Postinfectious and postvaccinal encephalomyelitis occur much more frequently than suspected as complications of many viral infections and all kinds of vaccinations. Their pathology and pathogenesis are well known due to the fact that exact experimental models exist. These conditions involve mostly but not exclusively the white matter of the brain and spinal cord but characteristically also often attack cranial nerves, spinal roots and peripheral nerves. Classically they have their onset 1–3 weeks after the infection or the vaccination but in some instances they may start coincidentally with the triggering infection, or as long as 4 or 5 months after a vaccination. They are examples of cell-mediated delayed immunity which, it has been suggested, causes the deposition of immune complexes in the walls of small vessels in the nervous system and a decrease in the impermeability of the blood-brain barrier, allowing serum, lymphocytes and macrophages to enter the nervous system producing oedema and an inflammatory reaction, which may progress, although not necessarily, to demyelination. The attack upon the endothelial cells and/or myelin is an illustration of the phenomenon of molecular mimicry. The immune system is unable to differentiate between antigenic fragments contained in the infecting virus or in the vaccine, and similar amino acid sequences of proteins in some of the vascular membranes and/or myelin basic protein; antibodies are then directed against normal nervous structures. The encephalopathic aspect of the illness is often confused with an acute encephalitis and, because of that, the diagnosis is often overlooked, and prompt initiation of therapy with corticosteroids or corticotrophic hormone is unduly delayed.

The immune responses to many viral infections and to vaccinations are often overlooked, or misdiagnosed, so that patients with these problems remain untreated. These conditions are much more common than realized but are unfortunately often confused with a true encephalitis, i.e. actual invasion of the nervous system by a viral organism. One reason for this is that physicians only rarely
question the patients and their families about preceding infections or vaccinations, or when they do so, restrict themselves to the 'traditional' one month prior to the onset of the neurological illness. It is also true that often the clinical manifestations of the preceding illness were so mild as to have been overlooked, or even completely forgotten. Many of them may also have been completely asymptomatic.

Definitions
In order to appreciate fully the nature of the neurological illness associated with a preceding or concurrent viral illness, it is important to define exactly the term encephalitis, which means inflammation of the brain, but which has been used interchangeably to designate both the actual invasion of the nervous system by the viral organism and the immune response to the antigenic proteins contained in the virus or the vaccine. In fact, the latter, which should more correctly be called post-infectious or postvaccinal encephalopathy, is much more common than the former, which consist mostly of herpes simplex and arbovirus encephalitides. The term disseminated encephalomyelitis has also been used to designate the immune-response illness, but it suggests that both brain and spinal cord are involved. It is for this reason that the broader designation disseminated vasculomyelinoapathy (DVMP) has been introduced to be applied only to the immune-response illness, reserving the word encephalitis for the actual viral infection of the brain. Obviously, the specific anatomic area affected by DVMP should be indicated in the description, such as myelopathy, or Guillaum-Barré syndrome, or cerebellopathy.

Historical Note
Many vaccinations and viral infections can produce severe and even life-threatening non-infectious reactions. Oddly enough even today the existence of these reactions, especially to vaccinations, is disputed on the basis of epidemiological studies by public health experts, who choose biostatistics over well-founded clinical, neuropathological and experimental data.2-6 The fact that the pathogenetic mechanism that produces the immune response to viral infections and to antiviral vaccines is identical to that of experimental allergic encephalomyelitis (EAE) and neuritis (EAN), seems to have been ignored by those who deny the fact that serious neurological illness may, although it rarely does, result from prophylactic vaccinations. This was recognized in 1954 by Miller & Stanton7 who stated:

The occurrence in identical clinical circumstances of radicular, polyneuritic, Landry, Guillaum-Barré, encephalitic, and myelitic syndromes, separately or in combination, strongly suggests a common denominator in the pathogenesis of these various conditions, whether they occur after prophylactic inoculation or arise, as they more commonly do in association with preceding infection...it has been generally accepted that the experimental encephalomyelitis produced by injections of heterologous brain tissue emulsified with Freund adjuvant is closely analogous with the acute disseminated encephalomyelitis with which we are familiar after Jennerian vaccination and the exanthemata in man.

They then postulated that
Neurological illnesses that arise after inoculation in apparently identical clinical context, and presumably therefore on the basis of similar pathological mechanisms, may affect any or every level of the nervous system from peripheral nerve to cerebral cortex. All neurological syndromes that follow inoculation may arise in other patients, either apparently spontaneously, or following specific or banal infections. The nervous system admittedly has a limited repertoire of clinical, as well as pathological responses. Yet it seems likely that common etiological and pathogenetic factors are involved in the syndromes under whatever clinical circumstances they arise.

The same authors also commented:
In the heat of the emotional battle provoked by propaganda for and against prophylactic inoculation, there has been a tendency on the part of the medical profession to turn a blind eye to unfortunate complications of procedures which have the indisputable sanction of social value. Despite the knowledge that has accumulated for almost 40 years, it is unfortunate that these admittedly rare responses to vaccinations and infections have been ignored, unrecognized, and untreated, often with very bad outcomes.

The Clinical Spectrum
Several authors7-8 had already pointed out that any part of the nervous system, both the central and the peripheral, may be involved separately or in various combinations. This is well-illustrated by the distribution of lesions of the nervous system following vaccination against influenza (Fig. 1). Multiple lesions are the rule rather than the exception, often leading to the erroneous diagnosis of multiple sclerosis (MS). Involvement of the brain may be paired with that of the peripheral nerves, a cerebellitis may occur concurrently with optic neuritis and a unilateral Bell's palsy, and a Miller-Fisher syndrome may be associated with evidence of spinal cord involvement. In fact, dissemination and the combined involvement of both central and peripheral nervous system provide an extremely valuable clue to the correct diagnosis. Devic's disease, or neuromyelitis optica, which is so often thought to be MS, is in fact, much more commonly a form of DVMP.9 It is important to remember that the flaccid paralysis and hypo- or areflexia of peripheral neuropathy may mask signs of cord lesions,10 while the spasticity and
hyperreflexia of myelopathy will obscure peripheral involvement. Clinical or electrophysiological demonstration of peripheral nerve lesions is an important differential diagnostic feature from MS. Extraneural organs such as muscle, heart or liver may also be involved by the inflammatory reaction. The involvement of isolated cranial nerves, or even cranial nerves in combination, have also been reported, in particular in children, and it easily escapes recognition as a manifestation of these complications of vaccinations or viral infections. Essentially all cranial nerves have been involved from the optic through the hypoglossal, usually unilaterally and occasionally bilaterally. Bilateral facial nerve involvement is of course a classic accompaniment of the Guillain-Barré syndrome.

Pathology

The major pathologic change consists of a vasculopathy that most commonly involves venules and capillaries but may also affect arterioles and even arteries. Demyelination is not an obligatory response, which may be restricted to inflammation and/or oedema (Fig. 2). This is well illustrated by the response seen after measles and which is illustrated in Table 1. Although demyelination is present in about two-thirds of the cases, inflammation is more common. The neuronal damage that is seen is secondary; it is ischaemic and occurs because the small blood vessels, including arterioles are often occluded by the inflammatory process that also causes oedema of the endothelium. In very young children the only response may consist of vascular congestion and oedema, causing what was often referred to in the old paediatric literature as serous or toxic encephalitis. Furthermore, many cases of so-called aseptic meningitis in fact represent this kind of response without any actual invasion of the nervous system by a viral organism. The severity of the pathological response does not depend upon a chronological progression: severe perivascular demyelination may

Figure 1. Anatomical distribution of lesions of the nervous system following vaccination against influenza (1956–1980). Cases meeting the 1978 National Institutes of Health (USA) criteria for Guillain-Barré syndrome, i.e. with involvement restricted to the peripheral nervous system were excluded. Forty-one cases resulted from vaccination against various strains of influenza, and 41 more followed vaccination against swine influenza (A/New Jersey/76) in the USA in 1976. (Adapted from Poser.)
Figure 2. Postulated pathogenetic mechanism for disseminated vasculomyelinopathy. Oedema affecting the myelin sheaths is the primary effect of the increased blood-brain barrier permeability resulting from the vasculopathy. Some, or all other pathological changes may occur but none, including destruction of myelin, are necessarily present. (Adapted from Poser.1).

occur within 24 h or not at all.8 The most severe reaction is seen in acute haemorrhagic leukoencephalopathy.13,14

Pathogenesis
The knowledge that EAE and EAN are exact models of the naturally occurring postinfectious and postvaccinal DVMP has helped us understand the pathogenesis of this condition. The mechanisms that damage the central nervous system are identical to those that involve the peripheral nervous system. The initial vasculopathy that results in the obligatory alteration of the blood-brain barrier (BBB) allows the penetration into the neural parenchyma of serum and cells, both lymphocytes and macrophages. Oedema and/or inflammation appear to be invariable consequences of this,15,16 but the characteristic stripping of myelin from the axon does not always take place. This crucial consideration has highly significant implications in terms of response to therapy, which will be discussed later.

Although the major, if not the only, target of the immune response is myelin basic protein (MBP), how this component of the myelin sheath becomes accessible to the immune system remains unexplained. Perhaps the fact that Freund's adjuvant, an essential component of the experimental model, contains lipid material and thus may permit passage through the blood-brain barrier, is relevant. Reik17 suggested that the alteration of the BBB may be due to the deposition of immune complexes on endothelial cells, altering their impermeability. It is a commonly held misconception that the immune response is directed against a single antigen, i.e. only one of the proteins of the viral envelope of the live, attenuated or killed organism contained in the vaccine. Isaacson & Stone18 have pointed out that there a multiplicity of antigens in any given viral vaccine preparation: (a) those associated with the virus, either as part of the virion or nonstructural proteins, interferons, etc. induced by the virus; (b) those of the host cell, either existing separately or attached to the virion, including host cell antigens whose antigenic specificity has been altered by viral actions; (c) those of the surrounding media, including nutrients and antibiotics; and (d) those derived from material or equipment used in purification and those which may be added to stabilize the final product.

The vigorous immune response to the viral or vaccinal protein-antigens may well be misdirected against either the endothelial cells and/or the basic protein component of myelin (MBP).

The theory of molecular mimicry suggests that antibodies are formed against certain characteristic amino acid sequences in antigenic proteins of the virus or the vaccine. These constitute the antigenic determinants. The same sequence or sequences may be present in endothelial cell membranes, in MBP or in P2, the peripheral nerve equivalent of MBP.15,19 The antibodies, being unable to differentiate between the

| Table 1 |
| Pathological changes in 41 cases of para-measles encephalopathy |

<table>
<thead>
<tr>
<th>Changes</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perivascular oedema</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Inflammation of vessel wall</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Perivascular inflammation</td>
<td>36 (88)</td>
</tr>
<tr>
<td>Perivascular demyelination</td>
<td>28 (68)</td>
</tr>
<tr>
<td>Perivascular haemorrhage</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Nerve cell damage</td>
<td>16 (39)</td>
</tr>
</tbody>
</table>

Adapted from Miller et al.9
antigens and the normal structures, then attack both. This antibody response may be augmented or activated by the presence in a new antigen of sequences recognized in a previous antigen. Thus, a vaccination against influenza may result in the activation of the immunological memory of a previous influenza infection or vaccination, or of a mild adenovirus infection several months or even years before because of the similarity of some amino acid sequences between the two viral antigens, which in turn share these sequences with MBP (Table 2). This is why the old belief that the old (Semple) rabies vaccine frequently caused DVMP because it contained neural material is no longer tenable, since several instances of reactions to human diploid cell rabies vaccine have now been noted. Clinical and pathological observations make it clear that not all individuals respond in the same manner and degree to the same antigenic stimulus. The reason is that the pathological type, anatomical distribution and severity of this response is determined by the immunogenetic constitution of the recipient rather than by the nature of the antigen. This was elegantly demonstrated by Kadlubowski & Hughes who showed that it is the species of the experimental animal receiving either central (MBP) or peripheral (P2) myelin, that determines if the central or the peripheral nervous system will be involved, or both, or neither (Table 3). This probably provides the best explanation for the great anatomical and pathological variability of the human reaction to viral infections and vaccinations. It also emphasizes the futility of attempting to apply biostatistical epidemiological techniques designed for considerably more predictable phenomena to persons of great immunogenetic disparity.

Immune responses causing DVMP are not restricted to viral organisms. They have been observed to occur after or concurrent with acute infections with brucella and mycoplasma as well as concurrently with

<table>
<thead>
<tr>
<th>Animal</th>
<th>Bovine myelin</th>
<th>Human myelin</th>
<th>Bovine P2</th>
<th>Human P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis rat</td>
<td>EAN</td>
<td>EAN</td>
<td>EAN</td>
<td>EAN +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EAE</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>EAN</td>
<td>EAN +</td>
<td>EAE</td>
<td>EAN +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EAE</td>
</tr>
<tr>
<td>Rabbit</td>
<td>—</td>
<td>—</td>
<td>EAN +</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EAE</td>
<td></td>
</tr>
</tbody>
</table>

(Predominant response in bold letters.)
Modified from Kadlubowski & Hughes. EAN: Experimental allergic neuritis. EAE: Experimental allergic encephalomyelitis.

more chronic, persistent infections such as malaria, borreliosis (Lyme disease) and AIDS. In fact, Toro & Roman have shown that one of the major pathological effects of *plasmodium falciparum* consists of an acute haemorrhagic leukoencephalopathy.

**Latency of Response**
The classical latency is considered to be 7–21 days. However, sometimes the DVMP may actually precede the clinical manifestations of the viral illness by several days (e.g. in measles). An example of the coincidental involvement of both grey and white matter is provided by a case of mumps encephalitis with paramumps leukoencephalopathy. Delayed reactions are well illustrated by cases in which the classical response to rubella vaccination took 99 days to declare itself or the most prolonged one on record, which occurred 5 months after anti-rabies vaccination.

**Diagnosis**
It is important to inquire about infections, in particular mild ones, which are presumably viral in origin, immunizations, or even close contacts with recently immunized persons, for at least 12
weeks prior to the onset of the illness. It is, however, quite common not to be able to learn of such a preceding event. Headache, backache and fever are common prodromes. Obviously the neurological signs and symptoms reflect the parts of the nervous system that are affected. Seizures are common in infants and young children; meningitis may be present at any age. The CT scan with contrast may show enhancing lesions located mostly but not exclusively in the white matter. Magnetic resonance imaging may show multiple scattered white matter lesions on T2 weighted images that have a tendency to be located towards the periphery, i.e. near the grey matter and not infrequently are seen in the cortex as well. A very suggestive MRI picture is that of very large areas of increased signal intensity in an almost lobar distribution (Fig. 3). The CSF may be normal or may reveal a modest elevation of lymphocytes and protein, but a normal glucose level. The CSF IgG may be elevated and oligoclonal bands may be present. A monospot test may be valuable, but the search for viral antibody titres is an intellectual exercise which has no practical value, since two specimens at a 3-week interval are required, much too long to wait for the institution of therapy. The absence of a peripheral polyleukocytosis need not be considered, but the sedimentation rate may be elevated.

One of the commonest errors in diagnosis, in particular in parts of the world where MS is common, is to confuse this disease with DVMP. Table 4 shows that the differential diagnosis must be based upon the history. It is obvious that MRI, evoked potentials or spinal fluid examinations will be of little if any value in the differential diagnosis. On the other hand, clinical or neurophysiological involvement of peripheral nerves, which is extremely rare in MS, will be of great help in establishing the correct diagnosis. The determination of HIV infection has now become important in all parts of the world, while in tropical areas or in dealing with patients

<table>
<thead>
<tr>
<th>Laboratory differential diagnosis of multiple sclerosis</th>
<th>MRI (1)</th>
<th>VEP (2)</th>
<th>OCB (3)</th>
<th>PNM (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Disseminated vasculomyelinopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Devic syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HTLV-I associated paraparesis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nervous system aids</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neurobrucellosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuroborrellosis (lyme)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neurosarcoidosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic fatigue postviral syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nervous system lupus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Not all these tests will be positive in all cases

(1): Magnetic resonance imaging.
(2): Visual evoked potentials.
(3): CSF oligoclonal bands.
(4): Peripheral nerve and/or muscle involvement.
results may be rewarding, even dramatic. Immunosuppressive agents are of no value, since damage from the misdirected immune response has already been done. Plasmapheresis, which has been used with some success, presumably is effective because it re-establishes the impermeability of the BBB by removing immune complexes\textsuperscript{17} and thus permits oedema and inflammation to resolve spontaneously. In this author's opinion, initiation of vigorous corticosteroid or corticotropin therapy is unequivocally indicated and should be started as soon as there is reasonable suspicion of the correct diagnosis (Table 5). Byers,\textsuperscript{14} 17 years ago, made a plea for such early treatment in cases of acute haemorrhagic leukoencephalopathy, the most severe form of the illness.

These treatments are directed against oedema, inflammation, and stabilization of the blood-brain barrier,\textsuperscript{28,29} but are powerless against demyelination. It is unfortunately impossible either clinically or by any known laboratory test or procedure to determine if demyelination has already occurred and if so, to what degree. This is one of the reasons why literature reports of series of patients treated with corticosteroids or corticotropins so often suggest that treatment is of no value. Such groups invariably include any number of patients in whom myelin destruction has already occurred and thus could not be expected to benefit from treatment with anti-oedematos and anti-inflammatory drugs.

It may be extremely difficult, especially in young children, to differentiate between an acute viral encephalitis and a para-viral encephalopathy, since both may give exactly the same clinical, EEG and CSF pictures. Both conditions may occur simultaneously.\textsuperscript{24} Except for herpes simplex and the arbovirus encephalitides, DVMP encephalopathies are considerably more frequent. Initiating therapy with acyclovir or an equivalent antiviral agent is recommended when there is suspicion of \textit{H. simplex} encephalitis, but this should not prevent the concurrent administration of vigorous corticosteroid or corticotropin therapy: even if the problem is dealing with a true viral encephalitis, the anti-oedema action of these drugs may have a salutary, and even a life-saving effect.\textsuperscript{28} The use of hypo-osmolar intravenous solutions, i.e. saline of concentration < 162 mmol/litre may contribute to the development of increased intracranial pressure.

Conclusion
Post- and para-infectious and vaccinal complications involving the nervous system are much more common than usually realized. Neurologists should keep them in mind so that immediate and vigorous treatment with corticosteroids or corticotropin may be given. An important clue to the nature of the illness is provided by the fact that

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**Table 5**

<table>
<thead>
<tr>
<th>Drug therapy for patients with neurological complications of infections and vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with acute severe disease: encephalopathy, transverse myelopathy, acute haemorrhagic leukoencephalopathy, life-threatening Guillain-Barré syndrome: DEXAMETHASONE 25 mg intravenously at onset, then 10 mg every 6 h for the first 48–72 hours; then reduce to 4 mg every 6 h or switch to oral steroids. Rapid reduction of dosage may result in rebound oedema and clinical relapse.</td>
</tr>
<tr>
<td>2. For patients with similar but less acute and less severe problems: COSYNTROPIN (SYNACTHEN, α-ADRENOCORTICOTROPIN) 1.0 mg in 500 ml 5% dextrose and water to run for 4–6 h daily for 10–15 days; as alternative, ACTH 100 units given according to the same regimen. Tapering of dosage is not necessary. Another alternative is to give METHYLPREDNISOLONE 1000 mg intravenously in 30–40 min daily for 5–7 days. It is necessary to follow up with a tapering regimen of oral corticosteroids.</td>
</tr>
<tr>
<td>3. For patients with optic neuritis, peripheral neuropathy, mild aseptic meningitis, etc. who do not require hospital admission: PREDNISONE given orally in a single morning dose, starting with 80 mg daily for 5 days, then 60 mg for 5 days, 40 mg for 5 days and 20 mg for 5 days. Occasionally, continue with 10 mg, then 5 mg each for 5 days.</td>
</tr>
</tbody>
</table>

**Precautions:** With every one of these regimens, blood pressure, and blood sugar and potassium levels must be monitored regularly. Salt intake must be severely restricted, and potassium supplements given on a regular basis. Antacids and histamine inhibitors such as ranitidine (150 mg twice daily) should be given, as well as diuretics such as acetazolamide (250 mg daily) to prevent or treat fluid retention. Increased appetite is another common side-effect and patients should receive dietary guidance in order to minimize weight gain. All these precautionary measures must be continued for 10–15 days after the termination of therapy.

who have recently come from such parts of the world, a search for antibodies against HTLV-1 is also imperative. Guidelines for differentiating HTLV-1 associated paraparesis from MS have been published.\textsuperscript{27} Most important in diagnosis is a high degree of suspicion.

**Treatment**
Controversy continues to rage regarding the treatment of this condition with corticosteroids or corticotropin. The many published reports of single cases or small series being treated in this way are casually dismissed as only anecdotal (which has become a pejorative term), despite the obvious fact that too often this disease's outcome may be severe permanent disability and even death. When proper precautions are taken, with courses of steroid treatment that should rarely last more than 3 or 4 weeks, serious complications are rare and the
often both the central and peripheral nervous systems are affected at the same time which rarely occurs in other acute illnesses of the central nervous system.

References