The widening spectrum of infectious neurological disease*

Three important areas of study reflect the widening range of neurological infections. These are (a) new technologies for pathogenetic studies and diagnosis, (b) the increasing range of neural pathogens and (c) new therapeutic tools.

(a) New technologies for pathogenetic studies and diagnosis of neurological disease

Until relatively recently most physicians specialising in infectious diseases relied largely on clinical bedside diagnosis and this is still of critical importance in, for example, many childhood infectious diseases such as chickenpox, measles and mumps, all of which have neurological sequelae. The development of modern investigative techniques can now supplement the classical methods of viral and bacterial isolation from body fluids and measurement of antiviral antibodies.

There are numerous problems when attempting to assign a particular virus to a neurological condition. When a virus is isolated from a patient during such an illness it may be the result of a co-existing and unrelated virus infection. The virus may not be isolated from the neurological or other site or there may be chronic asymptomatic secretion of virus. Moreover, serological studies may be misleading in that there may be non-specific polyclonal activation of virus as part of a generalised immune response to infection. There may also be persistent viral antibody levels from a previous infection. Virus isolation or antibody rises may also represent viral reactivation and not a primary infection. Other problems with serological viral diagnosis include: inadequate sensitivity, inadequate specificity (for example, unwanted cross-reactions), the fact that antibody elevations may be transient, as well as practical difficulties with the collection and timing of specimens.

Some of the more important new technologies available for viral and bacterial diagnosis will now be considered.

(i) Molecular analysis of viral and bacterial isolates

Molecular analysis of viral and bacterial isolates obtained from patients has proved to be very useful both in diagnosis and pathogenetic studies. For example, genetic analysis of herpes simplex virus (HSV) isolates using restriction enzyme techniques and methods for analysing polypeptide profiles have shown that HSV-1 isolates from human ganglia (trigeminal, superior cervical and vagus) are generally specific for individuals in that they can usually be distinguished from one another.

Similar techniques have also been used to show that HSV encephalitis may be due to various types of HSV infection including primary infection, reactivation of HSV which had remained latent in sensory ganglia, or reinfec-

(ii) Identification of antigens in body fluids and tissues

Increasingly sophisticated antigen detection methods including the use of monoclonal antibodies are proving useful diagnostic aids in both viral and bacterial infections of the CNS. For example, enzyme-linked immunosorbent assays (ELISA) have been used extensively to detect a variety of microbial antigens and have proved to be particularly useful in the differentiation of various causes of meningitis. This technique has also proved to be useful in the diagnosis of human immunodeficiency virus (HIV) infection, although the technique of Western blotting whereby antigens are detected on electrophoretic gels using specific antibodies, provides a standard confirmatory test for this infection.

Immunofluorescence has been used for a number of years in a variety of neurological conditions. While this technique is often only semi-quantitative, it has been particularly useful in the diagnosis of varicella-zoster virus (VZV) infections using the indirect membrane immunofluorescent assay which appears to be capable of distinguishing cases of varicella or herpes zoster with clinical CNS involvement from those individuals with VZV infections without neurological involvement.

The technique of double-labelling immunofluorescence whereby two different antigens can be visualised in tissue culture or tissues simultaneously using antibodies conjugated to two different fluorochromes has been particularly useful, especially in pathogenetic studies. Using this technique the differential susceptibility of neural cells to virus infection can be determined by localising viral proteins in marker-identified neural cell types. Immunofluorescence studies have also been of value in the diagnosis of herpes simplex encephalitis, although a rapid test for this condition is still urgently required.

Antigen detection by the horseradish peroxidase technique is more sensitive than immunofluorescence and is of considerable value in both diagnostic and pathogenetic studies. The avidin-biotin peroxidase technique is currently the most sensitive of these antigen detection methods. Peroxidase techniques have the advantage of enabling a permanent histological preparation to be made.

(iii) Nucleic acid detection in body fluids and tissues

The development of increasingly sensitive molecular techniques such as Southern-blot hybridisation, dot-blot hybridisation and in situ hybridisation (ISH) for localising viral genomes in pathological tissues has been of the greatest importance in understanding the basis of virally-induced neurological disease. Radionlabelled nucleic acid (DNA or RNA) probes are used in autoradiographic

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procedures which visualise specific hybridisation between the probes and nucleic acid sequences in the cell or tissue specimens under test. ISH has the advantage of being able to localise the viral genome within individual cells and is particularly useful in detecting a small amount of virus which is unevenly distributed within a tissue. These techniques have been used, for example, to demonstrate HIV in the brains of patients with HIV encephalitis,13 HSV nucleic acid in patients with HSV encephalitis9 and in latently infected sensory ganglia,17 and measles virus genome in some patients with multiple sclerosis.14

These techniques are also being employed in a number of laboratories to investigate the possible viral aetiology of other neurological disorders such as motor neuron disease15 and Alzheimer's disease.16 ISH can also be combined with immunocytochemistry to co-localise viral proteins or cell markers and nucleic acids within the same cell as has been demonstrated in the case of the visna retrovirus of sheep.17 Visna virus RNA has been localised within marker-identified oligodendrocytes in the brain of a sheep with encephalitis.1819 Class II antigens and nucleic acids have also been co-localised in macrophages in this disease.17 This double-labelling technique has also been of considerable value in recent pathogenesis studies of HSV encephalitis on human brain biopsies.9

Nucleic acid detection has recently been revolutionised by the polymerase chain reaction (PCR) in which considerable amplification of nucleic acids in cells and/or tissues is possible.20 The sensitivity of this technique can be exceptionally high with the ability to detect a single viral genome in a cell culture or tissue specimen containing many thousands of cells. Although care must be taken to exclude the possibility of contamination, PCR is already proving to be an exceptionally valuable technique for both diagnosis and pathogenetic studies. For example, it has been used to demonstrate HIV in patients' lymphocytes before the HIV antibody is detectable and thus is of use in early diagnosis.21 PCR may also clarify questions concerning acute versus chronic virus infections of the nervous system in that some neurological diseases may be due to chronic viral infection which can only be detected using such a very sensitive technique. Such an approach should be particularly useful in investigating cases of the post-viral fatigue syndrome and motor neuron disease.

(iv) Viral reassortants and recombinants

Although viral reassortant and recombinant techniques are not in routine use for ordinary diagnosis, they are mentioned here since they have been so valuable in studies of pathogenesis. For example, intertypic recombinant viruses between HSV-1 and HSV-2 strains have been shown to have a small region of the HSV-1 genome that has an important role in determining the ability of the virus to spread to and replicate in the CNS.27

Although the mammalian retroviruses are not of particular importance in human disease, Fields et al have used the mouse reovirus model highly effectively to study the genetic determinants of neurovirulence and neurotropism.23 Viral reassortants were constructed using segments of the genome from three different types of reovirus. These different serotypes differ in their capacity to infect neural cells and spread within the nervous system. The three main reovirus serotypes all contain segmental double-stranded RNA, but type 1 has an affinity for ependymal cells whereas type 3 infects neurons preferentially.23 Type 3 also results in fatal encephalitis in neonatal mice. Using the intertypic reassortant viruses it was shown that the S1 gene, which encodes the viral cell attachment protein (Sigma 1), determines whether the virus infects ependymal cells or neurons24 and also whether it spreads along nervous pathways or by haematogenous routes.25

(v) New brain imaging techniques

The relatively recent development of sophisticated neuroimaging techniques has played an important role in both disease diagnosis and increasing our understanding of pathogenesis. For example, computed tomography (CT) scanning has clarified some aspects of the natural history of tuberculous meningitis. It has shown, for example, that the incidence of tuberculoma of the nervous system is much greater than had previously been thought during the course of tuberculous meningitis and that many of these lesions do not produce symptoms.26 CT scanning has been particularly useful in the recognition and management of patients with neurocysticercosis. A variety of abnormalities can be identified by CT scanning including parenchymal cysts, hydrocephalus, areas of calcification and vasculitic infarction.17 Studies using contrast enhancement can also provide specialised information which is particularly useful for monitoring therapy. Moreover, the absence of cerebral oedema, as assessed by CT scanning in patients with cerebral malaria, has directly resulted in modification of therapy in that it has obviated the need for dexamethasone therapy in this condition.28

Magnetic resonance imaging (MRI) has already proved to be of great value in a variety of infectious neurological diseases. It has been particularly useful in detecting demyelinating lesions in HIV encephalitis29 and through its ability to detect white matter lesions with some precision it can also be used for the non-invasive diagnosis of such conditions as progressive multifocal leucoencephalopathy and post-infectious encephalomyelitis.29 A more recent development is single photon emission computerised tomography (SPECT) scanning in which abnormalities of blood flow have been demonstrated in both herpes simplex encephalitis and non-herpetic encephalitis.30

(b) The widening range of neural pathogens

Clinicians have recognised for some time that a wide variety of infectious agents can produce neurological disease. However, over the last decade the range of neurotropic viruses and bacteria has appeared to widen. This includes an increasing range of familiar pathogens as well as the recognition of new pathogens.

There are a number of examples of the first category. Immunosuppressive therapy for malignancy and other conditions with cytotoxic and other drugs has been increasingly effective in recent years. Unfortunately, one of the consequences of this increased therapeutic immunosuppression is an increase in the frequency and range of fungal infections (for example, Candidiasis), viral infections (for example, progressive multifocal leucoencephalopathy (PML) due to the JC papovavirus30) and bacterial infections (for example Listeria monocytogenes) in renal transplant patients.

In some cases there has been a change in the host response to familiar organisms which produce opportunistic infections. The increased range of a species within known pathogenic groups causing disease is well illustrated by spirochaetal infections. For example, while the spirochaete Treponema pallidum has been recognised for many years as being the cause of syphilis, the spirochaete Borrelia burgdorferi, which causes Lyme disease, was first recognised in 1975 in Connecticut, United States.31 Lyme disease, which is tick-borne, may well have been around somewhat earlier than this and the apparent increasing incidence of this disease at present is due, at least in part, to the fact that
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clinicians are actively seeking evidence of B burgdorferi infection where clinically relevant. A variety of neurological symptoms and signs occur in about 15% of cases when the nervous system is involved in the second stage of Lyme disease.32 This includes meningoencephalitis, cranial nerve palsies and radiculopathy.32

Another relatively recently recognised disease is legionnaires' disease caused by the bacterium Legionella pneumophila, which is also known to produce diverse neurological impairment.33 Interestingly, legionnaires' disease was prevalent as long ago as the 1940s and 1950s, as shown by retrospective studies,34,35 and may well have been the actual cause of some cases of so-called "virus pneumonia".

There are many causes of so-called "new" diseases. An environmental change such as the introduction of a toxin or irradiation may occur and be manifested in a variety of ways. There may also be a change in the host response to familiar pathogens as occurs frequently in immunosuppressed individuals. A further mechanism is through pathogen ‘jumping’ species as may well have occurred in the case of HIV. Moreover, a pathogen may be identified by a new technology as in the case of legionnaires' disease and PML. A hypothetical possibility is that a pathogen may be externally introduced either from extraterrestrial sources or through genetic engineering. For practical purposes the only genuinely new recent infectious disease is HIV. However, these various possibilities are not mutually exclusive, for example, for a pathogen to "jump" species thereby extending its own specificity there may well have to be a concomitant change in the properties of the virus itself as well as the host response.

Infection with human immunodeficiency virus (HIV) has now reached epidemic proportions and is emerging as the most serious public health problem that infectious disease physicians and others have to deal with. Neurological complications are a very significant feature of HIV infection at all stages ranging from HIV seropositivity through to AIDS-related complex (ARC) and the full-blown AIDS syndrome. These various complications have been reviewed in detail.36,37 About 10% of patients with HIV infection present neurologically,38,39 whilst approximately 70% of patients with AIDS have some evidence of neurological involvement and this figure may extend to around 80% if pathological data are also taken into consideration.36 The complications include a wide variety of infections including those caused by HIV itself and other viruses, fungi (especially candida and cryptococcus), bacteria and protozoa (toxoplasmosis) as well as tumours of the nervous system which are usually primary or systemic lymphomas.36 Cerebrovascular complications and a wide variety of peripheral nerve disorders including sensory and motor neuropathies of both axonal and demyelinating type are also well-recognised.40

Probably the most important of these complications is an HIV encephalitis, also known as the AIDS-dementia complex, which is caused by direct HIV infection within the brain.12 However, the precise pathogenesis of the brain lesions has not been clarified and although HIV has been demonstrated within macrophages, multinucleate giant cells and polymorphs, it has not been shown conclusively to cause destruction in situ. It is likely that indirect mechanisms are important, for example, the release of lymphokines, and simultaneous infection with HIV and other opportunistic viruses may play an important role.42 Whether the successful introduction of public health measures aimed at halting spread of the disease will be successful is unclear at present. It is clear, however, that HIV infection will be a major problem for some time to come and that neurological features will continue to be prominent.

(c) New therapeutic tools
These include well-recognised therapy for newly recognised diseases, newly developed therapy for well-recognised diseases, and newly developed therapy for new diseases.

Well-recognised therapy has been effective for newly recognised diseases, including established antibiotics such as penicillin in Lyme disease. Another example is the use of erythromycin in patients suffering from legionnaires' disease. In considering the role of newly developed therapies for well-recognised diseases, it is worth considering that what is new therapeutically today may seem very old-fashioned if not barbaric in the future. Over a 100 years ago Sir William Gowers in his classic textbook on diseases of the nervous system4 mentions a variety of somewhat disturbing treatments for meningitis. For example, leeching and local application of mercury along the spine were recommended and some of the treatments sound worse than the disease! Almost 20 years later we learn from the Medical Annual under "New Treatments" that oral Creosote is an effective treatment for tuberculosis meningitis.4 Nevertheless, there have been some recent advances which have produced truly outstanding results. Prominent is the use of the nucleoside analogue acyclovir for patients with herpes simplex encephalitis. Intravenous administration of this drug given early can drastically reduce both the mortality and morbidity of this condition which is the commonest cause of fatal sporadic encephalitis occurring in humans.43 The use of the helminthicide drug praziquantel has proved to be remarkably effective in treating neurocysticercosis and is likely to have a very significant impact on this disease in developing countries.44

If a disease is genuinely new, it may well be necessary to develop completely new therapy unless one is particularly fortunate in having to hand established therapies which might prove effective. An example of such newly developed therapy is the drug azidothymidine which has a definite effect on the systemic complications of HIV infection45 and in preliminary studies the AIDS-dementia complex and other neurological conditions also appear to respond favourably to this drug.46 In view of the theoretical and practical difficulties in developing a vaccine for AIDS the role of chemotherapy and immunotherapy is likely to be of considerable importance. The existence of HIV variants which may have different properties and sensitivities to drugs must also be taken into consideration.

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