FOR DEBATE

Factors in the Host–Virus Relationship which May Affect the Course of an Infection

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Introduction

Many differing clinical pictures may be caused by the same virus when introduced into humans or animals. It is generally accepted that in an epidemic of poliomyelitis one may see patients who have (1) no illness but develop immunity, (2) a mild febrile illness, (3) an aseptic meningitis, (4) lower motor neurone paralysis, or (5) encephalitis. One may also see patients with advanced complete paralysis who subsequently recover completely. These differing presentations are accepted as clinical facts, but little has been done to explain why one of these particular situations should apply to one individual and not to another. Recently, the role of viruses in disease processes has become even more intriguing by the finding of what appear to be viruses associated with more chronic long-term illnesses, such as subacute sclerosing panencephalitis (Bouteille *et al.*, 1965 ; Connolly *et al.*, 1967) and progressive multifocal leucoencephalopathy (Howatson *et al.*, 1965). There are many factors that will affect the course of a viral illness.

State of Immunity before Infection

Example in Animals

Gocke *et al.* (1967) showed how important the state of immunity is at the time of infection. They demonstrated that when canine hepatitis virus was inoculated into non-immune dogs it caused an acute fulminating hepatitis, death occurring between the fourth and ninth days. Animals which were fully immune to the disease did not fall ill. Some of the dogs inoculated turned out to have a low level of antibody in their blood at the time of inoculation. A few of them developed an illness which ran a subacute course and died between the eighth and twenty-first days ; the others developed a chronic hepatitis with little or no signs of illness. In the non-immune group the liver histology was one of acute necrosis with intranuclear inclusions in many cells. The virus could be labelled by fluorescent antibody techniques and virus itself was isolated. In the subacute and chronic forms the histology in the early stages was similar, with positive fluorescent antibody results, but virus could not be isolated. By the twenty-seventh day those dogs which developed the chronic disease showed histological changes in the liver consisting of dense accumulations of lymphoid and plasma cells. Biopsies at later dates showed progression from this state to extensive hepatic fibrosis. In these animals and the subacute group virus was not detectable by fluorescent antibody studies after the seventh to tenth day. Gocke *et al.* were able to reproduce these results exactly by infecting dogs which they had passively immunized.

Examples in Man

In human disease there are many examples in which it seems that partial immunity at the time of infection alters the course of the illness. Several authors have shown that the administration of dead measles vaccine to children may be followed by an atypical clinical response, when these children later experience either naturally occurring measles or the live measles vaccine (Fulginiti *et al.*, 1966, 1967 ; Buser, 1967 ; McNair Scott and Bonanno, 1967). Alteration in the rash, pain in the muscles, head, and abdomen, peripheral oedema, pneumonia, and occasionally pleural effusions were noted. Some children had signs suggestive of central nervous system involvement, and Schneck (1968) suggested that there might be an increased incidence of subacute sclerosing panencephalitis months or even years after vaccination with live measles virus.

Dixon (1962) drew attention to a "pulmonary allergy" which tends to affect persons vaccinated against smallpox who then come in contact with cases of that disease. It seems possible also that babies may be sensitized by respiratory syncytial virus vaccine of low potency, and as a result may have a more severe respiratory infection when they come in contact with the virus proper (Parrott *et al.*, 1967). It is also of interest that respiratory syncytial virus causes a severe disease in babies in the first and second months of life. It is a more common cause of infection at this time than later in the first year and is also more severe. Most of these babies may have an acquired low level of immunity passed on from the mother. The relation of age to illness is consistent with the hypothesis that passively acquired maternal neutralizing antibody may play an essential part in the pathogenesis of respiratory syncytial virus bronchiolitis (Chanock *et al.*, 1967). The very odd haemorrhagic disease associated with some dengue infections in the Far East may result from an infection in an already partially immune person (Halstead, 1966). All these examples strongly emphasize the importance of "hypersensitivity" reactions in virus diseases.

Infections in Utero

Example in Animals

Richards and Cordy (1967) showed that young foetal sheep get cerebral anomalies, but that older animals respond with a meningoencephalitis when infected with blue-tongue virus. The time during which the response of the central nervous system changes from one type to the other is probably between the seventieth and ninetieth day of gestation. It is at this stage that the foetal lamb is developing immunological responsiveness. Those workers also showed that with this virus the pathological lesions resulting from infection in the central nervous system of mice varied with the age of the host. They felt that this change was influenced by the stage of immunological maturity of the infected animals.

Example in Man

The earliest time an infection can take place in human beings is in utero. The congenital malformations caused by the rubella virus are well known. It is of particular interest that often these infected babies can continue to excrete virus for many months after birth in spite of being immunologically competent. We know little about the mechanism of these things or how many other viruses may behave in a similar way. Nor do we

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know as yet whether these in-utero infections can produce disease at an older age.

Causes of Variable Response in Non-immune Subjects

Interferon Production

There are then the changes which may occur after infection with a virus in a completely non-immune person. We do not know yet how important the quantity and rate of production of interferon may be in determining the course of the disease. It is quite clear that interferon has a protective effect against many virus infections. However, interferon production is itself suppressed by cortisone (Kilbourne *et al.*, 1961) and also by stress (Chang and Rasmussen, 1965). This implies that overactivity of the adrenals at the time of a viraemia may adversely affect the protector mechanisms of the host. Certainly production of interferon by one virus infection may protect considerably against a secondary virus invader (Baron *et al.*, 1966). Dual virus infections are being reported more frequently in the literature and are probably much more common than is clinically apparent. I have personally seen two cases of encephalitis—one occurring 12 days after primary smallpox vaccination and one when the scabs of chicken-pox were coming off—both of which showed a fourfold rise or more in antibodies to the Japanese encephalitis virus. How does one tell which virus caused the encephalitis or whether it was the combination of both ? Do they modify each other's clinical course or do they exacerbate it ? Little has been done as yet to elucidate these problems, and far too often it is taken for granted that only one virus is present at one time.

Antibody Production

Another mechanism of the host's defence in primary virus infections is the production of antibody. But this may carry its own dangers. Central nervous system damage in acute virus diseases occurs at the end of viraemia when antibodies are forming. It seems possible that the production of antibody may produce a hypersensitivity type reaction which adds to the damage caused by virus replication. Webb and Smith (1966) discussed this possibility and also the way in which virus infections may be responsible for some of the more chronic neurological disorders. Webb *et al.* (1968b) showed that antibody administered at a critical time in an encephalitic arbovirus infection in mice may increase the incidence of clinical neurological disorders, and Webb *et al.* (1968c) demonstrated that suppression of the immune response by irradiation may ameliorate it.

Connolly (1968) suggested that measles antibody may be produced in the central nervous system. Antibody to louping-ill virus appears to be developed in the central nervous system also (Webb *et al.*, 1968a). It is likely that this is the case with many virus infections which get into central nervous system tissue. However, antibody also probably leaks across the blood–brain barrier in the presence of inflammation of the meninges. If the antibody–antigen virus ratio is of importance in the causation of cellular destruction, then these two factors may be of vital importance when considering the problem of brain damage by viruses, particularly those with the capacity for latency.

Latency of Viruses

More and more viruses are being found to be capable of survival in their host for long periods of time, particularly in central nervous system tissue. Price (1966) demonstrated the long-term survival of Kyasanur Forest disease virus, one of the group B tick-borne arboviruses, in rodent brains. Webb *et al.* (1966) recovered Langat virus, another virus of the same group, from a human brain in the presence of considerable blood immunity. It is quite clear also from our own experiments that animals can survive with Langat virus in their brains for at least 36 days without any evidence of illness.

Reeves *et al.* (1958) showed that western equine encephalitis virus can be recovered from birds up to 10 months after the original infection. Reeves (1961) reviewed the problem of overwintering of arboviruses and referred to viruses being recovered from other animals and insects, including bats, snakes, and ticks, months after infection had taken place. That this can occur in animals which are immunologically competent and develop antibodies increases the importance of the finding. LaMotte (1960) studied the distribution of Japanese encephalitis virus in the organs of the mosquito vectors *Culex quinquefasciatus* and *Culex pipiens*. He commented specifically on the high concentration found in central nervous system tissue, there being 100 to 1,000 times more virus here than in larger organs. The multiplication of virus in this site does not cause cell damage, and the mosquitoes live as long as uninfected mosquitoes. So far as is known mosquitoes do not develop antibodies against virus infections. Perhaps if they did they would not survive so long.

Central nervous system cells in vertebrates have relatively great longevity, and provided the virus can multiply without destroying them a reasonably harmless state of affairs will exist. This does not take into account the virus acting as an antigen and promoting an antigen–antibody reaction, nor does it take into account the possibility that the virus itself may have changed the antigenic structure of the cell which it has invaded, thereby causing the body to reject the whole cell, resulting in an autoimmune type phenomenon. Let us consider some factors which are known to upset the status quo of latent virus infections. Latent herpes can be exacerbated by fever, emotional stress, mechanical irritation, heat, and exposure to ultraviolet light. Good and Campbell (1945) showed that latent herpes simplex encephalitis in rabbits can be precipitated by anaphylactic shock. Schmidt and Rasmussen (1960) showed also in rabbits that injections of adrenaline activated latent herpes simplex virus encephalitis.

A new virus infection which causes meningeal irritation may allow more antibody from the blood, formed from a previous virus infection, to leak across the blood–brain barrier because of the meningeal inflammation. This antibody could upset the status quo in the central nervous system if by any chance the former virus is latent there. Could this be one of the mechanisms involved in the exacerbation of disseminated sclerosis associated with intercurrent infections ? Zlotnik (1968) described how repeated infections with the same arbovirus may cause subacute and chronic disease of the central nervous system in experimental animals in which it does not cause acute disease. He described the proliferation and hypertrophy of the astrocyte as the earliest changes seen, even in a primary arbovirus infection of the central nervous system.

These changes occur before the perivascular lesions are seen. Further peripheral inoculations of the same virus produce a dense cerebral astrocytosis. This leads on to the problem of how viruses may affect cells themselves.

Alteration or " Transformation " of Cells

Viruses can in one instance produce infections in man and in animals produce or help to produce tumours. The adenoviruses type 7 (Hilleman *et al.*, 1958 ; Larson *et al.*, 1965) and type 31 (Pereira *et al.*, 1965) and the West Nile virus (Tanaka and Southam, 1962) are good examples. There are many others. There must be many combinations and permutations between the two extremes of simple infection and tumour formation which must depend on the host–virus relationship. It is possible that many viruses given the right conditions may produce

an abnormal overgrowth of certain cells. Maedi and visna viruses stimulate proliferation of the mesenchymal tissues of the lung (Abinanti, 1967). It may be that a part of a virus has the capacity to do this and that this part is more active in one virus than in others. This would mean that if a disease like disseminated sclerosis had a viral aetiology the excessive activity of the glial elements might be accounted for by an induced change in the glial cells by viral action. It is a negative approach to say that because so many different insults to the brain produce overreaction of the glial elements the effect of viruses on glial tissue is not of interest. Recurrent irritation to a layer of cells may produce a neoplasm. Irritation plus a virus can produce malignant reactions more quickly (Tanaka and Southam, 1965). If we can answer the question of why this happens some problems may be solved.

Conclusion

The state of the host's immunity at the time of infection with a virus will dictate the type of disease the host suffers. There will be a widely differing clinical picture ranging from those non-immune at the time of infection to those fully immune. Partial immunity can be created by minimal doses of the same virus, dead or alive, by a large dose of a different virus antigenically related, or by passive immunization with immune serum. "Hypersensitivity" type reactions to virus particles may play an important part in determining some clinical syndromes associated with virus infections. The quantity and rate at which the completely non-immune host produces interferon and antibodies after infection will determine the type of disease experienced. Primary viral destruction of cells and hypersensitivity reactions will also determine the histopathological changes produced. The less immunologically mature the animal the more emphasis there will be on primary destruction of cells by virus, whereas in the presence of immunological maturity the most destruction may result from an antigen–antibody reaction. The site of the destruction in both cases will depend on the location of the antigen.

Coombs (1968) suggested that many infecting micro-organisms would show very little pathogenicity on their own account or in an animal where allergic responses were completely suppressed; the pathogenicity, in fact, is due to the antigenicity of the organisms and their products and consequent tissue-damaging allergic reactions wherever the surviving organisms or their products happen to be. Different viruses prefer different types of cells to multiply in. This may well account for the difference in the histological picture in encephalitis following diseases like measles or smallpox vaccination as compared to infections with arboviruses.

More and more viruses are being shown to have the capacity of latency. How these latent viruses may react throughout life to subsequent infections with similar viruses and different viruses and to all the continually changing factors which protect the body against infection is not clear yet. All these things and the capacity for viruses themselves to behave so differently under differing circumstances presents a fascinating problem. The understanding of the mechanism of the different disease syndromes which can be produced by the same virus in the same host will be effected only by very careful comparative clinical, pathological, and virological studies.

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