Viral Encephalitis

PATHOLOGY, DIAGNOSIS AND MANAGEMENT

JOHN BOOSS
MARGARET M. ESIRI

Blackwell Scientific Publications

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JOHN BOOSS
MD
Neurovirologist, V.A. Medical Center, West Haven, Connecticut, and Associate Professor, Departments of Neurology and Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut

MARGARET M. ESIRI
DM(Oxon) MRCPath
Medical Research Council Senior Clinical Fellow in Neuropathology, University of Oxford and Senior Research Fellow, St Hugh's College, Oxford

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Preface

The diagnosis and management of viral encephalitis are often approached with considerable uncertainty. For the non-neurologist, neurological diagnosis may seem complex, and for the non-infectious diseases specialist the number of viruses which can infect humans seems countless. It is no surprise then that the clinical approach to encephalitis is occasionally fragmentary and based on anecdotal experience. This is unfortunate and in a way paradoxical. The paradox lies in the fact that clinical neurology and clinical virology each lend themselves to logical and patterned investigation. It is the purpose of this book to present a logical approach to the diagnosis of encephalitis and to present pathogenesis evidence in a way that allows formulation of rational therapy.

Our major concern in the preparation of this book has been its clinical usefulness. It has seemed to us that many clinical treatises on viral encephalitis are organized as if the infecting virus were known. That is, the discussions are organized by families of viruses. Unfortunately that is not how patients with encephalitis present themselves. This book is organized according to information available to the clinician during the initial stages of the evaluation. The discussion emphasizes the use of epidemiological, clinical virological and clinical neurological information to arrive at the few most likely causes in any given case. Based on this information, use of pathological and viral diagnostic studies to reach a specific diagnosis are discussed. Except in certain circumstances such as herpes simplex encephalitis, where therapy has been subjected to controlled study, treatment of patients with encephalitis often rests on medical concensus and personal clinical experience. Therefore we have emphasized human neuropathological reactions to serve as a basis to understand pathogenesis and to construct rational therapy. When disagreement on therapy exists we have tried to present the factors on which the decision to treat, or not, is based.

The major audience for whom the book has been written are clinicians with primary responsibility for managing patients with encephalitis. General practice physicians, family physicians, pediatricians and internists are often the first to evaluate such patients and their decisions are crucial. Neurologists and infectious diseases specialists may become involved at the start or after referral to a specialized center. On occasion, neurosurgeons or psychiatrists are the first specialists consulted. Pathologists and diagnostic virologists are crucial in the course of determining the precise process and infecting agent. It is hoped that the book will be useful for them and that it may also prove of interest to microbiologists and epidemiologists.

The first three chapters of the book provide introductory material. We feel strongly that the clinical understanding of encephalitis must rest on an understanding of the human pathology. Therefore the first chapter of the book and the first portion of discussion of most of the types of encephalitis deal with the human pathology. Studies of pathogenesis in experimental animals are discussed as they are relevant to the human disease. The second chapter provides the overall orientation for the clinical evaluation of the patient with suspected encephalitis. As such it is an integral introduction to each of the discussions of specific types of encephalitis. Chapter 3 discusses management problems common to the several types of encephalitis. In particular it discusses the issues of acute management of factors such as raised intracranial pressure, which may be of greatest danger to the patient.

The introductory chapters are followed by chapters on various types of encephalitis organized by clinical and epidemiological features. Chapters on sporadic encephalitis and epidemic encephalitis are followed by those on parainfectious encephalomyelitis and special types of encephalitis. The discussion of the failure to make a specific etiologic diagnosis in encephalitis follows the presentation of herpes simplex encephalitis (HSE). We have the most complete data on HSE and yet are clinically accurate in only something over 50% of cases. The parainfectious group is covered in three chapters, the first of which is on neuropathology. Brainstem encephalitis is covered separately because of its distinctive clinical presentations, although the etiologies are diverse and often obscure. In this day of oncotherapy, immunotherapy and organ transplantation, several virologic infections of the CNS present themselves in the immunocompromised patient. Since the agents involved are sometimes predictable, we have covered this topic and AIDS in a separate chapter. The slow virus encephalopathies present recognizable clinical patterns and are discussed within the final three chapters. In general we have not covered congenital nor neonatal infections, although neonatal herpes infection is summarized. When certain infections could have been discussed in various chapters, they were placed according to the clinical and epidemiologic information likely to be available to the clinician at the time of patient evaluation.

It should be noted that the book has been a collaborative effort throughout. Though each of us has been concerned with viral and immune-mediated processes for several years, we not infrequently discovered that we had arrived at somewhat differing conclusions about various processes. Discussion of the different perspectives was often the most interesting and productive part of the work. It is hoped that the reader will benefit from the collaborative perspective.

The book would not have been possible but for the patience and support of J.B.'s family and it is to them that he dedicates this book.

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In preparing a book such as this, one becomes intensely aware of the intellectual debts to one's teachers, colleagues and students. In addition, critical evaluation of the manuscript has been an important part of the book's development. David Oppenheimer, J. Trevor Hughes and Albert H. Tomlinson have reviewed major portions of the manuscript. Those who have reviewed chapters and sections are George F. Thornton, James W. Prichard, Donald Mayo, Joseph Piepmeier, Richard B. Tenser, Marie Landry, Frank Bia, David J. Giron, David Warrell, Edwin D. Kilbourne, Robert E. Shope, Lewis L. Levy, John C. Moench, Laura R. Ment, Louis Reik jun., Bennett A. Shaywitz, Thomas N. Byrne jun., Jeffrey Melin, Andrew R. Pachner, Richard H. Mattson, Arthur M. Seigel, Bruce B. Haak, and Jung H. Kim. We are grateful for their generous and spirited criticism. Any deficiencies that remain are, of course, our responsibility. We are grateful too for the willingness of several other investigators to provide information and to spend time in the discussion of various points. Fran Bernstein and the staff of the medical library of the V.A. Medical Center have provided invaluable support to J.B. in his role as staff neurovirologist. Preparation of the book was greatly eased by the skillful typing, often requiring cryptographic skills, of Deborah D. Beauvais. Permission to reproduce Tables 5.3 and 5.4 has been received from the US Centers for Disease Control.

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Chapter 1
Pathological Features of Encephalitis

This chapter aims to provide an overview of the pathology of human encephalitis. In it we describe procedures that are of value in examining central nervous system (CNS) tissues from cases of suspected encephalitis and histopathological features common to most forms of viral encephalitis. We also discuss factors that confer specificity in the case of particular viral infections of the CNS, such as selectivity with regard to a host cell type that a virus may show, the character of the immune response, and the tempo of the disease process.

Sources of information on the pathology of encephalitis

Knowledge about the pathology of encephalitis is based primarily on the study of human biopsy and autopsy material. Understanding of the pathological processes involved has also been immensely extended by experimental studies in animals. These have been of two main types: viruses that cause human disease have been administered to animals which are not their natural hosts; and naturally occurring viral diseases of animals have been studied in a search for parallels to human disease. The association of a virus with its natural host species is generally a very close and specific one, and it is therefore only with caution that findings in animals can be applied to man. However, these studies furnish almost the only evidence that can be obtained on the events that occur during the incubation period of a disease, that interval between the time of entry of a virus into its host and the onset of clinical disease. Most of the pathological descriptions in this book will be based on examination of human material, but animal studies will be referred to when these offer particular illumination that is relevant to the pathogenesis of human diseases. This chapter gives an overview of the pathology of human encephalitis. More detailed pathology of individual human diseases will be given in the appropriate succeeding chapters.

Many of the observations relating to the pathology of human encephalitis are based on examination of the brain at autopsy. Inflammatory changes in the brain were described in isolated reports during the nineteenth century, but it was with the abrupt appearance during the First World War of the epidemic of encephalitis lethargica, with its high mortality rate, that the first detailed pathology of series of cases came to be described.

It is important to realize that the evidence provided by autopsy examination is limited. First, in any individual case the disease process can only be studied at one time. Serial observations, such as those made available by sequential biopsy techniques, are not obtainable in these diseases. To some extent this drawback can be overcome by studying large numbers of cases in which death has occurred at differing stages of the disease. However, evidence of the earliest pathological changes is hard to come by, for patients do not die until the pathology is relatively far advanced. Information from CT scanning is providing useful supplementary evidence about the earliest stages of encephalitis. Second, autopsy material only provides information about the most severe forms of those diseases which are not uniformly fatal. These include most forms of encephalitis, for it is only with rabies virus infection and the very rare herpes B infection of the brain that the mortality rate approaches 100%. Milder forms of encephalitis, from which recovery with or without residual morbidity generally occurs, rarely become available for pathological study.

Examination of biopsy specimens affords valuable information, particularly on ultrastructural aspects of a disease, because the material is better preserved and more free from unwanted artefacts when it is immediately immersed in fixative than when it is removed after the inevitable delays that attend autopsy examination. Biopsy samples suffer, however, from the disadvantage that they are very small and may not have been taken from the part of the brain most likely to yield the greatest information on the pathological changes that are present. Every effort has to be made to extract as much information as possible from a biopsy sample. This will generally involve dividing it to provide samples for routine fixation for light microscopy, electron microscopy, viral and bacterial culture. These techniques are briefly described below (Fig. 1.1).

Naked-eye examination of the brain and routine light microscopy

These are the classical techniques of pathological examination, and formed the basis of the early studies of encephalitis. Although they are so routine and well established they are not always carried out to best advantage. Satisfactory naked-eye examination of the brain requires that the brain be removed from the skull with care to ensure that no artefactual tears are produced. These are easily caused when the brain is swollen or softened, particularly to the upper brainstem, if the cerebral hemispheres are not adequately supported while the brainstem and cerebellum are extracted from the posterior fossa.

After removal of the brain with full aseptic precautions it should be placed in a dish, weighed, and its external surface carefully examined. Small specimens for viral culture and, in some instances, cryostat sectioning and electron microscopy should be taken from selected regions that appear inflamed, congested or slightly softened. Such specimens are likely to be more

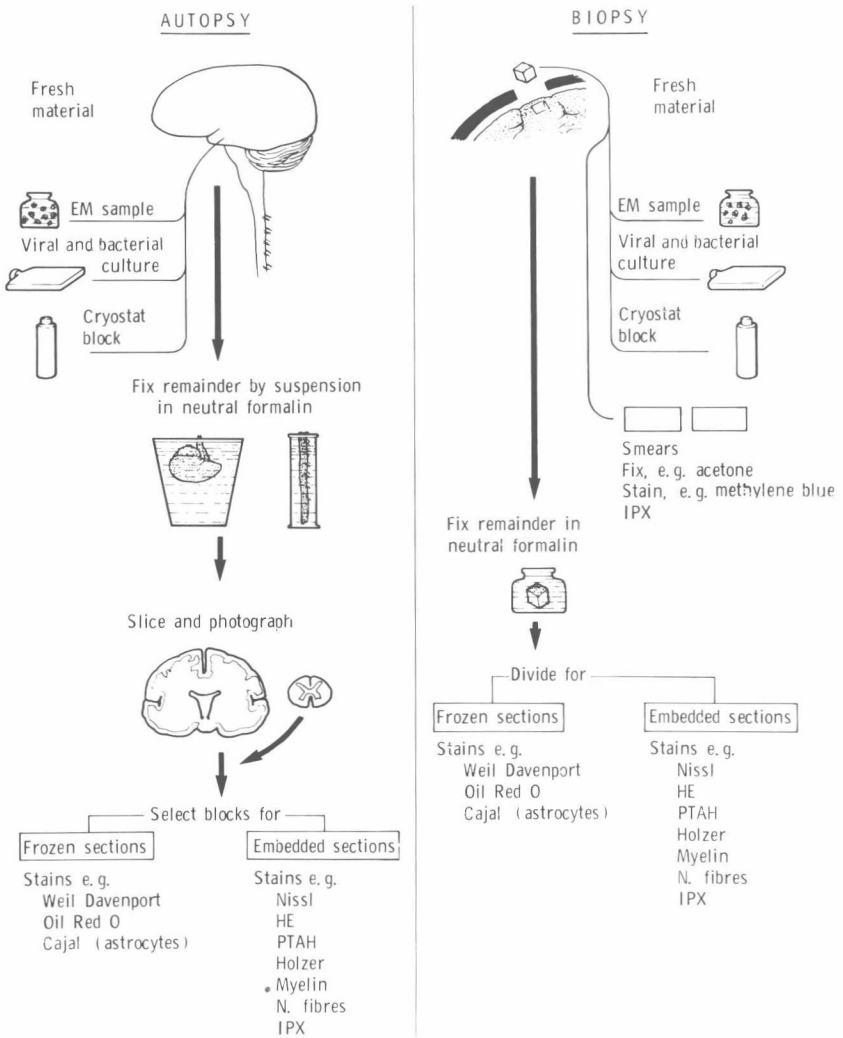

Fig. 1.1. Summary chart of recommended procedure when dealing with autopsy or biopsy specimens from a case of suspected encephalitis.

rewarding than those from frankly necrotic, liquefied areas of the brain. If there is no naked-eye abnormality, as is frequently the case, these fresh samples for special study are best taken from the part of the brain that might be expected from the clinical history and examination, or from CT scan appearances, to be the most involved. Thus, if a hemiparesis and/or focal epilepsy was clinically apparent, specimens should be taken from the appropriate cerebral hemisphere; if brainstem signs were present, and were not considered to be

simply a reflection of brain swelling and herniation, regions of the brainstem should be sampled, and so on. Direct consultation with the clinician concerned can make all the difference between success and failure in carrying out these investigations, and as the techniques involved are time consuming and expensive, time and effort spent in the judicious selection of specimens is well worthwhile. If insufficient cerebrospinal fluid (CSF) was obtained during life for all necessary investigations, a further sample can be taken at the time of autopsy, along with an additional sample of serum to allow corrections to be made for possible blood contamination of the CSF. Similarly, a throat swab and sample of large bowel contents should be taken if adequate specimens were not taken during life for viral culture. If possible the spinal cord and at least a few dorsal root ganglia should be removed, together with the brain.

After the necessary fresh samples have been taken the brain should be suspended in a large container of fixative and left for at least 3 weeks before being sectioned (Fig. 1.1).

After fixation the brainstem is separated from the cerebral hemispheres, the cerebrum sectioned at 1 cm intervals either in the coronal or horizontal plane, and the sections scrutinized for macroscopic pathology. The brainstem and cerebellum are sliced at smaller intervals. In many instances there are no specific changes to be seen on naked-eye inspection. The brain may show a variable amount of edema, with narrowing of the lateral and third ventricles, and flattening of cortical gyri, and there is frequently congestion and sometimes petechial hemorrhages present. Meninges are usually only mildly opaque in the acute stages of encephalitis but may be toughened and thickened over areas of chronic damage. More severe swelling and softening will be apparent, particularly in the temporal lobes in acute encephalitis caused by herpes simplex virus (Chapter 4).

Photography can be conveniently carried out after slicing the brain. Blocks for light microscopical examination are then selected and should be taken from relatively normal as well as abnormal areas, as microscopical changes are frequently found in areas that appear normal to naked-eye examination, and may represent an earlier stage of the disease process. Blocks for light microscopy should be taken for frozen sections, as well as for embedding in paraffin wax in many instances, and a variety of staining techniques employed. Those that are particularly helpful are the Weil–Davenport or similar stains for microglia, Oil Red O (or similar) for fat, Cajal's method for astrocytes on frozen sections, Nissl (a good cell stain), stains for myelin and nerve fibers, and the Holzer stain for fibrillary gliosis on sections of paraffin-embedded material. Paraffin sections can also be used to search for some viral antigens using the immunoperoxidase technique (see below). In cases of suspected Creutzfeldt–Jakob disease frozen sections should be avoided and embedded material only used for light microscopy. With regard to dealing with material from such cases the recommendations of the Howie Report (1978) from the UK and of the

Center for Disease Control and Department of Health and Human Services (1982) in the US are appropriate. Dissecting instruments should be sterilized in, and dissecting surfaces exposed for 2 h to a 10% hypochlorite solution or 1 N-NaOH. Histopathology specimens can be fixed in neutral formalin to which phenol has been added to give a final concentration of 10%. Care should be taken to avoid cutting oneself with a microtome knife, and the knife itself, if not disposable, should be chemically sterilized and then autoclaved after use (single cycle 134°C (207 KPa, 30 lbs psi) for 18 min). No excess risk of developing Creutzfeldt–Jakob disease relates to laboratory technical or mortuary work, nor to pathologists, even though special precautions have only been taken for about the last 10 years (Brown *et al.* 1982).

The preparation of smears may be useful, particularly in the evaluation of biopsy material, when a rapid diagnosis is required. A small fragment of the biopsy is smeared thinly on a clean glass slide, air-dried, fixed and stained with methylene blue, or a similar stain, or by the immunoperoxidase technique. Sections stained with methylene blue take only a few minutes to prepare, and the immunoperoxidase technique using an antibody to herpes simplex virus takes less than half an hour. A positive result provides rapid confirmation of the diagnosis; a negative result does not exclude the diagnosis because of the possibility of sampling error, and it is necessary to await viral culture and other investigations before a definitive answer can be obtained.

Immunohistological techniques

A variety of techniques are now available to enable a search to be made in histological material for specific viral antigens. Immunofluorescence was the first of these and has been in routine use for many years. More recently, the development of immunohistochemical techniques has considerably extended the scope of these investigations. These techniques rely, like immunofluorescence, on the use of highly specific antisera which bind to the antigens being sought in the tissue section or smear. The sites of antibody binding are detected by means of a histochemical reaction, usually the reaction of peroxidase with diaminobenzidine, instead of a fluorescent marker. The technique has several advantages over immunofluorescence (Sternberger, 1979): it is more sensitive and can therefore detect smaller quantities of antigen; it circumvents the problem of autofluorescence; it does not require the use of a fluorescence microscope; and the preparations do not fade rapidly. The technique can be used for electron microscopy and, best of all, as a result of the enhanced sensitivity, several viral antigens can be detected after formalin fixation, presumably because a sufficient number of unaltered antigenic sites remain. Herpes simplex virus (Benjamin and Ray, 1975; Kumanishi and Hirano, 1978; Budka and Popow-Kraupp, 1981; Esiri, 1982; Lohler, 1982), varicella zoster virus (Horten *et al.*, 1981), rabies virus (Atenasiu, 1973; Budka

and Popow-Kraupp, 1981), measles virus (Kumanishi and Seichii, 1979; Budka *et al.*, 1982; Esiri *et al.*, 1982), papova virus (Itoyama *et al.*, 1982), cytomegalovirus (Lohler, 1982) and influenza A virus (Lohler *et al.*, 1982; Reinacher *et al.*, 1983) have all been detected using the immunoperoxidase technique on routinely processed formalin-fixed, paraffin-embedded material, sometimes years after processing (Fig. 1.2). Such a procedure is clearly a safer as well as a more convenient means of searching for viral antigens, and the tissue architecture is better preserved than in cryostat sections.

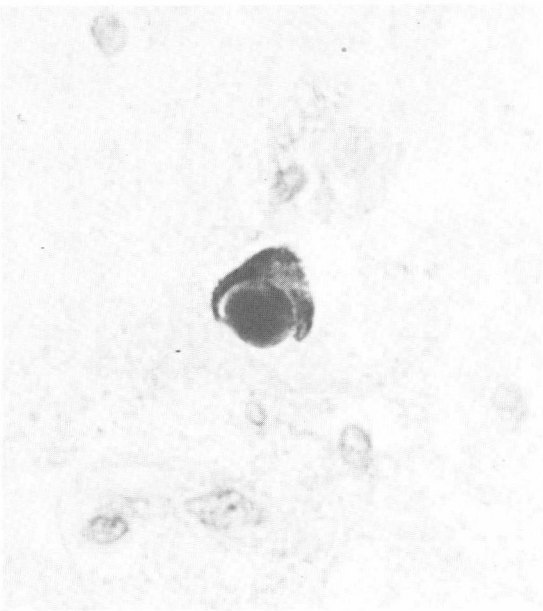

Fig. 1.2. Immunoperoxidase staining using anti-measles antibody to demonstrate measles antigen in neuron nucleus and cytoplasm in the cerebral cortex of a case of subacute sclerosing panencephalitis (SSPE). Counterstained with hematoxylin. ×800.

In adddition to their use in searching for viral antigens, immunohistological techniques may also be used to examine in detail the character of the inflammatory infiltrate present in the brain in encephalitis. Immunoglobulin antisera can be used on formalin-fixed tissues to detect those immunoblasts and plasma cells that contain heavy and light chain immunoglobulin determinants (Fig. 1.3), and the recently developed monoclonal antibodies to human T lymphocyte and other antigens can be used to examine lymphocyte subpopulations present in acetone-fixed cryostat sections (Booss *et al.*, 1983) (Fig. 1.4). The detection of extracellular deposits of immune complexes and complement is also within the scope of this technique, though some workers

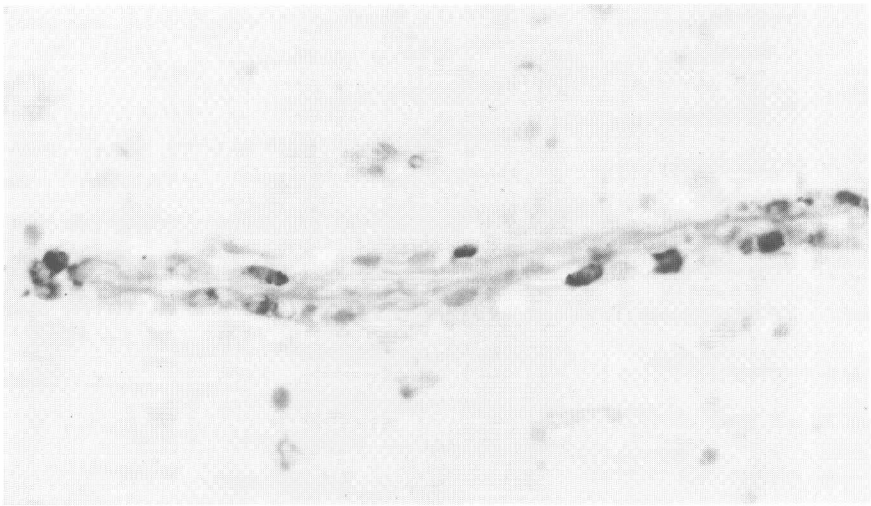

Fig. 1.3. Scanty perivascular infiltrate from a case of herpes simplex encephalitis stained using the immunoperoxidase technique to demonstrate IgG in plasma cell cytoplasm. Counterstained with hematoxylin. ×200.

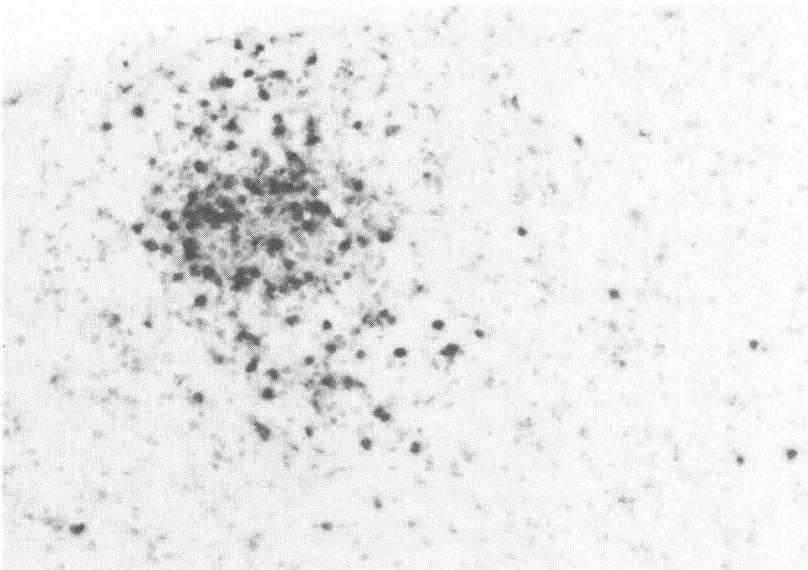

Fig. 1.4. Helper T cells demonstrated by the immunoperoxidase technique using antibody Leu 3a on a frozen section of CNS from a case of multiple sclerosis. Counterstained with hematoxylin. ×200.

still prefer immunofluorescence for searching for these extracellular antigens. The widespread use of these techniques in the study of encephalitis should considerably increase understanding of these diseases.

Electron microscopy

Thin-section transmission microscopy is the form of electron microscopy most commonly used to examine biopsy and autopsy samples from cases of encephalitis. The demonstration of virus-like particles using this technique was instrumental in initially demonstrating the viral nature of two diseases, subacute sclerosing panencephalitis and progressive multifocal leukoencephalopathy (Bouteille *et al.*, 1965; Zu Rhein and Chou, 1965). The chief value of electron microscopy lies in the demonstration of distinctive virus structure, as in encephalitis due to herpes simplex virus, rabies virus or adenovirus. Virions can be detected in autopsy as well as biopsy samples as their structure is not significantly degraded after death of the patient. However, because of the very small size of the samples that can be examined in this way it is a relatively insensitive technique for demonstrating the presence of virus. This problem can to some extent be overcome, either by selecting for ultrastructural examination only those blocks which can be shown, using the immunoperoxidase technique at the light microscope level on 1 μ sections, to contain viral antigen, or by using the negative staining technique. In this technique a homogenate is made of the fresh or frozen tissue to be sampled; this is then centrifuged at intermediate speed and the supernatant examined for viral particles after negative staining (Dayan and Almeida, 1975). The technique is more likely than thin-section electron microscopy to detect viral particles if there are only small numbers present in the tissue, particularly if antibody to the suspected virus is added to the brain suspension. The virus is clumped by the antibody and becomes easier to spot. Even if these maneuvers are employed, the technique of negative staining remains relatively insensitive, and the procedure necessitates the loss of all tissue structure so that no information is obtained on the type of cell harboring the virus. On the other hand, valuable information can be obtained on the substructure of the virus particles, and this can be of great value in characterizing the virus and in distinguishing those particles which are truly viruses from those components of brain ultrastructure which superficially resemble viruses and which, in transmission electron micrographs, have sometimes been mistakenly assumed to be viruses. Negative-stain electron microscopy has recently demonstrated the presence of fibrils, possibly representing transmissible agent in Creutzfeldt–Jakob disease (Merz *et al.*, 1984) (Chapter 14).

Pathological features common to most forms of viral encephalitis

Although the types of virus that may produce encephalitis are diverse, there is considerable uniformity in the pathology they produce, at least in the mature nervous system of an immunocompetent host. In many cases this will enable a shrewd guess to be made as to the nature of the illness even in the absence of supportive clinical or virological evidence. There are some well known diseases in which no viral agent has been identified, but in which such an etiology remains suspected on pathological grounds. Such conditions include encephalitis lethargica (Chapter 6). Those features common to many forms of viral encephalitis are described below, followed by an account of some of the features that are restricted to specific viral infections.

Cell death

Virus infection of brain cells, as of cells elsewhere in the body, is followed by alterations in the cells' metabolism which, in lytic infections, lead to the death of the host cells. Simultaneously, there evolves a general inflammatory response with the development of edema, and an immune response. The extent, rate and selectivity of cell death vary considerably, but in all cases cell death is evident. Degenerate features that are recognizable microscopically are swelling and cloudiness, or shrinkage with eosinophilia of neuronal cytoplasm and pyknosis of nuclei. This is followed by loss of staining properties of the cell, giving it a faint 'ghost' appearance. At this stage a macrophage reaction is frequently present, with a small cluster of microglial cells and a few lymphocytes surrounding the remnant of the neuron. Microglial cells are distinguishable in routinely stained sections by the presence of their elongated, or comma-shaped, slightly irregular nuclei. The whole configuration of dead neuron and surrounding cells is termed 'neuronophagia' (Fig. 1.5). In an acute lytic process many such figures will be seen, for example in the anterior horns of the spinal cord in acute poliomyelitis, but in a more slowly evolving disease they will only occasionally be seen, for example in the late stages of subacute sclerosing panencephalitis. The microglial cells, sometimes admixed with a few astrocytes and lymphocytes, remain at the site after the neuron remnant has disappeared. Such foci of reactive cells are termed glial stars, nodules, clusters or knots. Animal studies indicate that it takes no more than a few days for a dead cell to disappear under these conditions, but some residual glial cells remain for months or years. Glial cells as well as neurons undergo cell lysis in some virus infections, but the process is less conspicuous in glial cells than in neurons. Although in some cases of encephalitis cell death occurs on a relatively small scale and is only appreciable on microscopical examination, in other cases the damage to cells can be massive and lead to areas of necrosis that are easily visible to the naked eye. This is especially the case in herpes simplex

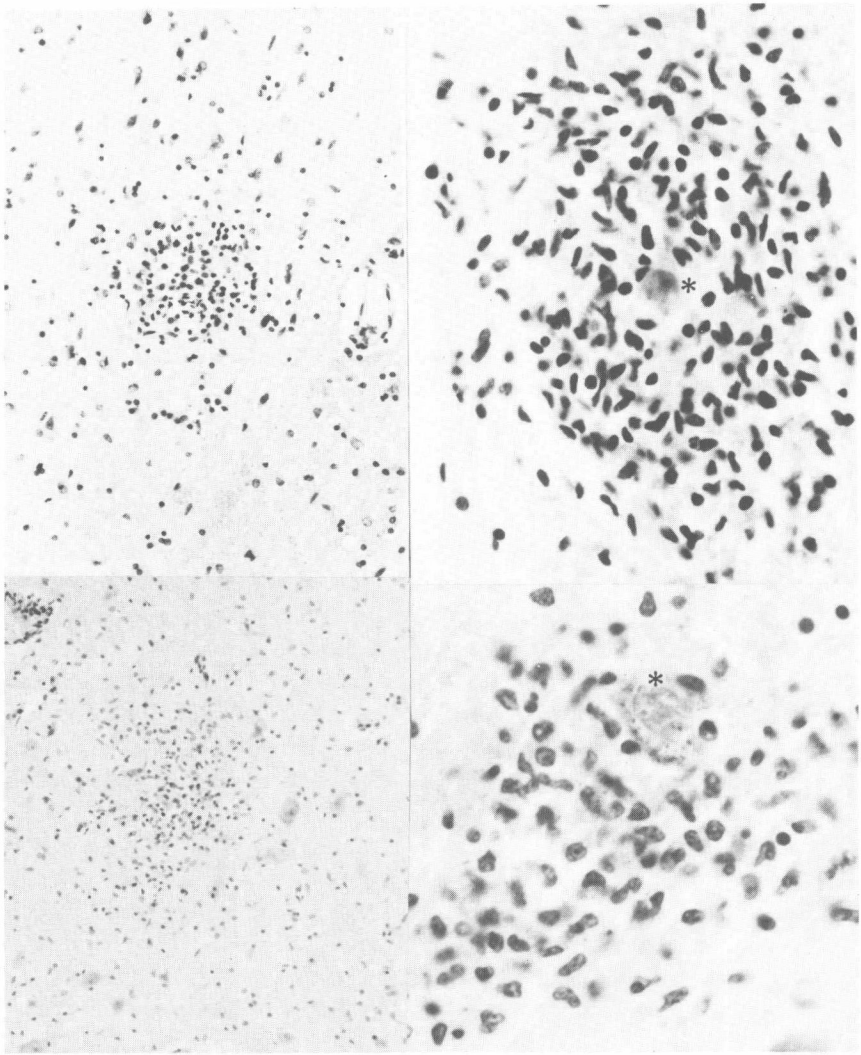

Fig. 1.5. Examples of neuronophagic and glial nodules. Low power views of glial nodules on left, higher power views of neuronophagia, with neuron remnant visible (*) on right. H&E stain. Left upper and lower, ×180; right upper, ×600; right lower, ×800.

encephalitis, in which the extent of the necrosis of the temporal lobes is such as to resemble infarction. In this instance it is the bilateral distribution of the lesions, and the fact that the areas of necrosis do not coincide with arterial territories that should alert the pathologist to the encephalitic nature of the lesions.