response may actually serve to 'grow up' a tissue culture for a subsequent virus infection and this may explain the very high levels of viræmia produced in second attacks of dengue.

(3) The antibodies produced may be of low affinity and therefore ineffective in eliminating the pathogen. The work of Soothill & Steward (1971) has brought this possibility to general attention. They showed that strains of mice prone to develop immune-complex disease from neonatal LCM infection are strains that when immunized with other antigens have a tendency to make low affinity antibody. In conjunction with Dr Stephen Fazekas de St Groth in Basel, we have been attempting to measure the affinity of anti-measles antibodies in SSPE. These results are at a highly preliminary stage but it does seem that the anti-measles antibodies found in children with SSPE do not give linear regression lines in equilibrium filtration experiments. At the present time, these findings cannot be accurately interpreted, but a possible explanation is that such sera contain a mixture of low affinity antibody with some high affinity antibody. It is therefore possible that this production of poor quality antibody may be important in measles infection as well.
(4) Complement deficiency is not a situation which is obviously involved in measles infection. However, in certain situations it seems that animals who are complement deficient may be less capable of eliminating infective organisms even in the face of a normal antibody response.

It should be emphasized that all these factors apply not only in the case of the acute failure of elimination, as occurs in the post-vaccinal syndromes, but also to the chronic situations discussed below.

The Role of Immunopathological Reactions to Measles in Diseases not Obviously due to Measles at all

Partial lipodystrophy: The association of partial lipodystrophy with measles appears to be mainly anecdotal but this curious condition has been reported as following upon measles infection and occurring particularly at the site of the measles rash. It is of interest that there is a strong association between partial lipodystrophy and various states of complement activation and also with glomerulonephritis (Peters *et al.* 1973).

Systemic lupus erythematosus: It has been shown that there is elevation of antibodies to measles in patients with systemic LE. It is, however, still doubtful whether this elevation of antibody titre to measles is any greater than would be expected from the rise in total immunoglobulin (Phillips & Christian 1971). However, one should not too readily dismiss the association of systemic lupus with persistent virus infections since both in the New Zealand mice and in dogs with canine lupus – the two best models for human lupus – there is now evidence available suggesting most strongly that these diseases are associated with persistent virus infection. In the case of the New Zealand Mice (Lerner *et al.* 1974) a murine leukæmia virus related to but distinct from the Gross and Maloney viruses has been isolated and in canine lupus too a C-type virus particle has recently been implicated (Lewis & Schwartz 1971). These, of course, are not paramyxoviruses and it remains to be seen whether human lupus is a consequence of persistent virus infection and if so what type of virus is involved.

Chronic neurological disease: This topic is fully explored in subsequent papers and two diseases are discussed:

(1) Subacute sclerosing panencephalitis: This is an extremely rare disease where there is clear evidence of chronic measles virus infection with very high titres of anti-measles antibodies and some degree of anergy. The pathogenesis of the disease has not been clearly worked out and we are still hoping to learn whether this disease represents a normal response to an abnormal virus or an abnormal response to a normal virus or a combination of both; and whether the damage in the brain is produced by the measles virus or by the allergic response to it or again by both.

(2) Multiple sclerosis: This is a relatively common disease. Evidence for measles virus infection here is still indirect although growingly impressive. This is clearly a subject of the greatest possible importance since it raises the hope that the eradication of measles may carry with it in due course the elimination of multiple sclerosis.

REFERENCES

Bokisch V A, Müller-Eberhard J J & Dixon F J (1974) In: Advances in the Biosciences 12. Ed. G Raspe. Pergamon & Vieweg, Braunschweig; p 417
Coombs R R A, Smith C E G & Lachmann P J (1974) In: Clinical Aspects of Immunology. 3rd edn. Ed. P G H Gell *et al.* Blackwell, Oxford (in press)
Fulginiti W C, Eller J J, Downie A W & Kempe C H (1967) *Journal of the American Medical Association* **202**, 1075
Halstead S V, Marchette N J & Sung Chow J S (1974) In: Advances in the Biosciences 12. Ed. G Raspe. Pergamon & Vieweg, Braunschweig; p 401
Lerner R A, Dixon F J, Croker B P, Del Villano B C, Jensen F C, Kennel S J & McConahey P J (1974) In: Advances in the Biosciences 12. Ed. G Raspe. Pergamon & Vieweg, Braunschweig; p 356
Lewis R M & Schwartz R S (1971) *Journal of Experimental Medicine* **134**, 417
McDevitt H O & Bodmer W F (1974) *Lancet* i, 1269
Parrott R H, Kim H W, Arrobio J, Canchola J G, Brandt C D, DeMeio J L, Jensen K E & Chanock R M (1967) In: Vaccines against Viral Rickettsial Disease of Man. Pan American Health Organization Scientific Publications. No. 147, Washington; p 35
Peters D K, Williams D G, Charlesworth J A, Boulton-Jones J M, Sissons J G P & Evans D J (1973) *Lancet* ii, 535
Phillips P E & Christian C L (1971) *Arthritis and Rheumatism* **14**, 180
Soothill J F & Steward M W (1971) *Clinical and Experimental Medicine* **9**, 193