of injury to the renal pelvis. As a result of the continued leakage of sterile urine, this fluid becomes encapsulated in the loin and collects around the kidney. On intravenous pyelography the kidney itself appears normal, but the leakage of dye can be detected in later films, as it diffuses into the space of the pseudo-hydronephrosis.

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Virus meningitis

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THE TERM aseptic meningitis was first introduced by Wallgren (1925) to designate what was thought to be a specific disease and was defined as a syndrome characterized by meningeal irritation associated with a cellular response in the cerebrospinal fluid which was sterile bacteriologically. It is now recognized as being due to a variety of agents the majority of which are viruses. Aseptic meningitis should now only be acceptable as a preliminary term pending investigations and as undifferentiated aseptic meningitis when an etiological diagnosis cannot be established.

The diagnosis of virus meningitis presupposes no overt involvement of the nervous system although separation from encephalitis is not always easy because in some patients a non-specific drowsiness or confusion may be present when, in fact, there is no evidence of an inflammatory reaction in the substance of the brain. Conversely in some patients with encephalitis the cerebral involvement may be so mild as to escape notice and only the meningitic signs and cerebrospinal fluid abnormality may be manifest.

Etiology

The recent advances in virus isolation enable an etiological diagnosis of virus meningitis to be reached in 50–70% of cases in the best equipped laboratories.

A. *Common causes*

(i) Enteroviruses:

Poliomyelitis	3 types
Coxsackie group A	23 types
Coxsackie group B	6 types
ECHO	30 types

(ii) Mumps.

B. *Uncommon causes*

(i) Lymphocytic choriomeningitis.
(ii) Glandular fever.
(iii) Herpes simplex.
(iv) Adenoviruses.
(v) Arbor viruses.

An increase of cells in the cerebrospinal fluid is found in most cases of herpes zoster but as it is a disease of characteristic presentation and meningitic signs are rarely present it has been purposely excluded from this classification.

Epidemiology

Virus meningitis is world wide. The enteroviruses and mumps account for 90% of the known causes (Ch'iu, Ts'ao, Jen & Chang, 1965; Grist, 1965). Not all Coxsackie and ECHO viruses are associated with meningitis but an increasing number have been reported in recent years and in addition further types have probably yet to be identified. The enteroviruses although occurring at any time of the year reach their peak in the late summer and autumn. Surveys have shown that in any one place the incidence of the various viruses differs from one year to the next (Combined Scottish Study, 1964).

Children and young adults account for most of the cases and virus meningitis is infrequently encountered in infancy. The enteroviruses are spread by the faecal–oral route and as in poliomyelitis symptomless infection with Coxsackie and ECHO viruses are common, clinical illness developing in only a small minority. Lymphocytic choriomeningitis is rare in the British Isles and of little importance in most countries. Human infec-

tions are probably derived from mice and the patients are usually between 15 and 40 years. The rare herpes simplex meningitis is seen primarily in infants and adults.

Clinical manifestations

A. *Headache, pyrexia and meningitic signs*

Virus meningitis is usually of acute onset and found essentially in children and young adults, headache, pyrexia and meningitic signs being features common to all. The headache is most commonly frontal but may be generalized. Pyrexia is variable (up to 104°F) and lasts from 24 hr to 10 days with an average of 5 days. Neck stiffness and inability to kiss the knees are the most useful signs of meningitis, and other signs such as Kernig's and Brudzinski's have little place in clinical practice. Many cases have minimal meningitic signs, i.e. can just kiss knees although this causes some discomfort in the back or back of the neck, these lasting less than 24 hr and undoubtedly many cases are missed. At the other end of the scale meningitic signs may be as marked as in cases of severe pyogenic meningitis.

B. *Abdominal pain*

Abdominal pain is commonly present with nausea and vomiting but diarrhoea is rare.

C. *Rashes*

Macular and maculopapular eruptions (rarely petechial) are present in some cases of ECHO infections especially in children. The rashes are usually rubelliform and most commonly on the face and neck. Occasionally rashes occur also with Coxsackie virus infections especially group A.

D. *Muscle pain and weakness*

Generalized muscle pain in the back and limbs may occur with the enteroviruses. Pleurodynia is suggestive of a Coxsackie group B infection. Mild paresis of a limb with associated loss of reflexes occurs rarely in Coxsackie (especially A 7—Grist, 1965) and ECHO infections. With the virtual disappearance of paralytic poliomyelitis in many countries there is as yet no evidence of an increased neurotropism of the other enteroviruses.

E. *Other manifestations*

Mumps meningitis may occur without any other manifestations of mumps but is more common in association with salivary gland involvement, sometimes preceding the latter. In Coxsackie group B infections, parotitis, pericarditis and orchitis have all been described (Murphy & Simmul, 1964).

Neurological complications of glandular fever are uncommon and are rarely those of an aseptic meningitis (Gautier Smith, 1965) and this applies also to herpes simplex. Aseptic meningitis due to infection with one of the arthropod-borne viruses has occurred usually during an epidemic in which most of the cases present the more characteristic encephalitic picture. Louping ill is the only indigenous member of this group in the British Isles and a case presenting as virus meningitis has been reported in Scotland (Combined Scottish Survey, 1961).

It is evident from the above that in most cases there is little assistance from the clinical findings as to the nature of the virus involved.

Laboratory findings and diagnosis

The cerebrospinal fluid shows a pleocytosis of 10–2000 cells (Lepow *et al.*, 1962) with a varying percentage of polymorphs and lymphocytes (in enteroviral infections polymorphs frequently preponderate in the early stages). Only mumps shows characteristically a lymphocytic picture. The protein is only slightly raised (less than 100 mg/100 ml), the sugar normal and the chlorides normal or slightly reduced. The white cell count is usually within the normal range.

The advances in tissue culture techniques have greatly increased the frequency of isolation of an etiological agent. Although most enteroviruses can be isolated in routine cell cultures such as monkey kidney, many of the Coxsackie A strains may only be grown in suckling mice and some ECHO viruses may require human thyroid or amnion culture. Identification is by neutralization with specific antisera.

The enteroviruses can be isolated from the faeces and, in the early stages, from throat swabs, the former being the most convenient material to examine. Cerebrospinal fluid culture is more difficult owing to the smaller number of particles but some workers have reported isolation of Coxsackie B 5 in 50% of cases, mainly in the first 3 days (Nakao *et al.*, 1964) and recovery of it was inversely related to the number of cells (as was reported with ECHO 9 by Chang & Weinstein, 1962).

Where viruses are isolated other than from the CSF it is necessary to show by paired sera a significant rise (four-fold or greater) of specific neutralizing or complement fixing antibody in convalescence. Mumps virus isolation (preferably from the urine) is not yet a routine procedure and diagnosis is based on the mumps CFT. Similarly sera may be submited to complement-fixation tests for lymphocytic choriomeningitis, herpes simplex and adenoviruses but these are rare causes and hardly justify their use as a routine procedure.

Differential diagnosis

It is most important that virus meningitis should not be confused with other causes of aseptic meningitis which may require urgent and specific treatment.

A. *Bacterial pyogenic meningitis*

The unfortunately increasing practice of indiscriminate use of antibiotics in unknown febrile conditions may sometimes lead to delay in diagnosis of pyogenic meningitis and at subsequent lumbar puncture a sterile cerebrospinal fluid may be obtained with the cytology of a virus meningitis. If the infection has not been eradicated, and this is likely as few antibacterial drugs, with the exception of chloramphenical and sulphonamides, penetrate in adequate concentration into the CSF, such cases may flare up with a greater likelihood of neurological sequelae. Occasionally a meningococcal CFT may identify an unsuspected meningococcal meningitis which has been treated unknowingly before admission.

B. *Neighbourhood reactions*

A focus of infection near the meninges, e.g. mastoids, sinuses, brain abscess, etc., may give rise to a cerebrospinal fluid identical with that of a virus meningitis. Even the most careful history and clinical examination may not initially give any clear indication of such a focus and this stresses the importance of careful observation of a presumed virus meningitis which does not rapidly show evidence of improvement.

C. *Tuberculous meningitis*

Although usually more gradual in onset this may be relatively acute. Unlike virus meningitis the protein is always raised, rising with the cell count, the rise not infrequently of the same order, e.g. cells 200/mm^3 and protein *c.* 200 mg/100 ml. In untreated cases at the onset the cells may be up to 50–70% polymorphs although lymphocytes usually preponderate. The total number of cells rarely exceeds 500/mm^3. The sugar is reduced and the chlorides < 700 mg/100 ml but it is only in the late cases that the very low figures so frequently quoted in textbooks are encountered. The tubercle bacillus can be identified in nearly all cases on first examination if at least 5 ml of CSF is obtained and the entire spun deposit examined after Ziehl Nielsen staining, a further 5 ml of CSF being retained for Löwenstein Jensen culture. The diagnosis of tuberculous meningitis is urgent and a delay of even 12 hr may lead to meningovascular complications and sequelae. Other signs of tuberculosis may not be evident and the Mantoux test is sometimes negative if the meningitis has occurred within 3 months of the primary infection.

D. *Leptospirosis*

Anicteric leptospiral fever, e.g. due to *L. canicola,* may simulate a virus meningitis and the cerebrospinal fluid findings be identical. An acute onset with rigors, muscle pains and suffusion of conjunctivae is usual, and rashes, especially morbilliform and scarlatiniform, may occur. It should be remembered that these cases are sometimes associated with severe renal damage with oliguria and a raised blood urea. Diagnosis is by the leptospiral complement fixation test.

E. *Syphilis*

The meningitic manifestations of syphilis generally occur in the late secondary stage and are more typically subacute with little or no fever. The CSF sugar may be reduced and the protein higher than is found in virus meningitis.

F. *Brain tumours*

Especially in children these may rarely present as a meningitis, e.g. medulloblastoma, craniopharyngioma, ependymoma and dermoid, but once again a detailed history will usually reveal a gradual onset of symptoms. Cerebral metastases in adults may lead to meningeal involvement but confusion with a virus meningitis is unlikely.

G. *Post-infectious encephalomyelitis*

In some cases there may be no overt evidence of encephalitis and pyrexia, irritability and meningitic signs may be the only findings with apparent rapid and complete recovery.

H. *Toxoplasmosis*

Acquired toxoplasmosis due to the protozoon parasite, *Toxoplasma gondii,* may rarely present as meningitis with little evidence of encephalitis. Lymphadenopathy and splenomegaly may be present. Although the neurological examination is usually negative the illness may progress to a fatal issue or survival with residual brain damage as shown by epilepsy or personality change but complete recovery can occur. Lymphocytes usually predominate in the cerebrospinal fluid which resembles that of a virus meningitis. The demonstration of a rising neutralizing antibody titre by the dye test confirms the diagnosis.

I. *Mycoplasma infections*

M. pneumoniae (Eaton agent) has been reported as a rare cause of aseptic meningitis (Skoldenberg, 1965).

J. *Torulosis* (*Cryptococcosis*)

This is a rare chronic systemic fungal disease, respiratory in origin which may disseminate to the

meninges and nervous system. Lymphocytes usually predominate in the cerebrospinal fluid but in contradistinction to virus meningitis the glucose is low and the protein high. Unless suspected the spherical fungal cells may be mistaken for lymphocytes in unstained preparations of CSF but the capsules can be demonstrated by the India ink preparation. This condition more often occurs in association with such conditions as leukaemia and Hodgkin's disease.

K. *Listeriosis*

Meningitis due to *Listeria monocytogones* is uncommon and the cytology of the cerebrospinal fluid may resemble either virus or bacterial pyogenic meningitis. As in Torulosis diagnosis is dependent on good laboratory facilities and any clinical and laboratory evidence of meningeal infection said to be caused by a diphtheroid should be suspected of being due to Listeria.

Prognosis and treatment

By definition one presupposes no overt involvement of the nervous system and recovery is rapid and complete (usually less than a week). Treatment is symptomatic and the headache usually yields to simple analgesics. Not surprisingly cases are occasionally seen where involvement of the nervous system occurs and a follow-up by Lepow *et al.* (1962) suggested that such complaints as fatigue, irritability and decreased ability to concentrate were not uncommon in convalescence although even they admitted that over 95% were fully recovered within a year. More detailed follow-up should be undertaken by other workers to clarify whether virus meningitis is perhaps less benign than usually thought to be. It is evident that there is no clear-cut division between virus meningitis and meningoencephalitis. Some of the viruses mentioned have a predilection for brain tissue and minor involvement in other cases would be difficult if not impossible to define.

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