Immunology and Virus Diseases

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Almost all infections and systemic infestations cause both humoral and cell-mediated immunological responses. The few exceptions occur in the unusual circumstance where a state of tolerance exists between a host and its parasite, or where, in some way not yet understood, the parasite (perhaps by having some non-antigenic covering such as the hyaluronic acid capsule of group A streptococci) is able to avoid inducing immunological responses. The latter situation appears to occur in filariasis where the microfilaria are able to circulate in large numbers in the bloodstream without, apparently, engendering responses.

In the state of tolerance, the host regards the antigens of the parasite as 'self' antigens: the phenomenon has been widely studied in experimental animals, particularly in the model of lymphocytic choriomeningitis virus (LCM) infections of mice where an apparent (although only partial) state of tolerance readily occurs if the animals are infected *in utero*, or in the neonatal period. In these circumstances, their blood and tissues contain large amounts of virus for long periods without evidence of disease: however, relatively low amounts of antibody are formed and hence only small numbers of virus-antibody complexes. After a period of about nine months, chronic degenerative disease becomes manifest, probably due to the immune complexes but perhaps also to an element of autoimmune disease. The outcome depends on the strain of mouse used; genetic differences appear to be important in determining the amount of virus produced and of the antibody response (Benson and Hotchin, 1969; Oldstone and Dixon, 1969, 1970). Lesions can be precipitated earlier by passively administered antibody or immunologically reactive cells (Oldstone and Dixon, 1970). In older animals with fully developed immunological mechanisms, LCM infection leads to fatal encephalitis. Both the acute and chronic types of disease depend on interactions between the host's responses and the parasite. Whether true immunological tolerance or this partial form of it occur in human virus disease is unknown, but at least the latter may be more common than we realise, particularly with slow virus (Gajdusek *et al.*, 1965) infections. True tolerance appears to occur in at least one natural

infection (Machupo virus) of wild animals (Justines and Johnson, 1969). The carrier state in virus (serum) hepatitis seems to be in this category.

These examples of tolerance or partial tolerance show that virus infections in the absence or near-absence of immunological responses do not lead to unrestrained and harmful virus multiplication, and, in addition, point to the role of the immunological responses in the pathogenesis of disease. Before considering this role further a brief review is necessary of some relevant features of cellular and humoral immunology. 'Although future analysis will certainly uncover a fundamental affinity between them, it is at present operationally sound to distinguish between immunological reactions mediated through circulating antibodies and those that are transacted by the direct engagement of antigens with lymphoid cells' (Medawar, 1969). The manifestations of cell-mediated immunity may depend both on cells actively and passively allergised (Coombs, 1967) but it is at present difficult to distinguish these types of activity in virus infections. As it is unlikely that cells have an antigen-recognition mechanism completely different from that underlying antibody specificity, it is postulated that reactive (sensitised) cells either produce antibody at their surface (actively allergised) or that antibody attaches to them (passively allergised).

Humoral immunity appears to develop as follows: perhaps after some sort of 'processing' by macrophages (Pribnow and Silverman, 1967; Argyris, 1968) antigen stimulates responsive marrow-derived (MD) (or 'gut-associated') lymphocytes to differentiate, proliferate, and mature into plasma cells that produce antibody (Roitt *et al.*, 1969). Thymus-derived (TD) lymphocytes appear to play some part in initiating the response by MD lymphocytes (Lischner and DiGeorge, 1969). After a small amount of an antibody has been produced and has combined with antigen, the resultant immune complexes, which may be more antigenic than antigen (Levi *et al.*, 1969), may promote rapid antibody synthesis so long as antigen is still available (Terres and Morrison, 1967). The antibodies (Humphrey, 1967) produced are the immunoglobulins IgM, IgG, IgA, and perhaps others: Thind and Price (1968, 1969a, b) have described an additional active material in serum, which they have called serum protective factor. In an infection, IgM antibody is usually detected first and appears to be induced especially by particulate antigens: because of its size, IgM diffuses poorly, if at all, into tissues. However, the IgM molecule has five active sites and appears to be important in reacting with and opsonising large antigenic structures such as bacteria and perhaps viruses. IgG antibody is present in blood and tissue fluids roughly in proportion to their protein content, and diffuses into the cerebrospinal fluid and mucous secretions when vascular permeability is increased by inflammatory reactions.

It may also be produced locally at mucous surfaces (Rossen *et al.*, 1966) and in the central nervous system (Cohen and Bannister, 1967; Connolly *et al.*, 1967). IgA, when excreted at mucous surfaces, has an additional 'piece' attached to it compared with serum IgA. Excreted IgA is found in respiratory and intestinal secretions and in colostrum, and seems to be produced locally in response to antigens applied to mucous membranes.

In the development of cell-mediated (CM) immunity, antigen (possibly macrophage-processed) appears to stimulate responsive TD lymphocytes to transform to lymphoblasts which provide: (*a*) specific antigen-sensitive cells with a long life span and responsible for immunological memory; (*b*) 'killer' cells, which destroy cells carrying the specific antigen (infected cells with virus antigen(s) on their surfaces); (*c*) antigen-sensitive cells, which react specifically with antigen to release the factors responsible for delayed-type hypersensitivity and other manifestations of CM immunity (Roitt *et al.*, 1969). These factors may include a cytotoxic 'lymphotoxin' (Williams and Granger, 1969). Within about 60 hours of an infection, lymphoblasts begin to increase in the lymph and reach a peak in about 100 hours. During a response in man, perhaps as many as 10^{10} of these highly motile lymphoblasts are produced daily and, as rapidly, infiltrate tissues (Hall, 1969). Dwyer and Mackay (1970) have shown in man that the proportion of antigen-binding lymphocytes in the circulation increases about 8-fold during the 14 days following immunisation. The reactive cells were blast-like early in the response but blasts had disappeared by the 14th day.

ANTIGENS IN INFECTIONS

The complexity of the immunological responses to an infection depends on the antigenic complexity of the infecting parasite. All proteins may be assumed to be potentially antigenic so that the number of antigens involved can range from two to four proteins in poliovirus (Summers *et al.*, 1965) to several hundreds in so relatively simple a parasite as *Escherischia coli*. *E. coli* carries sufficient genetic information to code for two to three thousand proteins (Watson, 1965) and judging by the number of enzymes required for known metabolic steps, perhaps a fifth of these are produced. Dr A. P. MacLennan (personal communication) has estimated that during a bacteraemia (e.g. in plague or staphylococcal septicaemia) of 10^3—10^6 organisms/ml in an 11 stone man, 10^{-9}—10^{-6}g of each of these hundreds of antigens is produced. Judging by the antigenicity of flagellin in mice (Shellam and Nossol, 1968), amounts of this order would be potentially antigenic if the bacteria were lysed and their antigens rendered 'soluble', or if the released products of phagocytosis remain antigenic. Thus, the complexity of the

immunological responses in such infections is potentially very great although they tend to be dominated by surface antigens because of their ready accessibility to cellular recognition sites.

In virus infections (and perhaps in some other intracellular infections) the complexity is greater than that indicated by the number of antigens in the virus, because the virus codes enzymes produced by the host cell during virus replication: these virus-coded proteins (about ten have been demonstrated in poliovirus infection—Summers *et al.*, 1965) are released when the cell breaks down and may provide a substantial number of additional antigens. Poxvirus infections have been shown to generate antibodies to as many as 17 or 20 antigens (Appleyard and Westwood, 1964; Westwood *et al.*, 1965) while only 8 were demonstrated in purified virus (Zwartouw *et al.*, 1965).

The responses to surface antigens are probably the most important in protection and recovery from infection: for instance, Boulter (1969, and unpublished) has shown that it is the antigen(s) of the outermost coat of a poxvirus (which it acquires only when it is naturally released from the host cell) that is responsible for generating an antibody, which not only confers passive protection but actually has therapeutic value in an infection.

When parasites die, all their antigens are released and so may cause responses. If a large number of parasites are rapidly destroyed during an infection (for example by the over-enthusiastic use of antibiotics in typhoid fever or relapsing fever) very severe immunological reactions (Herxheimer reactions) can occur.

Some organisms cause relapsing disease because as each population of parasites is dealt with by the immunological responses a new and antigenically different population of parasites arises and thus evades the immunological defences. These antigenic changes are most probably mainly in surface antigens. Outstanding examples are malaria and relapsing fever.

THE EFFECTS OF IMMUNOLOGICAL INTERACTIONS

During an infection, antigens may be present in the tissues, in the circulation, or in both, so that they will interact with humoral and cell-mediated responses in a variety of situations. During the early stages of a first infection, antigens are present in excess over the corresponding antibodies and the immune complexes formed are small and 'soluble'; as antibody builds up the relationship swings through equivalence to antibody excess, when large ('insoluble') complexes are formed. If antigen formed in tissue diffuses to form complexes with circulating antibody in vessel walls, an Arthus reaction results with polymorphonuclear infiltration which appears to be responsible for necrosis of the vessel walls since it does not occur in the absence of a polymorph response.

When immune complexes are formed in the circulation (e.g. during viraemia), they are deposited in a variety of tissues on vessel walls and, notably, at filtration points such as the kidney and the joints: the reaction consists of endothelial proliferation, increased vascular permeability, and a variable polymorph response followed by mononuclear infiltration. In the course of a virus infection, it is at about the point at which symptoms and signs are becoming marked that antibody becomes detectable (i.e. in excess) in serum. Some idea of the amount of antigen-antibody complexes formed before antibody is in excess can be obtained by considering the maximum possible antibody that circulating infective virus is capable of combining with at the height of viraemia (taken to be of the order of 10^8 virions/ml) in, for example, yellow fever. The total area of virus surface antigen in the circulation under these circumstances would be of the order of 4,500 mm^2 which, assuming tight packing, might be capable of adsorbing about 0·1 mg of the specific antibody (G. Appleyard, personal communication)—a large amount of a single immunoglobulin species. It should be remembered that the virus population during the rise in viraemia is being recruited at a rate greater than that at which it is being eliminated and that, at the peak, the rate of turnover is large. Moreover, there is probably as much or more virus-coded antigen as there is on mature particles.

Where the antibody response is inadequate to clear antigen from the circulation but sufficient to cause long-term production of immune complexes, chronic inflammatory and degenerative disease (immune complex disease) results (Dixon, 1963). The quantitative relationships between the rates of production of antigens, on the one hand, and of antibodies, on the other, are critical in determining the outcome of an infection. It should be noted that virus combined with antibody may have unimpaired infectivity (Notkins *et al.*, 1966; Ashe and Notkins, 1966). Indeed, Hawkes and Lafferty (1967) have shown that in some circumstances infectivity is enhanced by the addition of serum containing antibody. Virus coated with antibody can be rendered non-infective by reaction with an antiglobulin, and a similar result may occur in antibody excess; or antibody to the initial virus-antibody complexes may act as an antiglobulin (Henney and Stanworth, 1966; Najjar *et al.*, 1967).

Antibody reacts not only with the free antigens of the parasite but also with cell-fixed antigens. When a cell is infected with one of the viruses (for example, myxoviruses and arboviruses) which acquire their outer lipoprotein coats by budding through the cell membrane, areas of the cell surface carry virus antigens which will react with antibody and complement to cause cell lysis. Wiktor *et al.* (1968) found that rabies-infected cells were lysed by antibody even before virus-budding could be observed. This may be a reaction of great

importance in reducing the virus yield from infected cells, as it destroys them before they can release mature virus. It might, for instance, have particular significance in limiting the spread of latent virus infections, especially herpes simplex, between exacerbations. In some circumstances the surface of infected cells may react with and trap immune complexes, which may account for some of the localisation that is hard to account for in immune complex disease.

During an infection, specifically 'sensitised' lymphocytes proliferate (Marshall *et al.*, 1969), circulate and invade infected tissues. There they react with their corresponding specific antigens and transform to lymphoblasts which are probably capable of destroying infected cells by reacting with antigen on their surface (Roitt *et al.*, 1969) or by the release of a cytotoxic mediator-substance (Ruddle and Waksman, 1968). They also react with antigen to release pharmacologically active substances, such as macrophage-inhibiting factor, which contribute to the manifestations of delayed-type hypersensitivity. In mice infected with a parainfluenza virus, the affected areas of lung are heavily infiltrated with lymphoblasts by about five days after infection and the tissue virus titre falls rapidly at this point although circulating antibody does not reach its peak until about the fourteenth day (Robinson *et al.*, 1968).

Leucocytes play a particular role in virus multiplication in some infections (Webb *et al.*, 1966). Simons (1968) has suggested that rubella virus persists in congenitally infected babies as a persistent infection in long-lived lymphocytes. Wheelock and Edelman (1969) have studied yellow fever virus in human leucocytes: it did not multiply in polymorphs, multiplied well in monocytes, poorly in untransformed lymphocytes, but well in transformed lymphocytes. During the course of infection in man, lymphocytes, even when transformed *in vitro*, failed to support virus replication from the fourth until the tenth or twelfth day after infection of their host. These lymphocytes were probably carrying antibody on their surface. Transformed lymphocytes also supported the multiplication of herpes simplex, vesicular stomatitis, mumps, and vaccinia viruses. Benezra *et al.* (1969) observed that lymphocyte transformation during an immune response correlates with both cellular and humoral responses, not only with the development of delayed-type hypersensitivity.

The pathogenesis of skin rashes in virus infections depends on both humoral and cell-mediated responses (Mims, 1966). Taking poxvirus lesions as an example, the pock itself is caused by virus multiplying in the skin, destroying cells, and interacting with a cellular immune response. Pincus and Flick (1963a) showed that delayed-type hypersensitivity could be elicited as early as the fourth day after infection and (1963b) that the papule and vesicle (but

not the erythema) were prevented by intradermal administration of an antiserum against mononuclear cells. As in the case of sensitisation to skin-bound chemicals (Medawar, 1969), skin-bound virus antigens may induce delayed-type responses by direct contact with peripheral lymphocytes circulating between the skin and the lymph nodes. In immunologically tolerant rabbits, in which no detectable antibody developed, skin lesions were abortive or absent (Flick and Pincus, 1963). In animals irradiated so as to depress an antibody but not a delayed-type response, pocks developed normally. The surrounding erythema, however, depends on humoral immunity; it appears in man around the seventh day and coincides with the appearance of detectable (excess) antibody. Virus antigen is present in the circulation (Hughes, 1933) and has been shown capable of causing anaphylaxis in passively sensitised animals (Davis, 1931). Thus, the erythema probably depends on the formation of immune complexes, with consequent increased permeability and the release of pharmacological substances by immunological interactions.

During an infection many and complex immunological interactions are occurring and it is not at present possible to get any clear idea as to how one may influence others. There is probably competition between antigens: Edinger *et al.* (1968) showed that a primary antibody response to one antigen caused moderate suppression of both IgM and IgG responses to another and also inhibited the corresponding cell-mediated response as judged by skin graft survival; a secondary antibody response to one antigen completely suppressed primary IgM and IgG responses to another. Competition also occurs between antibodies: Henry and Jerne (1968) found that previously administered IgG antibody, even in very low concentration, suppressed a primary antibody response to the same antigen (probably because it attached to and covered antigenic determinants); previously administered IgM enhanced a primary antibody response (probably because it attached to macrophages and captured antigen to them). Axelrad and Rowley (1968) showed that intravenously administered antigen and antibody prevented the development of delayed-type hypersensitivity although it had no effect on established hypersensitivity. Stuart *et al.* (1968) confirmed this in terms of enhancement of the survival of renal allografts. Very detailed and patient studies will be needed to assess the possible roles of these and other factors in the very complex situation of an infectious disease.

PARTIALLY IMMUNE HOSTS

Where, because of previous immunisation or infection with the same or a related organism, the immunological mechanisms are already primed at the time of infection, both humoral and cell-mediated responses may be much

accelerated and, in most instances, succeed in localising and terminating the infection. In some circumstances, however, the concurrence of vigorous immunological responses and large amounts of antigens can lead to disease more severe than that in an immunologically virgin host. Excellent examples are provided by several virus diseases. Abnormally severe and clinically unusual measles followed natural infection in children previously vaccinated with an inactivated measles vaccine (Fulginiti *et al.*, 1967). Similarly, Parrott *et al.* (1967) found that children immunised with a poorly immunogenic respiratory syncytial virus (RSV) vaccine developed more severe disease when subsequently infected. Chanock *et al.* (1967) observed that RSV infections were most severe during the first two months of life and suggested that this could be attributed to Arthus-type reactions between large amounts of virus material produced by the child and high levels of antibody passively transferred from the mother. Blandford (1970) has suggested that the pneumonia is due to obstruction of the bronchioles caused by cellular debris resulting from a widespread Arthus reaction. Gardner *et al.* (1970), however, point out that while virus is abundant in the tissues in RSV pneumonia, it is scanty in bronchiolitis where immunoglobulin can be detected in the tissue with about the same distribution as virus. On this basis they suggest that bronchiolitis is due to a second infection, with the same virus causing an anaphylactic reaction. The frequency of RSV infections in infancy is certainly high enough to make repeated infections probable.

Another situation where second infections (in this case probably with closely related viruses) appear to cause exceptionally severe disease is in dengue haemorrhagic fever which has caused large numbers of cases and many deaths in children of cities in south and south-east Asia since 1958 (Halstead, 1966). In contrast to the normally minor although unpleasant disease caused by dengue virus infection, a severe form with haemorrhages and hypotensive shock occurs in children during annual dengue epidemics. In this aberrant severe form of disease, accelerated immunological responses occur (due to previous infection with a related virus) and interact with virus antigens and probably with virus-infected cells: during the immunological crisis complement ($\beta_{1\ c/a}$) disappears from the circulation. These secondarily infected patients had IgG but not IgM or IgA responses to the infection (Russell *et al.*, 1969). The deposition of immune complexes on vessel walls probably triggers off acute disseminated intravascular coagulation (McKay and Margaretten, 1967), platelet depletion, and consequent haemorrhages. As a related virus has been shown to multiply in vascular endothelium (Kundin *et al.*, 1963) it is possible that such cells with virus antigen on their surfaces trap immune complexes and account for the widespread intravascular effects. The shock

is probably attributable to widespread increased vascular permeability due to the sudden release of pharmacologically active compounds by a variety of immunological reactions.

Jolke *et al.* (1967) showed that hepatitis virus infection in dogs caused acute necrotic disease in non-immune animals but chronic and progressive hepatitis in dogs with a low level of pre-existing immunity. Almeida and Waterson (1969), observing antigen and antibody in the serum of patients by electron microscopy, have suggested that the type of disease in human hepatitis virus infection also depends on the immunological state: the carrier has circulating (and presumably tissue) antigen but no known immunological responses and no disease; the normal self-limited case of hepatitis has immunological responses that are efficient in amount and timing to terminate the disease and eradicate the infection; fulminating necrotic hepatitis is due to a state of anaphylaxis where large antigen-antibody complexes are formed in massive quantities during antibody excess (i.e. infection in an immunologically primed host); chronic and progressive hepatitis is attributable to a prolonged state of antigen excess and immune complex disease. The difficulty in accepting this view is in seeing why the various types of immune complex disease postulated should be localised or largely localised in liver. This might be accounted for if the hepatitis virus turns out to be a budding virus and multiplies wholly or mainly in the liver. Although immune complexes appear to be responsible for this type of degenerative disease, Oldstone and Dixon (1970) found that in LCM infections in mice, disease could be aggravated by passive administration of either additional antibody or additional sensitised spleen cells. In the late stages of degenerative disease attributable to chronic infections, autoimmunity may play a part (*vide infra*).

IMMUNOSUPPRESSIVES

Defective immunological responses can greatly influence the course of an infection; the defects can be congenital, caused by drugs or by infections. In the Bruton type of agammaglobulinaemia, delayed-type hypersensitivity (and probably other types of cell-mediated response) is unimpaired but immunoglobulin synthesis is severely defective, and recovery from virus infections is quite normal. In the Swiss type, however, where the cell-mediated responses are also defective, localisation of infections may be severely impaired. Cell-mediated immunity must therefore be important in the localisation of and recovery from virus infections. This is a point to which more attention should be paid by those who develop virus vaccines. The tendency has been to accept an antibody response as evidence of effectiveness but now that methods are being developed for the measurement of cell-mediated immunity,

evidence of its induction should be sought in the assessment of virus vaccines. Other responses are, however, also involved in recovery from virus infections. Chandra *et al.* (1969) reported seven cases of generalised but non-progressive vaccinia infection in patients with IgM deficiency. The deficiency of IgM seems to have permitted prolongation of the viraemia.

Immunosuppressive treatments are being more and more widely used in clinical medicine and in transplant surgery. Most clinicians are aware that clinical infections can be aggravated, subclinical or latent infections made manifest, and even that normally harmless organisms can cause serious infections in patients under such treatments. But as the means for immunodepression become more powerful and widely used, it is important that the full range of dangers from infections is appreciated. Merely as one instance among many, Montgomerie *et al.* (1969) reported four fatal cases of generalised herpes simplex in renal transplant patients treated with azathioprine and prednisone. The fact that they all had pre-existing complement-fixing antibody to the virus strongly suggests that they had pre-existing latent herpes simplex, as indeed have a high proportion of the general population.

The experimental use of immunodepressants can help to elucidate the role of immunological mechanisms in infectious disease although, with most existing procedures, interpretation is often difficult because their action is either multiple or poorly understood. Antilymphocytic serum (ALS) is believed to act entirely on cell-mediated immunity and to have little or no effect on humoral responses (Medawar, 1969). Hirsch and Murphy (1968) studied its effect on a number of virus infections in mice: in general, ALS aggravated the disease and also the mortality in mice infected by a peripheral route, while little change in outcome was apparent in mice infected intracerebrally. Cell-mediated responses thus appeared to be important in limiting the spread and severity of systemic infections but to play little part in the central nervous system; this, however, was probably because the course of infection in intracerebrally infected mice is relatively short and, without a preceding systemic infection, there may have been insufficient time for the immunological responses to develop. The central nervous system seems in any case to be relatively inert in cell-mediated responses when antigen is directly implanted, as judged by its general failure to reject tissue grafts. Hirsch and Murphy also found that ALS caused a recrudescence of viraemia in mice that had recovered from a LCM infection and that had high levels of circulating antibody. Wenner *et al.* (1969) found that ALS prolonged the disease in monkey pox and greatly increased tissue necrosis (including gangrene): the rash progressed to ulceration and there was little evidence of repair. These effects are presumably due to impairment of cell-mediated responses which localise the

infection into pocks, although the picture is slightly complicated by the observation of Barth (1969) that ALS also inhibits interferon production. Weissenbacher *et al.* (1969) found that thymectomy within 24 hours of birth protected mice against disease when they were subsequently infected intracerebrally with Junin virus. Passive administration of antibody failed to precipitate disease but pathogenesis was triggered off by the passive administration of sensitised spleen cells.

Experiments with cyclophosphamide illustrate the effects of cytotoxic immunosuppressants. Cyclophosphamide probably exerts its influence by destroying or inhibiting the proliferation of specifically sensitised lymphocytes (Medawar, 1969) and hence affects both humoral and cell-mediated responses. It may also inhibit interferon production (Robinson *et al.* 1968). In studies of virus infections of the central nervous system (CNS) in monkeys, Nathanson and Cole (1970) and Zlotnik *et al.* (1970, in press) have shown that cyclophosphamide greatly reduced inflammatory lesions (perivascular cuffing, cellular infiltration) in the CNS but that the resulting disease was much more severe, and deaths occurred even following infections which, without immunosuppression, would not have been completely apparent clinically. The CNS lesions observed in cyclophosphamide-treated monkeys were severely necrotic and degenerative, with little evidence of inflammation (Zlotnik *et al.*, 1970, in press). Indeed, the pattern of neuronal necrosis and spongy degeneration was very similar to that seen in scrapie—a slow virus infection where immunological responses have not been demonstrated (Zlotnik, 1962; Zlotnik and Rennie, 1965).

Clearly, inflammation in the CNS is not dependent on virus alone but requires the concurrence of immunological responses. The evidence above suggests that cell-mediated responses may be responsible for the characteristic perivascular cuffing of encephalitis. But humoral antibody and, therefore, immune complexes also appear to be involved (Webb and Smith, 1966). If antibody is administered to mice at the height of viraemia, paralysis is delayed in onset but aggravated (Webb *et al.*, 1968). In the CNS, inflammation has a much greater importance than in other tissues because the associated oedema within the rigid walls of the skull leads to increased pressure and dysfunction of neurones. It is the recovery of these neurones when the inflammation subsides that accounts for the rapid partial recovery following the acute stage of, for example, poliomyelitis. There may therefore be a case for the judicious use of an immunodepressant before the inflammation reaches its peak in encephalitis.

A number of virus infections are themselves immunodepressive and may influence the outcome of concurrent infections. For instance, measles causes

a loss of delayed-type hypersensitivity to tuberculin and tends to aggravate concurrent tuberculosis; intercurrent measles also seriously aggravates malaria. Mouse carriers of Rauscher virus have markedly more severe disease from infections with *Plasmodium bergei yoeli* than normal mice (Salaman, 1970). Blumhardt *et al.* (1968) observed that following live measles vaccination there was a reduction, for 3 to 6 weeks, of cutaneous sensitivity to poison ivy. Mims and Wainwright (1968) described the immunodepressive effect of LCM infection in mice: there was a temporary depression in the antibody-producing cells and a decreased susceptibility to anaphylaxis with ovalbumin. Mouse leukaemia viruses cause similar effects. Mims and Wainwright suggest that these effects are caused by viruses capable of establishing long-term non-cytopathic infections involving lymphoid tissue. Hanaoka *et al.* (1969) described apparent selective destruction of TD lymphocytes and of thymocytes in LCM infections. Pollard and Sharon (1969) described, in normal carriers of LCM virus, enlargement of the lymph nodes and spleen with enlarged germinal zones and a great increase in plasma cells. In germ-free carriers, the thymus was cystic and depleted of cortical cells and the Peyer's patches lacked germinal zones. They suggest that some normal feed-back mechanism has been impaired so that the thymus is drained of functional cells and plasma cells increase disproportionately. A number of virus infections cause impaired responsiveness of lymphocytes to transformation by phytohaemagglutinin (Olson *et al.*, 1968) but the significance of this is still uncertain.

INFECTIONS AND AUTOIMMUNE DISEASE

Adams (1969) has reviewed the possible role of infections in the pathogenesis of rheumatic fever, glomerulonephritis and other autoimmune diseases triggered by infection. He postulated that those susceptible probably have some genetic defect which permits a particular 'forbidden clone' (hence, for instance, the familial tendency in thyroiditis) and that the causative organism may have an antigen similar to the relevant host antigen. There is no doubt that prolonged deposition of immune complexes formed during an infection can cause chronic degenerative disease (Dixon, 1963; Oldstone and Dixon, 1969, 1970; Benson and Hotchin, 1969). However, as all viruses with lipoprotein coats (arboviruses, myxoviruses, etc.) incorporate host cell antigens as they bud through the cell membrane, and infected cells thus have mixed host and virus antigens on their surfaces, there is an obvious possibility that when such infections are prolonged immune responses may be induced against altered host antigens and, later, against host antigens themselves. Chronic destruction alone of a particular tissue or class of cells (e.g. neurones) may yield altered

host antigens capable of generating autoimmune responses. Holterman and Majde (1969) have demonstrated evidence suggestive of an antigenic change in the cells of mice chronically infected with LCM virus in that grafts from infected donors were rejected by non-infected syngeneic recipients. Similar findings were reported by Bryere and Williams (1964) in mice infected with a leukaemia virus. Robertson and Black (1969) demonstrated changes in the surface antigens of cells transformed by SV40 virus: Forssman antigen was found on SV40- or polyoma-transformed hamster cells but not in adenovirus-transformed hamster cells or SV40- or polyoma-transformed mouse cells.

If such antigenic changes occur during chronic virus infections, they may lead to autoimmune destructive processes. Subacute sclerosing panencephalitis (*Neurology*, 1968) which, although Katz *et al.* (1968) have reported isolation of a slow virus, appears to be caused by a chronic infection of the CNS with measles virus in the presence of exceptionally high levels of circulating antibody (Connolly *et al.*, 1968; Horta-Barbosa *et al.*, 1969) is a situation where such changes may occur. Burnet (1968) has suggested that the fundamental lesion may be a specific deficiency of cell-mediated immunity, while Koprowski *et al.* (1970) suggest that SSPE, and also progressive multifocal leucoencephalopathy may be due to activation of a latent papovavirus infection by a paramyxovirus. Similar disease may well be caused by other budding viruses—particularly other myxoviruses—and it must be regarded as at least a possible hazard of live myxovirus vaccines, including live measles vaccine. Other budding viruses—the arboviruses—have been shown to be capable of long persistence in the CNS (Price, 1966; Illavia and Webb, 1969). The possibility must be considered that other degenerative conditions of the CNS (such as disseminated sclerosis) and degenerative autoimmune diseases of other tissues, may be due to persistent virus infections, perhaps without a previous clinically apparent virus disease. Clinically apparent encephalitis is in any case an unusual complication even of infections normally regarded as virus encephalitides (only about one in a thousand infections caused by poliovirus or Japanese encephalitis virus actually cause encephalitis). Clinical encephalitis is a rare complication of most, if not all, virus infections, and there is little doubt that subclinical infections of the CNS are much more common (Gibbs *et al.*, 1959). Similarly, Adams (1969) has suggested that virus thyroiditis is the probable initiating factor in autoimmune thyroiditis.

CONCLUSIONS

The outcome of any virus infection clearly depends (apart from the general health, nutrition, etc. of the host) on the relative rates at which virus multiplies (its virulence), the cells in which it multiplies, the rate at which it destroys

functional cells in relation to their rate of replacement and the functional reserves of them possessed by the host, the rates at which immunological responses occur (dependent on previous antigenic experience or, on the other hand, on absent or inhibited responses), and the rates and sites at which interactions occur. The immunological interactions involved in a virus infection are probably very complex and it is only very recently that immunological theory and technique have reached a stage at which we may begin to elucidate the mechanisms involved and to separate those that are beneficial to the host from those that are not. Most, if not all, immunological interactions can be either beneficial or adverse, depending on when, where, and in what quantity and circumstances they occur.

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Reference

Adams, D. D. (1969) *Clin. exp. Immunol.*, **5**, 105.
Almeida, J. D. and Waterson, A. P. (1969) *Lancet*, **ii**, 983.
Appleyard, G. and Westwood, J. C. N. (1964) *J. gen. Microbiol.*, **37**, 391.
Argyris, B. F. (1968) *J. exp. Med.*, **128**, 459.
Ashe, W. K. and Notkins, A. L. (1966) *Proc. nat. Acad. Sci. (Wash.)*, **56**, 447.
Axelrad, M. and Rowley, D. A. (1968) *Science*, **160**, 1465.
Barth, R. F., Friedman, R. M. and Malmgren, R. A. (1969) *Lancet*, **ii**, 723.
Benezra, D., Gery, I. and Davies, A. M. (1969) *Clin. exp. Immunol.*, **5**, 155.
Benson, L. and Hotchin, J. (1969) *Nature*, **222**, 1045.
Blandford, G. (1970) *Brit. med. J.*, **1**, 758.
Blumhardt, R., Pappano, J. E. and Moyer, D. G. (1968) *J. Amer. med. Ass.*, **206**, 2739.
Boulter, E. A. (1969) *Proc. R. Soc. Med.*, **62**, 295.
Bryere, E. J. and Williams, L. B. (1964) *Science*, **146**, 1055.
Burnet, F. M. (1968) *Lancet*, **ii**, 610.
Chandra, R. K., Kaveramma, B. and Soothill, J. F. (1969) *Lancet*, **i**, 687.
Chanock, R. M., Smith, C. B., Friedewald, W. T., Parrott, R. H., Forsyth, B. R., Coates, H. V., Kapikian, A. Z. and Charpure, M. A. (1967) In: *Vaccines against Viral and Rickettsial Diseases of Man*, Pan American Health Org. Scientific Publ. No. 147, Washington, p. 53.
Cohen, S. and Bannister, R. (1967) *Lancet*, **i**, 366.
Connolly, J. H., Allen, I. V., Hurwitz, L. J. and Miller, J. H. D. (1967) *Lancet*, **i**, 542.
Connolly, J. H., Allen, I. V., Hurwitz, L. J. and Miller, J. H. D. (1968) *Quart. J. Med.*, New Ser., **37**, 625.
Coombs, R. R. A. (1967) *Proc. R. Soc. Med.*, **60**, 594.
Davis, G. E. (1931) *Amer. J. Hyg.*, **13**, 79.
Dixon, F. J. (1963) *Harvey Lectures*, **58**, 21. Academic Press, N.Y., Lond.
Dwyer, J. M. and Mackay, I. R. (1970) *Lancet*, **i**, 164.
Edinger, D., Khan, S. A. and Millar, K. G. (1968) *J. exp. Med.*, **128**, 1183.
Flick, J. A. and Pincus, W. B. (1963) *J. exp. Med.*, **117**, 633.
Fulginiti, V. A., Eller, J. J., Downie, A. W. and Kempe, C. H. (1967) *J. Amer. med. Ass.*, **202**, 1075.
Gajdusek, D. C., Gibbs, C. J. and Alpers, M. (1965) *Slow, latent and temperate virus infections.*, NINDB Monograph No. 2, U.S. Dept. Hlth. Educ. Welfare.
Gardner, P. S., McQuillin, J. and Court, S. D. M. (1970) *Brit. med. J.*, **1**, 327.
Gibbs, F. A., Gibbs, E. L., Carpenter, P. R. and Spies, H. W. (1959) *J. Amer. med. Ass.*, **171**, 1050.
Hall, J. G. (1969) *Lancet*, **i**, 25.
Halstead, S. B. (1966) *Bull. Wld. Hlth. Org.*, **35**, 1.
Hanaoka, M., Suzuki, S. and Hotchin, J. (1969) *Science*, **163**, 1216.
Hawkes, R. A. and Lafferty, K. J. (1967) *Virology*, **33**, 250.
Henney, C. S. and Stanworth, D. R. (1966) *Nature*, **210**, 1071.
Henry, C. and Jerne, N. K. (1968) *J. exp. Med.*, **128**, 133.
Hirsch, M. S. and Murphy, F. A. (1968) *Lancet*, **ii**, 37.
Holterman, O. A. and Majde, J. A. (1969) *Nature*, **223**, 624.

Horta-Barbosa, L., Fuccillo, D. A., London, W. T., Jabbour, J. T., Zeman, W., and Sever, J. L. (1969) *Proc. Soc. exp. Biol., N.Y.*, **132**, 272.
Hughes, T. P. (1933) *J. Immunol.*, **25**, 275.
Humphrey, J. H. (1967) *Proc. R. Soc. Med.*, **60**, 591.
Illavia, S. J. and Webb, H. E. (1969) *Brit. med. J.*, **1**, 94.
Jolke, D. J., Preisig, R., Morris, T. Q., McKay, D. C. and Bradley, S. E. (1967) *J. clin. Invest.*, **46**, 1506.
Justines, G. and Johnson, K. M. (1969) *Nature*, **222**, 1090.
Katz, M., Rorke, L. B., Masland, W. S., Koprowski, H. and Tucker, S. H. (1968) *New Engl. J. Med.*, **279**, 793.
Koprowski, H., Barbanti-Brodano, G. and Katz, M. (1970) *Nature*, **225**, 1045.
Kundin, W. D., Chien Liu, Hysell, P. and Hamachige, S. (1963) *Arch. Virus*, **12**, 514.
Levi, M. I., Kravtzov, F. E., Levova, T. M., Fomenko, G. A. (1969) *Immunology*, **16**, 145.
Lischner, H. W. and DiGeorge, A. M. (1969), *Lancet*, **ii**, 1044.
Marshall, W. H., Valentine, F. T. and Lawrence, H. S. (1969) *J. exp. Med.*, **130**, 327.
McKay, D. G. and Margarretten, W. (1967) *Arch. intern. Med.*, **120**, 129.
Medawar, P. (1969) *Proc. R. Soc. London.*, B, **174**, 155.
Mims, C. A. (1966) *Bact. Rev.*, **30**, 739.
Mims, C. A. and Wainwright, S. (1968) *J. Immunol.*, **101**, 717.
Montgomerie, J. Z., Becroft, D. M. O., Croxson, M., Doak, P. B. and North, J. D. K. (1969) *Lancet*, **ii**, 867.
Najjar, V. A., Robinson, J. P., Lawton, A. R. and Fidalgo, B. V. (1967) *Johns Hopk. Med. J.*, **120**, 63.
Nathanson, N. and Cole, G. A. (1970) *Clin. exp. Immunol.*, **6**, 161.
Neurology (1968), **18**, No. 1, Pt. 2.
Notkins, A. L., Mahar, S., Scheele, C. and Goffman, J. (1966) *J. exp. Med.*, **124**, 81.
Oldstone, M. B. A. and Dixon, F. J. (1969) *J. exp. Med.*, **129**, 483.
Oldstone, M. B. A. and Dixon, F. J. (1970) *J. exp. Med.*, **131**, 1.
Olson, G. B., Dent, P. B., Racols, W. E., South, M. A., Montgomery, J. R., Melnick, J. L. and Good, R. A. (1968) *J. exp. Med.*, **128**, 47.
Parrott, R. H., Kim, H. W., Arrobio, J., Canchola, J. G., Brandt, C. D., DeMeio, J. L., Jensen, K. E. and Chanock, R. M. (1967) In: *Vaccines against Viral and Rickettsial Diseases of Man*, Pan American Health Org. Scientific Publ. No. 147, Washington, p. 35.
Pincus, W. B. and Flick, J. A. (1963a) *J. Pediat.*, **62**, 57.
Pincus, W. B. and Flick, J. A. (1963b) *J. inf. Dis.*, **113**, 15.
Price, W. H. (1966) *Virology*, **29**, 679.
Pollard, M. and Sharon, N. (1969) *Proc. Soc. exp. Biol., N.Y.*, **132**, 242.
Pribnow, J. F. and Silverman, M. S. (1967) *J. Immunol.*, **98**, 225.
Robertson, H. T. and Black, P. H. (1969) *Proc. Soc. exp. Biol., N.Y.*, **130**, 363.
Robinson, T. W. E., Cureton, R. J. R. and Heath, R. B. (1968) *J. med. Microbiol.*, **1**, 89.
Roitt, I. M., Greaves, M. F., Torrigiani, G., Brostoff, J. and Playfair, J. H. L. (1969) *Lancet*, **ii**, 367.
Rossen, R. D., Alford, R. H., Butler, W. T. and Vannier, W. E. (1966) *J. Immunol.*, **97**, 369.
Ruddle, N. H. and Waksman, B. H. (1968) *J. exp. Med.*, **128**, 1237.
Russell, P. K., Intavivat, A. and Kanchanapilant, S. (1969) *J. Immunol.*, **102**, 412.
Salaman, M. H. (1970) *Proc. R. Soc. Med.*, **63**, 11.
Shellam, G. R. and Nossol, G. J. V. (1968) *Immunology*, **14**, 273.
Simons, M. J. (1968) *Lancet*, **ii**, 1275.
Stuart, F. P., Saitoh, T., Fitch, F. W. and Spargo, B. H. (1968) *Surgery*, **64**, 17.
Summers, D. E., Maizel, J. V. and Darnell, J. E. (1965) *Proc. nat. Acad. Sci.* (Wash.), **54**, 505.
Terres, G. and Morrison, S. L. (1967) *J. Immunol.*, **98**, 584.
Thind, I. S. and Price, W. H. (1968) *Amer. J. Epid.*, **88**, 287.
Thind, I. S. and Price, W. H. (1969a) *Amer. J. Epid.*, **89**, 593.
Thind, I. S. and Price, W. H. (1969b) *J. Immunol.*, **103**, 1424.
Watson, J. D. (1965) *Molecular Biology of the Gene*. N. Y., W. A. Benjamin Inc.
Webb, H. E., Wetherley-Mein, G., Smith, C. E. G. and McMahon, D. (1966) *Brit. med. J.*, **1**, 258.
Webb, H. E. and Smith, C. E. G. (1966) *Brit. med. J.*, **2**, 1179.
Webb, H. E., Wight, D. G. D., Platt, G. S. and Smith, C. E. G. (1968) *J. Hyg., Camb.*, **66**, 343.
Weissenbacher, M. C., Schmunis, G. A. and Parodi, A. S. (1969) *Arch. Virus.*, **36**, 63.
Wenner, H. A., Bolano, C., Cho, C. T. and Kamitsuka, P. S. (1969) *J. inf. Dis.*, **120**, 318.
Westwood, J. C. N., Zwartouw, H. T., Appleyard, G. and Titmuss, D. H. J. (1965) *J. gen. Microbiol.*, **38**, 47.
Wheelock, E. F. and Edelman, R. (1969) *J. Immunol.*, **103**, 429.
Wiktor, T. J., Kuwert, E. and Koprowski, H. (1968) *J. Immunol.*, **101**, 1271.
Williams, T. W. and Granger, G. A. (1969) *J. Immunol.*, **103**, 170.
Zlotnik, I. (1962) *Acta Neuropath.*, Suppl. I, 61.
Zlotnik, I. and Rennie, J. C. (1965) *J. comp. Path.*, **75**, 147.
Zlotnik, I., Smith, C. E. G., Grant, D. P. and Peacock, S. (1970) *Brit. J. exp. Path.*, (in press).
Zwartouw, H. T., Westwood, J. C. N. and Harris, W. J. (1965) *J. gen. Microbiol.*, **38**, 39.