

## Para-infectious and post-vaccinal encephalomyelitis

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### Summary

The incidence of encephalomyelitis in association with acute specific fevers and prophylactic inoculations is discussed. Available statistics are inaccurate, but these conditions are of considerable importance—it is likely that there are about 400 cases of measles encephalitis in England and Wales in an epidemic year.

The pathology of these neurological complications is discussed and emphasis placed on the distinction between typical perivenous demyelinating encephalitis, and the toxic type of encephalopathy which occurs mainly in young children.

The clinical syndromes occurring in association with measles, chickenpox and German measles are considered. Although encephalitis is the most frequent complication, myelitis and polyradiculitis also occur. There is evidence that 'uncomplicated measles' is associated with brain involvement in the prodromal phase. Similar para-infectious disorders occur in association with other infections including smallpox and influenza.

The post-vaccinal types of encephalomyelitis are also considered with particular reference to post-vaccinal encephalitis and rabies post-vaccinal encephalitis.

The pathogenesis of these disorders is discussed and it is concluded that there is direct viral invasion of the nervous system, followed by an antigen-antibody reaction. At times virus may remain latent within the nerve cell without destroying it.

### Introduction

Although the majority of cases of encephalitis and other neurological disorders which occur in association with acute viral infections such as measles, develop some days after the onset of the exanthem, in a few patients the neurological disorder is either simultaneous with or precedes the development of the rash. It is, thus, more logical to describe these conditions as para-infectious rather than post-infectious. Similarly, although the encephalitis following vaccination against smallpox (*post-vaccinal* encephalitis) is the typical example of encephalitis as a sequel to prophylactic inoculations, the term *post-vaccinal* should be used for the range

of neurological disorders following vaccinations of all kinds (de Vries, 1960).

The incidence of para-infectious and post-vaccinal encephalomyelitis in Great Britain is difficult to estimate. It is certain that many cases are not notified to the Registrar General, whose published figures must be an underestimate. In addition there is a lack of precise diagnostic criteria and this aspect will be considered later. In the years 1964–66 the mean number of deaths registered annually in England and Wales as due to acute infectious encephalitis was ninety-seven (Registrar General, 1967). During the same period the mean annual number of deaths registered as due to the late effects of acute infectious encephalitis was seventy-four—this presumably includes patients with post-encephalitic Parkinsonism. During this 3-year period there were five deaths from post-vaccinal encephalitis, while the mean number of deaths registered annually as due to 'encephalitis, myelitis and encephalomyelitis, excluding acute infectious encephalitis' was 110.

To put these figures into perspective, in 1966 612 deaths were registered as due to motor neurone disease, 836 to disseminated sclerosis, 7363 to motor vehicle traffic accidents and 18,554 to primary carcinoma of the lung.

During 1966 the number of deaths from encephalitis certified as secondary to infectious diseases was fifteen for measles encephalitis (out of a total of eighty deaths attributed to measles) and two for chickenpox encephalitis (from a total of seventeen deaths due to chickenpox).

Notifications of infectious diseases in 1966 included 343,642 cases of measles, eighty-three cases of acute infectious encephalitis and 114 cases of post-infectious encephalitis. Miller (1964) estimated the incidence of measles encephalitis as 1 per 1000 and this agrees with other figures (Miller, Stanton & Gibbons, 1956). On this basis one would have expected over 340 cases of measles encephalitis in 1966, and of course not all cases of measles are notified. The figure of 114 cases of post-infectious encephalitis of all kinds in 1966 is certainly much below the true incidence.

The death rate in measles encephalitis has varied but has often been estimated at about 20% (McNair

Scott, 1967). If, making allowance for non-notification, there were up to 400 cases of measles encephalitis in 1966, deaths from this disorder should have been about eighty. This contrasts with the fifteen patients actually registered as having died from measles encephalitis.

However inaccurate the statistics may be, it is clear that post-infectious encephalitis and encephalomyelitis is a significant problem in the United Kingdom, as it is in the United States, where about 30% of the total cases of encephalitis are in the post-infectious group (McNair Scott, 1967).

### Pathology

For many years a distinction has been drawn between primary polioclastic encephalitis, involving predominantly neurones of the grey matter, and due to direct invasion by virus (e.g. rabies and arbovirus), and secondary myelinoclastic leuco-encephalitis. Here the myelin sheaths of the white matter are the main site of damage with axis cylinders less affected, and neurones largely spared (Miller, 1961). The second group is often, but not always, a sequel to a viral infection.

The early work of Turnbull & McIntosh (1926) showed that in post-vaccinal encephalitis the usual underlying process is one of perivenous demyelination, mainly in relation to small veins in the white matter. Similar changes were found in encephalitis associated with measles, chickenpox and rubella (Miller *et al.*, 1956).

Further studies led de Vries (1960) to consider that the classical change in post-vaccinal encephalitis is one of perivenous demyelination, with an associated microglial reaction—'microglia encephalitis'. In this type of encephalitis, which commonly occurs 5–15 days after vaccination, the illness runs an acute course, and if recovery occurs there are often few sequelae, though permanent neurological deficit is more common when the disorder is primarily a myelitis. Similar changes are found in the para-infectious group of neurological disorders, and also in sporadically occurring acute disseminated encephalomyelitis.

In some patients acute haemorrhagic leuco-encephalitis occurs and Russell (1955) argued that this, and acute disseminated encephalomyelitis, are variants of a single pathological process. She referred to the literature on experimental allergic encephalitis and discussed the possibility that the naturally occurring acute disseminated encephalomyelitis and acute haemorrhagic leuco-encephalitis are due to a process based on an allergic response to an antigenic stimulus.

de Vries (1960) emphasized that some children with post-vaccinal encephalitis do not show the typical demyelinating changes, but instead an encephalo-

pathy of toxic type characterized by cerebral oedema, vacuolization of neurones and neuronal degeneration, especially in the cortex. This syndrome occurs mainly in children under 2 years, but may occur in older children. Acute encephalopathy is also found in fatal cases of para-infectious neurological illness in young children. Lyon, Dodge & Adams (1961) described similar cases in infants and children, without obvious precipitating cause, though in most cases there was a febrile illness of variable and unidentified type. The lesions in post-vaccinal and para-infectious encephalopathy resemble those following status epilepticus, anoxic episodes or severe hypoglycaemia.

### Clinical aspects

There are many reviews of the neurological syndromes occurring after vaccination and in association with acute viral infections. Miller *et al.* (1956) made a detailed study of the literature at that time, and discussed their own experience, while the review of McNair Scott (1967) included more recent work.

Miller *et al.* (1956) emphasized that although the majority of patients under consideration had encephalitis, in some the spinal cord was the main site of the disease. Polyradiculitis was less common than these forms of central nervous system involvement.

In the para-infectious groups of disorders, the distribution of the various syndromes was as follows (Table 1):

TABLE 1. Distribution of the various syndromes

	Measles	Chickenpox	German measles
Encephalitis (%)	96	90	92
Myelitis (%)	3	3	4
Polyradiculitis (%)	1	7	4

The average latent period between the acute infection and the neurological illness was shortest for rubella and longest for varicella, while measles held an intermediate position. With each infectious disease the latent period was shortest for cases of encephalitis and longest for those of polyradiculitis (Table 2).

TABLE 2. Latent period (days)

	Measles	Chickenpox	German measles
Encephalitis	4.7	6.3	3.8
Myelitis	5.5	8.3	6.7
Polyradiculitis	9.0	11.3	8.7

There was a wide range of latent periods, and mention has already been made of the occasional patient in whom the encephalitis precedes, or occurs

at the same time as the exanthem. These pre-exanthematous cases were excluded from their calculations of average latent periods, and the numbers of cases of myelitis and polyradiculitis are small, especially after chickenpox and German measles.

#### *Para-infectious encephalomyelitis*

*Measles.* The most common type of para-infectious encephalomyelitis is that associated with measles. The earliest account is that of Lucas (1790) who described a young woman in whom myelitis developed 6 days after the measles rash, and who 9 years previously had had a similar illness after smallpox, although no details are given of the earlier neurological episode.

The incidence of measles encephalitis varies in different epidemics and is also affected by the process of selection of clinical cases. However, Miller *et al.* (1956) gave an estimate of 1 per 1000. Most cases show a typical picture of perivenous demyelinating 'microglia encephalitis'. Perivenous demyelinating encephalitis does not occur in children under 2 years who may develop a toxic encephalopathy, usually of grave prognosis. It is important to note that not all neurological symptoms occurring in association with measles are due to measles encephalitis. Some children may have febrile convulsions without any other manifestations of encephalitis. Boughton (1964) pointed to the importance of distinguishing febrile convulsions from true measles encephalitis, and commented that a persisting postictal stupor, especially if accompanied by meningism, was indicative of encephalitis. Tyler (1957) felt that cases of sudden hemiplegia in association with epilepsy complicating measles were due to a local vascular occlusion and not encephalomyelitis. However, only a minority of patients with permanent hemiplegia after encephalopathy show evidence of old infarction. Most cases show cerebral hemiatrophy of the Schob type due to predominantly unilateral cortical neuronal damage (Norman, 1963).

In assessing the incidence of measles encephalitis, it is important to realize that milder cases are probably not recognized, and Boughton (1964) thought that such cases might have exclusively psychological symptoms which might be confused with the usual miserable state of a child with measles. This distinction, however, becomes almost theoretical when considering the findings of investigation of cases of 'uncomplicated measles'. Gibbs *et al.* (1959) in investigating EEG changes found 51% of patients with uncomplicated measles had EEG abnormalities, while 100% of patients with measles encephalitis had abnormal EEGs. Similar findings of EEG abnormalities were made in mumps, chickenpox, scarlet fever and German measles.

Pampiglione (1964) studied EEGs during the incubation of and during measles, and found a moderate to severe excess of slow activity developing 1-4 days before the rash, unrelated to the height of the fever and often declining as the rash developed. This would suggest that the brain is 'normally' involved during the prodromal phase.

A precise definition of measles encephalitis is, therefore, impossible. From a practical standpoint such a diagnosis will require the development of significant neurological and/or psychiatric abnormalities, but excluding simple febrile convulsions. EEG records will support the diagnosis, but cerebrospinal fluid results are unhelpful. Although abnormalities in the fluid, mainly pleocytosis, have been found in 'uncomplicated measles' (Ojala, 1947), other workers have found normal fluids frequently in definite encephalitis, and invariably in those who are considered not to have had brain involvement (McKendrick, personal communication 1969).

The latent period between the rash and encephalitis varies from -2 to +13 days but is usually 4-5 days with 93% developing between 2 and 7 days (Boughton, 1964). Miller *et al.* (1956) had similar findings. Holliday (1950) reviewed the pre-eruptive neurological complications of measles and other exanthemata and concluded that pre-eruptive encephalitis and encephalomyelitis must be considered in the differential diagnosis of children's diseases characterized by acute neurological symptoms of unknown aetiology.

The clinical picture is very varied. Some patients have a sudden onset with convulsions, while in others the onset is slower with the development of headache, photophobia, anorexia and vomiting just as the initial symptoms of measles are improving. Retention of urine is a common presenting symptom of measles encephalitis. The physical signs vary greatly depending on the areas of central nervous system affected.

Neurological sequelae are found in 23% (Boughton, 1964) or more. Intellectual and behaviour disorders are common after encephalitis, and about 50% of patients with transverse myelitis are left with residual signs.

The fatality rate in different series varies greatly and la Bocetta & Tornay (1964) emphasized that the mortality rate has declined of recent years (32% before 1947 and 11.5% after this date). Other figures for mortality rates are 20% (Miller *et al.*, 1956) and 8.8% (Boughton, 1964). In assessing prognosis, continued convulsions, deep coma, hyperpyrexia and tonic spasms in the arms are grave signs.

Treatment includes control of convulsions and of hyperpyrexia, and other methods of intensive care including intermittent positive pressure respiration. There is no doubt that the recent decline in mortality is due largely to such intensive care.  $\gamma$ -Globulin has

not proved effective (Greenberg *et al.*, 1955). The use of ACTH and steroids was recommended by Miller, Stanton & Gibbons (1957) but considered to be without demonstrable benefit by Ziegra (1961) and Karelitz & Eisenberg (1961). Bøe, Solberg & Saeter (1965) found that both the mortality and the incidence of sequelae were higher in post-infectious meningo-encephalitis which had been treated with corticosteroids. The difficulties in obtaining enough cases for an adequately controlled trial in a relatively rare disorder are self-evident.

There is no relation between the severity of the measles and the incidence of encephalitis. Encephalitis has occurred rarely after modification of measles by  $\gamma$ -globulin (Riley, 1958; Bauer & Howard, 1964) and extremely rarely after measles vaccination (Schneck, 1968).

*Chickenpox.* Neurological disorders associated with varicella are less common than with measles. Miller *et al.* (1956) found the frequency difficult to assess but were able to review only 134 cases from the literature in contrast with 911 cases associated with measles. As with measles, encephalitis accounted for the majority (90%) of the cases. Boughton (1966) reviewed 1517 patients admitted to hospital with chickenpox of whom thirty-nine had neurological complications—thirty-eight acute meningo-encephalomyelitis and one polyneuritis. The mortality rate was 10% in the cases reviewed by Miller *et al.* (1956) and 18% in the smaller series of Boughton (1966).

The time from the rash to onset of encephalitis was usually 3–7 days, but as with measles the encephalitis may occur with the rash or even up to 3 days before its onset (Rotens, 1961).

The clinical features are in general very like those of measles encephalitis, but cerebellar signs are much more common with chickenpox encephalitis (34%) than with measles encephalitis (10%), while in contrast hemiplegia, coma and convulsions, and abnormal plantar responses are all less common in chickenpox than in measles encephalitis. In non-fatal cases sequelae are less frequent after chickenpox encephalitis.

Myelopathy may be a complication of chickenpox and the prognosis for functional recovery seems to be better than with cord lesions due to measles (White, 1962). Polyneuropathy may also occur (Miller *et al.*, 1956; Welch, 1962).

The pathological changes are usually said to be similar to the perivenous demyelination of measles encephalitis, but not all cases fall into this pattern. Blair, Jamieson & Smith (1965) reported a case with changes of 'viral encephalitis' without demyelination, but with gross fatty changes in the liver. Heppleston, Pearce & Yates (1959) described a fatal case in a girl of 4 years in which there was little

demyelination but there were lesions mainly in the grey matter of the cerebral cortex and basal ganglia. They concluded that the essential abnormality was damage to blood vessels possibly on an allergic basis.

Severe fatal generalized varicella presents another problem. If chickenpox encephalitis were due to direct invasion of the central nervous system the brains of fatal disseminated cases should show ample evidence of this. However, only a few reported cases show cerebral involvement (Cheatham *et al.*, 1956; Rotter & Collins, 1961). One of the former authors' cases showed inclusion bodies in posterior root ganglia but not in the cord or brain. Chickenpox encephalitis may follow relatively mild varicella.

Abruzzi (1961) described a case dying within 36 hr. He found large areas of focal demyelination and small focal areas of subarachnoid haemorrhage and agreed with Heppleston *et al.* (1959) that the cerebral blood vessels might be sensitized to a circulating antibody related to the exanthematous disease.

Evidence of benefit from steroid therapy is conflicting and Boughton (1966) refers to the risk of precipitating severe haemorrhagic varicella by the use of steroids.

*Rubella.* This may affect the central nervous system in two ways; (i) the congenital rubella syndrome, and (ii) para-infectious encephalomyelitis.

The congenital rubella syndrome is a manifestation of a persistent infection and virus can be isolated from the brain and other organs. The condition is reviewed by Horstman (1967). Desmond *et al.* (1967) concluded that encephalitis or encephalomyelitis might be a major manifestation of the congenital rubella syndrome, even in the absence of ocular or cardiac lesions. Rorke & Spiro (1967) reviewed the cerebral lesions in the congenital rubella syndrome and found extensive degenerative change in vessels (arteries and veins) and vascular damage with foci of necrosis in both grey and white matter. In infants surviving for several months there was evidence of retardation of myelination in the neuraxis.

Acute encephalomyelitis complicating acquired rubella was considered by Miller *et al.* (1956) to be much less common even than varicella encephalomyelitis. Margolis, Wilson & Top (1943) had estimated the incidence at 1 per 6000 and Sherman, Michaels & Kenny (1965) at 1 per 5000. From a limited number of cases in the literature both groups of authors concluded the mortality to be about 20%.

Cantwell (1957) considered sequelae to be rare, and Kenny, Michaels & Davis (1965) commented that this was probably because demyelination was not so constant a finding as in measles encephalitis. Pathologically there are fewer cases with typical perivenous demyelination and more with non-

specific changes with perivascular infiltration with mononuclear cells, although Cijarelli & Freireich (1966) described a fatal case with perivascular demyelination. Miller *et al.* (1956) speculated that as many fatal cases died within 72 hr of the onset of encephalitis, they might have developed typical demyelination had they survived longer. However, de Vries (1960) found typical demyelination in patients with post-vaccinal encephalitis who died within 24–48 hr, and there is no evidence that there is any progress from acute encephalopathy to microglia encephalitis.

*Encephalitis after other infections.* Apart from the three infectious exanthemata already discussed, encephalitis follows other infections but more rarely. It occasionally follows *smallpox* (Freind, 1730); and Marsden & Hurst (1932) emphasized that it is more often after a mild clinical attack than a severe one. It is well recognized that *mumps* may be associated with a mild lymphocytic meningeal reaction in as many as 51% of cases (Bang & Bang, 1943). Less often encephalitis occurs and Donohue, Playfair & Whitaker (1955) reported two fatal cases with perivenous demyelination. Scheid (1961) emphasized that neurological symptoms are as much a manifestation of mumps as are orchitis and pancreatitis. He felt that most cases of meningo-encephalitis were due to direct invasion by the virus, which may sometimes be recovered from the cerebrospinal fluid.

The neurological complications of *glandular fever* were reviewed by Gautier-Smith (1965). He considered that they might be due either to direct virus invasion or to an allergic encephalomyelitis similar to that with the specific fevers. Lymphocytic meningitis was most common, followed by encephalomyelitis, polyneuritis and mononeuritis.

*Influenza* may be associated with encephalomyelitis and there were several reports of cases of this type in the 1957 epidemic of Asian influenza. Flewett & Hoult (1958) and Hoult & Flewett (1960) concluded that there were two main types of disorder—an acute encephalopathic variety occurring early in an attack of influenza with minimal histological lesions, and a perivascular demyelinating leuco-encephalitis as with the specific exanthemata.

#### *Post-vaccinal encephalomyelitis*

*Smallpox vaccination.* Post-vaccinal encephalomyelitis is the classical form of post-vaccination neurological reaction, and reference has already been made to the early studies of Turnbull & McIntosh (1926), who described the typical perivenous demyelination. Spillane & Wells (1964) discussed the neurology of Jennerian vaccination in the light of their experience in the smallpox epidemic in South

Wales in 1962. They emphasized the view of de Vries that distinction must be made between post-vaccinal encephalomyelitis and encephalopathy. Encephalomyelitis, which is unknown in children under 2 years, occurs after an incubation period of 8–15 days, has an acute onset, and if the patient recovers there are usually few sequelae. If death occurs, typical perivenous demyelination is found. In children under 2 years, and occasionally in older children, there may be a more explosive onset of a post-vaccinal encephalopathy, frequently fatal and characterized by cerebral oedema.

The incidence of these sequelae of vaccination against smallpox varies greatly in different countries with figures per 100,000 vaccinations ranging from one to fourteen or more. Conybeare (1964) reviewed the neurological illnesses associated with smallpox vaccination in the decade 1951–60, and reported to the Ministry of Health. Among a total of just over  $5 \times 10^6$  vaccinations the incidence was 1.3 per 100,000. There was a greater incidence after primary than after re-vaccination, while a long interval between primary and re-vaccination increased the incidence. The highest incidence was for primary vaccination in children of school age (3 per 100,000).

Death rates of about 30% have been recorded, but in some series no distinction has been drawn between encephalopathy and encephalomyelitis (Miller, 1953). Conybeare (1964) found an overall mortality rate of 34% (or 4.3 per  $10^6$  vaccinations). In young children under 2 years the prognosis in acute encephalopathy is grave, but Hoefnagel (1962) reported a group of such patients presumed to have had acute transient post-vaccinal encephalopathy. In three cases of encephalopathy in older children reported by Spillane & Wells (1964) there were no fatalities. They emphasized that prognosis in typical post-vaccinal encephalomyelitis may be better than is usually accepted—only one of their eleven patients died. They found marked improvement after use of ACTH and steroids but were unable to draw any firm statistical conclusions as to the effectiveness of such treatment. Persisting sequelae were especially likely to result from cord lesions.

*Encephalomyelitis after rabies vaccination.* Neurological complications after rabies vaccination include meningeal reactions, and mononeuritis and polyneuritis as well as encephalomyelitis. The situation differs from that of post-vaccinal reactions in that, until recently, rabies vaccination involved the use of vaccines containing neural tissue so that there were some resemblances to the circumstances of production of experimental allergic encephalomyelitis. In recent years vaccines prepared from duck embryos have been used, but although the incidence of neurological complications is lower with vaccines free

from neural material, they do occur (Prussin & Katabi, 1964). The incidence with non-neural vaccines is of the order of 1 per 50,000 compared with 1 per 7000 or even higher with neural vaccine. The modern management of rabies immunization in the United States is reviewed by Habel (1967). The death-rate in post-rabies-vaccination encephalomyelitis is about 25%, and sequelae occur in about one-third of cases, being more severe in patients who have dorsolumbar myelitis. ACTH and steroids have apparently been of value in isolated cases.

*Other vaccinations.* Encephalopathy may occasionally occur after pertussis vaccination (Berg, 1958), and after influenzal immunization (Woods & Ellison, 1964).

### Pathogenesis

The mechanism of production of para-infectious and post-vaccinal encephalomyelitis is not yet established. Three main theories have been considered:

- (a) That the condition is due to direct viral invasion of the nervous system,
- (b) That there is activation of some other virus previously present but quiescent within the patient, and
- (c) That the disorders are due to some form of allergic reaction occurring within the nervous system.

There are many facts which have been taken as evidence against the first theory. The pathological changes of perivenous demyelination are quite unlike those of an acute viral encephalitis. Usually there is a latent interval of 5–15 days between the development of the acute specific fever and the associated encephalitis. Also there has been very little evidence of virus material in the nervous system in cases of parainfectious encephalitis. For many years the report of Shaffer, Rake & Hodes (1942) stood alone—they reported the recovery of measles virus from the brain of a fatal case of encephalitis, the patient dying 9 days after developing the measles rash. Many other workers studied fatal cases of para-infectious and post-vaccinal encephalitis without succeeding in isolating virus or finding evidence of inclusion bodies.

The similarities between the various syndromes under consideration were taken by some as evidence of a latent virus activated by the vaccination or by the specific fever. In considering measles encephalitis, Greenfield (1929) concluded that 'it is therefore probable that these diseases are caused by an unknown virus which spreads in epidemic waves, but produces no disease unless stimulated to activity by the exanthem'. However, no evidence of such a virus of wide distribution has ever been found.

Following the extensive work on experimental allergic encephalitis, support grew for the concept that the para-infectious and post-vaccinal syndromes were due to an allergic response. The usual latent period between the specific infection and the encephalitis were regarded as support for this view, as were the histological similarities. However, it must be remembered that in some patients, the neurological illness occurs at the same time as, or even antedates the rash of the acute specific fever.

Acute disseminated encephalomyelitis occurring naturally, but without known precipitating cause except possibly some banal upper respiratory infection, has been accepted as forming a link between the para-infectious and post-vaccinal cases and experimental allergic encephalitis. Although relapse is rare in para-infectious and post-vaccinal encephalitis, in some cases of acute disseminated encephalomyelitis such relapses do occur. Campbell (1961) described a boy who recovered from measles encephalitis, and 18 months later became blind following a coryzal illness. Both episodes were treated with steroids with good results. It is of interest that the original case of Lucas (1790) showed neurological complications after both smallpox and measles. Alcock & Hoffman (1962) discussed children with recurrent encephalomyelitis—they commented that in adults it is difficult to distinguish relapsing encephalomyelitis from chronic disseminated sclerosis. Miller (1954) described cases of familial recurrent encephalomyelitis in three members of a family, and in some episodes the use of ACTH was followed by rapid improvement. Selling & Meilman (1955) and Ziegler (1966) also discussed the treatment of acute disseminated encephalomyelitis by steroids.

Uchimura & Shiraki (1957) studied cases of rabies post-vaccination syndromes in Japan, and found close similarities with disseminated sclerosis and acute disseminated encephalomyelitis.

Ferraro & Roizin (1957) and Ferraro (1958) considered that there was little appreciable difference between acute disseminated sclerosis, early disseminated sclerosis and acute and subacute post-infectious, post-vaccinal and post-exanthematic encephalomyelitis. They commented that relapses and remissions could not be regarded as diagnostic of disseminated sclerosis. They thought that the toxic aetiological agent (measles, varicella, influenza, vaccinia virus, etc.) combined with a partial antigen to create a complete encephalitogenic antigen which triggers off an allergic reaction.

Waksman (1959) reviewed the problem of experimental allergic encephalomyelitis and the 'autoallergic' diseases. As far as human disease is concerned, he felt that the acute monocyclic para- or post-infectious diseases associated with viral

infections were part of the viral disease and due to a hypersensitivity reaction to the virus. He thought that chronic diseases of remittent character with no known precipitating cause were true autoallergies. A similar histological picture resulted although the responsible antigens differed.

Koprowski (1962) discussed at length the concept of hyperergy in measles encephalitis. He felt that a hypersensitive reaction of the host to multiplying virus or to the products of damage inflicted by the virus on the tissues is a better, although more complicated explanation of the disease syndrome than is an inflammatory reaction of tissues associated with spread of the virus. Damage of brain by the virus would release antigenic material which would pass the blood-brain barrier to reach immunologically active host cells passing through brain capillaries. These sensitized cells might then be removed in organs of the reticulo-endothelial system, where some might divide to form a clone from which cells could attack the brain tissue of the host. Since little is known of the changes in the antigenic make-up of virus-infected cells, he thought that it was impossible to speculate whether antigen, which possibly provoked immunological reaction of the host against itself, was associated with the virus or not. If it were, then sensitized lymphoid cells would attack only virus-infected cells of the central nervous system. Conversely if virus invasion had by brain damage caused only an initial release of antigen by the central nervous system, and from then on the antigen were essentially unrelated to the virus, the number of brain cells destroyed by the sensitized cells of the host would be large. Some as yet unknown mechanism would be necessary to halt the process of production of antibodies against brain tissue.

There are several theoretical ways in which an allergic process might be established. The virus might share antigenic determinants with some component of brain tissue—the brain would then be damaged incidentally by anti-virus antibodies. Alternatively the virus might damage other tissues sharing antigenic determinants with brain, so that specific antibody to the tissue antigen would again damage the brain incidentally.

Other mechanisms would require the presence of virus in the brain. After entering the brain the virus might damage brain cells, releasing brain antigens into the circulation and causing the production of anti-brain antibodies, as suggested by Koprowski. Alternatively the virus might enter the brain and remain latent in cells until an explosive antigen-antibody reaction destroys both virus and host cell.

Webb & Smith (1966) and Webb (1967) considered the two mechanisms whereby viruses might damage the nervous system—direct cellular destruction by multiplying virus, and hypersensitivity due to

reaction between antibodies and virus-protein antigens at varied sites in the nervous system. They postulated that when there is neurological involvement, there is a biphasic illness as typified by paralytic poliomyelitis. In the first phase, sometimes mild and unnoticed, viraemia occurs, while in the second phase recovery of virus is very rare. The disappearance of the viraemia is associated with antibody production, which means that the virus cannot persist in the blood, but passes into the cells where replication may occur if the environment is suitable—that is if the virus has an affinity for that particular cell. They discussed instances of recovery of certain viruses from nervous tissue in the face of established immunity in the blood. The virus might persist for varying times—even indefinitely as with herpes simplex—and any change in cell-membrane permeability would permit an allergic reaction.

Angulo & de Salles Gomes (1964) described a fatal case of post-vaccinal meningo-encephalitis in which vaccinia virus was isolated from the brain, but felt that this did not prove that the encephalitis was caused directly by the virus, but rather that it was an allergic reaction. Adams, Baird & Filloy (1966) reviewed the evidence in favour of direct involvement of the central nervous system by virus in measles encephalitis, including cytoplasmic and nuclear inclusion bodies, and the onset of the neurological illness before the rash. A leading article in the same journal concluded that 'it is now generally agreed that several of the so-called post-infectious encephalitides are due directly to virus invasion of the nervous system'. Adams (1968) discusses this further.

The recent work on measles and subacute sclerosing panencephalitis (Sever & Zeman, 1968) is of especial interest in this connection, but is discussed in detail elsewhere in this symposium (Dayan, 1969).

The reasons why the host only occasionally develops a neurological illness in association with a viral infection are not understood, but are discussed by Webb (1968). They include interferon production, antibody production (which may take place within the nervous system—Connolly, 1968; Webb *et al.*, 1968), the development of latent viruses and transformation of cells. Illavia & Webb (1969) have recently reported on the long-term continued production of two highly encephalitogenic viruses in tissue-cultured mouse and human brain glial tissues, without apparent cytopathic effect.

The tendency for children under 2 years to develop an acute encephalopathy rather than a perivenous demyelinating encephalomyelitis may represent in part at least differences in immunological capabilities of the young child.

Although many problems remain, it seems likely that the para-infectious and post-vaccinal neuro-

logical disorders are due first to viral invasion of the nervous system and then to a subsequent antigen-antibody reaction. What relation there is between these disorders and the chronic demyelinating and other degenerative disorders of the nervous system is a matter for speculation.

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