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VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM: SELECTED ASPECTS

Introduction

The first part of this review deals with the epidemiologic assessment and current status of acute viral infections of the central nervous system (CNS) occurring in the United States. This assessment is performed in terms of clinical syndromes (aseptic meningitis, encephalitis and paralytic poliomyelitis) as these are encountered in medical practice. The next topic considered relates to the specific viral etiologies of these syndromes. Which agents are most commonly involved? Are any trends in incidence discernible? In what per cent of cases can no etiology be ascertained? The answer to this last question is related both to methodology (virus isolation techniques, antigens available for serological tests) and criteria for case inclusion.

A discussion of herpes simplex encephalitis would appear essential because of the recent availability of a promising therapeutic agent in this infrequent but oftentimes lethal disease. Finally, practical suggestions are advanced related to the etiologic workup of CNS viral infections.

The following general references are recommended:

1. Viral encephalitis. A symposium. Edited by Fields, W. S., and Blattner, R. J. Charles C. Thomas, Publisher. Springfield, Illinois, 1958.
2. Encephalitides. Proceedings of a Symposium on the Neuropathology, Electroencephalography and Biochemistry of Encephalitides. Edited by Van Bogaert, J., Radermecker, J., Hozay, J., and Lowenthal, A. Elsevier Publishing Co., New York, 1961.
3. Infections of the Nervous System. Association for Research in Nervous and Mental Disease. Edited by Zimmerman, H. M. The Williams & Wilkins Co., Baltimore, Maryland, 1968.

Definition of Clinical Syndromes

It has been found useful to classify viral infections of the CNS into various syndromes. Of historical interest are Wallgren's criteria for aseptic meningitis (4,5).

1. Acute onset with obvious signs and symptoms of meningeal involvement
2. Alteration of cerebrospinal fluid typical of meningitis. The cerebrospinal

fluid may show a small or large number of cells
3. Absence of bacteria in cerebrospinal fluid, as demonstrated by appropriate direct or cultural techniques
4. Relatively short benign course of illness
5. Absence of local parameningeal infection (otitis, sinusitis, trauma, etc.), or a general disease which might present meningitis as a secondary manifestation
6. Absence from the community of epidemic disease in which meningitis is a feature

A classification that is generally recognized follows (6):

Aseptic meningitis: Acute onset of febrile illness with signs and symptoms of meningeal involvement, pleocytosis and sterile CSF (cultures negative for bacteria and fungi). Illnesses seldom exceed ten days' duration and recovery is without sequelae.

Encephalitis: Meningeal signs plus clinical evidence of more deep-seated neurological involvement (focal paralysis, disorientation, stupor, excessive drowsiness, convulsions, tremor, ataxia, slurred speech, pathological reflexes).

The category, meningoencephalitis, probably should be discarded in favor of encephalitis. Most patients with encephalitis have meningeal signs and the term, encephalitis, gives precedence to the more severe signs and symptoms.

Paralytic poliomyelitis: Acute febrile onset, meningeal irritation, pleocytosis and persistent flaccid paralysis, without objective evidence of sensory defect or cortical damage.

[Cases with residual flaccid paralysis (60 days after onset) and compatible clinical and epidemiological features are designated in the phrase, "the best available paralytic poliomyelitis case count" by the National Communicable Disease Center (NCDC) and represent the most reliable indication of the number of paralytic illnesses of poliovirus etiology (7).]

Inapparent infection: Laboratory evidence of viral infection in the absence of clinical symptomatology.

Other: (Febrile headache, transverse myelitis, etc.)

Incidence and Mortality

Because of variable reporting, it is difficult to arrive at exact numbers of cases with the different clinical syndromes. The problem is compounded by the fact that, in the past, patients with infections of the CNS secondary to mumps and lymphocytic choriomeningitis have been classified and reported as cases of encephalitis, although it is widely recognized that these viruses most commonly cause aseptic meningitis. With these considerations in mind, surveillance data for 1967, the most recent complete year for which statistics are available, reveal the following (Table I) (7,8,9):

TABLE 1

Surveillance of Viral Infections
of the Central Nervous System
United States - 1967

Syndrome	No. Cases	No. Deaths
Aseptic meningitis	3,082	
Encephalitis (including mumps, LCM and cases associated with childhood illnesses)	2,368	245
Paralytic poliomyelitis	40	
	5,490	

Secular Trends. The number of cases of aseptic meningitis reported in the United States by month and year is shown. The expected summer peak, characteristic of enterovirus infections, the most common cause of aseptic meningitis, occurs yearly (Figure 1) (9).

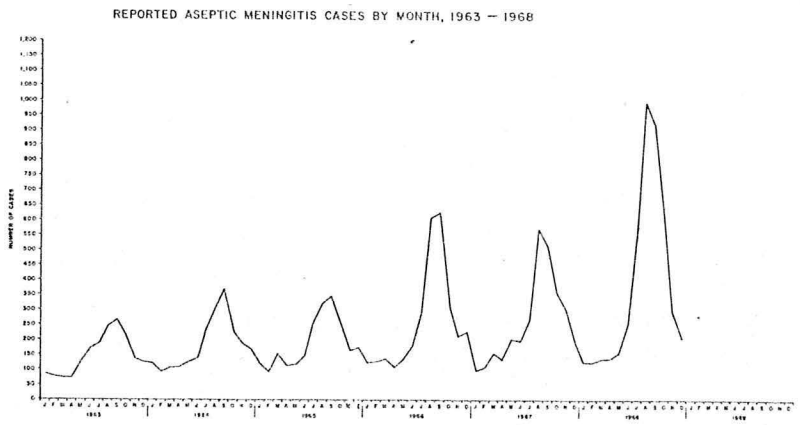


FIGURE 1

The incidence of reported cases of encephalitis is also highest in summer. Part of the variation in peak incidence by year can be related to the occurrence of epidemics of arboviral encephalitis (Figure 2) (8).

REPORTED CASES OF ENCEPHALITIS BY MONTH OF ONSET,
UNITED STATES, 1962 - 1967

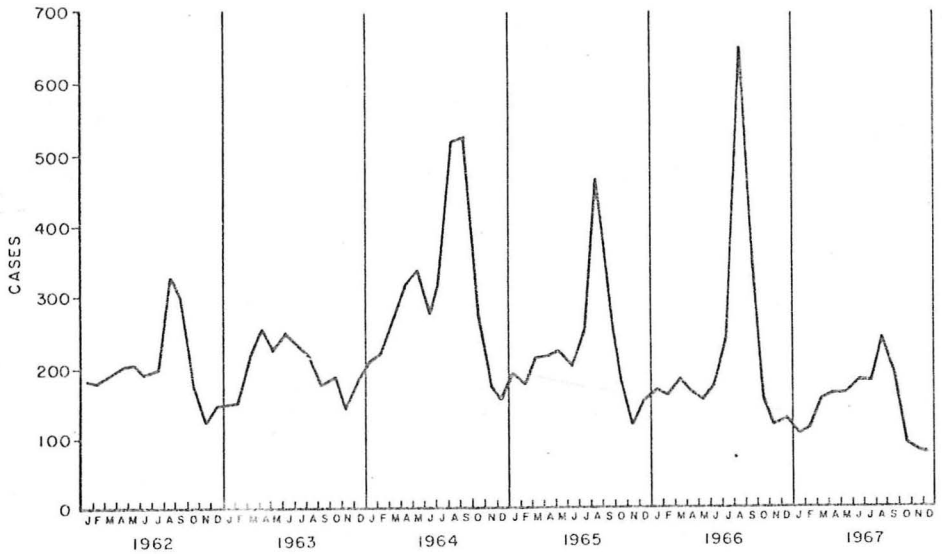


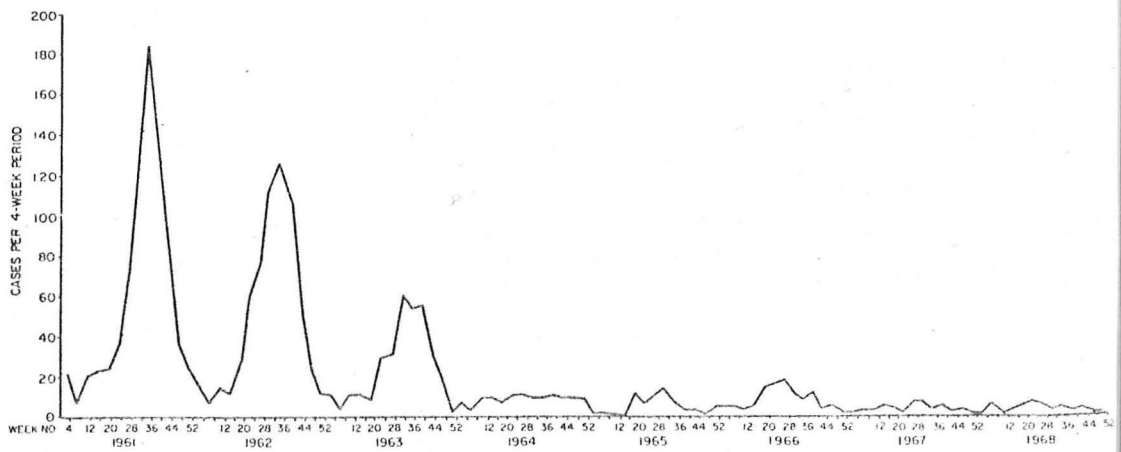
FIGURE 2

A second lesser peak in encephalitis cases occurs each spring, coincident with increased numbers of cases of rubeola, rubella, varicella and mumps. The height of this second peak would appear to be decreasing by year. This decrease is related to the diminished incidence of rubeola after widespread immunization campaigns.

As expected, the incidence of paralytic poliomyelitis has declined markedly since the introduction of effective immunizing agents [inactivated poliomyelitis vaccine (IPV, Salk), oral poliomyelitis vaccine (OPV, Sabin)] (Figure 3) (7).

PARALYTIC POLIOMYELITIS CASES BY DATE OF ONSET
UNITED STATES, 1961-1968

FIG. 3



A disturbing note should be raised in relationship to paralytic poliomyelitis, however. As case rates have declined, the necessity for immunization has seemed less urgent. As a consequence, the immunization status of preschool children (< 4 years of age), particularly from lower socioeconomic classes in certain areas of the country, is less than desirable. In 1968, the National Immunization Survey revealed that 10.5% of U.S. children 1-4 years of age had received no OPV or IPV. This figure decreased to 3.3% for children 5-9 years old, since immunization is often accomplished with entry into elementary school. This lowered immunization status coupled with free movement across the U.S.-Mexico border led to 66 cases of paralytic poliomyelitis in Texas in 1966, 9 cases in 1967 and 20 in 1968. The majority of these cases occurred in children < 4 years of age. The geographic distribution of 1968 cases shows the clustering of patients in Texas (Figure 4) (7).

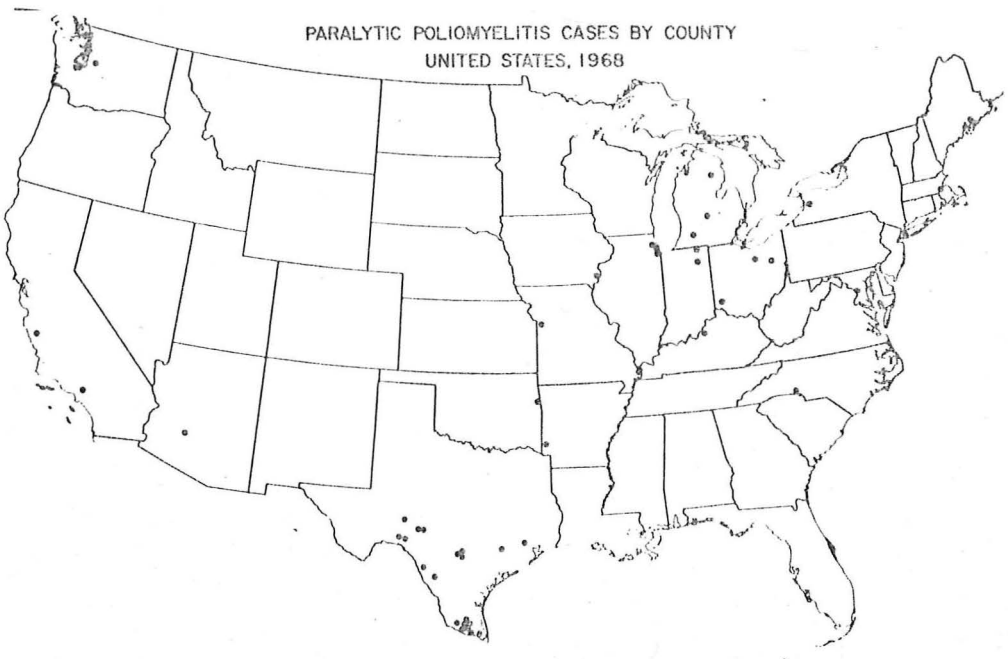


FIGURE 4

Human cases of arthropod-borne encephalitis vary markedly by year, related to the occurrence of epidemics (Table 2) (8).

TABLE 2

Human Cases of Arthropod-Borne Encephalitis
1955-1967

	Etiology				
Year	WE	EE	SLE	CE	Total
1955	37	15	107	0	159
1956	47	15	563	0	625
1957	35	5	147	0	187
1958	141	2	94	0	237
1959	14	36	118	0	168
1960	21	3	21	0	45
1961	27	1	42	0	70
1962	17	0	253	0	270
1963	56	0	19	1	76
1964	64	5	470	42	582
1965	172	8	58	59	297
1966	47	4	323	64	438
1967	18	1	11	53	83

Specific recent events underlying some of this yearly variation can be listed. Increased numbers of cases of Western equine encephalitis (WEE) occurred in 1965, particularly in Colorado, after flooding of the South Platte and Arkansas River basins. In 1962, an epidemic of St. Louis encephalitis (SLE) occurred in the Tampa Bay area, Florida (10). In 1964, major SLE epidemics occurred in Houston, Texas, and the Delaware River Valley, New Jersey and Pennsylvania (11-13). In 1966, SLE epidemics occurred in Dallas and Corpus Christi, Texas. The 1959 Eastern equine encephalitis epidemic in New Jersey has recently been extensively detailed (14-20). This epidemic caused severe problems, related not only to the severity of the disease and the high incidence of sequelae in survivors but also because cases were occurring near resort areas along the New Jersey coast with resultant economic losses. Following the reports of children in Florida and Wisconsin with encephalitis due to California encephalitis virus (CEV), this antigen has been used increasingly to elucidate the etiology of cases of encephalitis occurring in the summer (21,22). CEV infections occur throughout the country, predominantly from rural areas and particularly from the midwest (Ohio, Wisconsin, Indiana). CEV has been isolated from mosquitoes in both Beaumont and Houston, Texas. Therefore, this arbovirus should be considered in the differential diagnosis when children, particularly boys, from rural East Texas present with encephalitis.

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Status of Knowledge of the Specific Etiology of CNS Viral Infections

Six series of cases of CNS viral infections have been reviewed (6, 23-27). In each of these series, an attempt had been made to determine the specific etiologic diagnosis in as many cases as possible. The following factors would appear to influence the success of such studies: 1) Criteria for case inclusion. Many non-viral conditions can simulate CNS viral infections and it is important to exclude as many of these cases as is reasonably possible. 2) Timing, number and types of specimens submitted for analysis. Specimens should be submitted from patients early in the course of illness. Multiple specimens and those from different sources (stool, CSF, throat swabs, etc.) increase the likelihood of diagnosis. 3) Virus isolation techniques should include the use of both primary monkey kidney tissue culture and suckling mice, at least. Some Coxsackie A virus strains are readily isolated only in suckling mice. 4) Necessarily, these studies have usually relied on virus isolation ± serological evidence of infection with the homotypic enterovirus. Due to the multiplicity of enteroviral types (Coxsackie viruses of Group A, types 1-24; Coxsackie viruses of Group B, types 1-6; and ECHO viruses, types 1-34) it is not possible to test for infection with most of these agents by serological means alone (28). Conceivably, if this were possible, cases of infection in which the virus was not isolated might be detected. The number of such cases should, however, be small. 5) Antigens used for serological diagnosis. These studies have, to a varying extent, tested paired sera against a pertinent number of antigens, e.g., Coxsackie virus A-9; Coxsackie viruses, Group B, mumps, lymphocytic choriomeningitis (LCM), herpes simplex virus, polioviruses, types 1-3, appropriate arboviruses, etc. CEV antigen was not used prior to 1964 and was not included in any of the series reviewed.

To illustrate the difficulties associated with case selection, the differential diagnosis of CNS viral infections will be reviewed. Of 120 patients referred to a Scottish hospital as cases of encephalitis, 52 were found during investigation to have other conditions (Table 3) (29).

TABLE 3

Final Diagnosis in Patients Not Having Encephalitis (10)

Diagnosis	Number
Cerebral abscess	8
Cerebral tumor	8
Subarachnoid hemorrhage	7
Cerebral atrophy	6
Disseminated sclerosis	5
Occlusive cerebrovascular lesion	4
Tuberculous meningitis	3
Idiopathic epilepsy	3
Subdural hematoma	2
Polyneuritis	2
Myocardial infarct	1
Drug overdose	1
Idiopathic hypoparathyroidism	1
No diagnosis made	1
Total:	52

Although extensive, this list does not include many other important differential diagnostic considerations. Prominent among these are partially treated bacterial meningitis, early bacterial meningitis (rare), early granulomatous meningitis (tuberculosis, fungi), leptospirosis, brucellosis and syphilis.

All the biases mentioned must be considered in attempting to ascertain what percentage of CNS viral infections are, in fact, caused by unknown agent(s). The prototype of these studies is the continuing series of investigations performed at the Walter Reed Army Institute of Research (5,6,23). Patient information and specimens were sent to Walter Reed from various military and Veterans Administration hospitals; > 90% were hospitalized in the U.S. The results of the two most recent published studies can be summarized as follows (Table 4) (6,23).

TABLE 4

Specific Etiology of CNS Syndromes of Viral Etiology,
Walter Reed Army Institute of Research
(1953-1957) (1958-1963)*

Etiological Agent	Number of Cases with Indicated Clinical Syndrome							
	(1953-1957)				(1958-1963)			
	Aseptic Meningitis	Encephalitis	Paralytic Disease	Total	Aseptic Meningitis	Encephalitis	Paralytic Disease	Total
Mumps	68	22	1	91	28	11	1	40
LCM	38	20	0	58	7	0	0	7
Herpes simplex	6	13	0	19	2	7	0	9
Polio	38	5	113	156	18	5	66	89
Coxsackie A	0	2	0	2	18	1	0	19
Coxsackie B	77	2	1	80	71	4	0	75
ECHO	51	1	1	53	55	3	1	59
Arboviruses	3	20	0	23	3	5	0	8
Other	6	4	0	10	0	7	0	7
Total Studied	412	128	144	684	365	84	107	556
% Unknown Etiology	30%	30%	19%	28%	45%	49%	36%	44%

* Revised to exclude cases of leptospirosis and tuberculosis

The per cent of cases of CNS viral infections of unknown etiology in the six series reviewed can be compared (Table 5) (6, 23-27).

TABLE 5

CNS Viral Diseases of Unknown Etiology*

Reference	Total Cases Studied	Per Cent With Unknown Etiology
6‡	684	28
23‡	556	44
24	511	35
25	407	46
26	391	41
27	310	46

* All clinical syndromes combined

‡ Revised to exclude cases of leptospirosis and tuberculosis

The number of CNS viral illnesses decreases with increasing age. The per cent of cases associated with enteroviruses would also appear to be less after 40 years of age, in keeping with the known age specific distribution of clinical illnesses caused by these agents. It is often difficult to establish an etiologic diagnosis in patients $\geq$ 40 years of age with a "viral infection of the CNS" (Table 6) (24).

TABLE 6

Age Distribution of CNS Viral Illnesses: Per Cent of Cases Associated With Enteroviruses and of Unknown Etiology

Age Group	Total Cases	Per Cent Associated With Enteroviruses	Per Cent With Unknown Etiology
0-9	243	55* (45)‡	29
10-19	117	55 (47)	40
20-29	88	55 (45)	34
30-39	37	43 (35)	43
40+	26	27 (15)	65
Total	511	53 (44)	35

* Polio, Coxsackie and ECHO viruses

‡ Coxsackie and ECHO viruses only

Other conclusions can be drawn from these six series. In general, specific etiologies are found most commonly in patients with paralytic poliomyelitis, less often in aseptic meningitis and least often in cases of encephalitis. Although Coxsackie and ECHO viruses can eachproduce paralytic poliomyelitis and encephalitis, by far the most common syndrome produced with these agents is aseptic meningitis. Coxsackie, ECHO and mumps viruses account for the majority of cases of aseptic meningitis in each of the respective series. There has been an absolute decrease in the numbers of cases of LCM, ascribed to a relative decline in the rural population (23).

Fatal cases of CNS viral infections have been studied and reported by investigators at Walter Reed (23). By a combination of serological and isolation (antemortem specimens, tissues obtained at autopsy) methods, during the period 1958-1963, they were able to ascribe a viral etiology to 15 of 16 fatal cases. Polioviruses accounted for 6; herpes simplex for 6; and Coxsackie B4, Eastern equine encephalitis and mumps for 1 each.

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Herpes Simplex Encephalitis

A promising therapeutic agent, 5-iodo-2'-deoxyuridine (IDU, IDUR), is presently available for treatment of this disorder, which carries a high mortality. Early recognition and reliable diagnosis thus become essential.

Virology: Herpes simplex virus (Herpesvirus hominis, HVH) is 145-200 mμ in diameter with a DNA core, a capsid with icosahedral symmetry and a surrounding envelope derived from host cell membrane (38). It is now clear that there are two types of herpes simplex virus, Type 1 and Type 2 (39). The distinction between the two types was originally based upon antigenic differences. More recently, other differences have been found (Table 7) (39).

TABLE 7

Differences Between Herpesvirus hominis Types 1 and 2

	Antigenic Type	
	Type 1	Type 2
I. Clinical	Infects primarily non-genital sites	Infects primarily genital sites
II. Epidemiological	Transmission primarily via non-genital route	Transmission primarily via genital route (venereal or mother-to-newborn)
III. Laboratory Host Systems*		
A. Tissue culture		
1. Cytopathic effect	Tight adhesion of rounded cells	Loose aggregation of rounded cells; syncytia common
2. Plaques	Small	Large
B. Chick embryo		
1. Pocks on CAM‡	Small	Large
2. Histological findings on CAM	Primarily ectodermal proliferation	Involvement of all membrane layers; syncytia more common
C. Mice		
Genital or intramuscular inoculation	Less neurotropic	More neurotropic

* Refers to fresh virus isolates

‡ Chorioallantoic membrane

Separation into Types 1 and 2 serves as an epidemiological marker. Nahmias and Dowdle typed 13 herpes isolates recovered from neonatal infections: 12/13 were Type 2. These same authors typed 28 isolates from non-neonatal CNS herpetic infections (spinal fluid, brain); all were Type 1. They have also reported that several Type 2 strains were more resistant to IDU than Type 1 strains (39).

Epidemiology: Most primary infections with herpes simplex virus are inapparent. In early childhood, herpetic gingivostomatitis is common. After infection, neutralizing and complement fixation (CF) antibodies appear. It is apparent from serological surveys that the majority of adults have had contact with this agent (Table 8) (40).

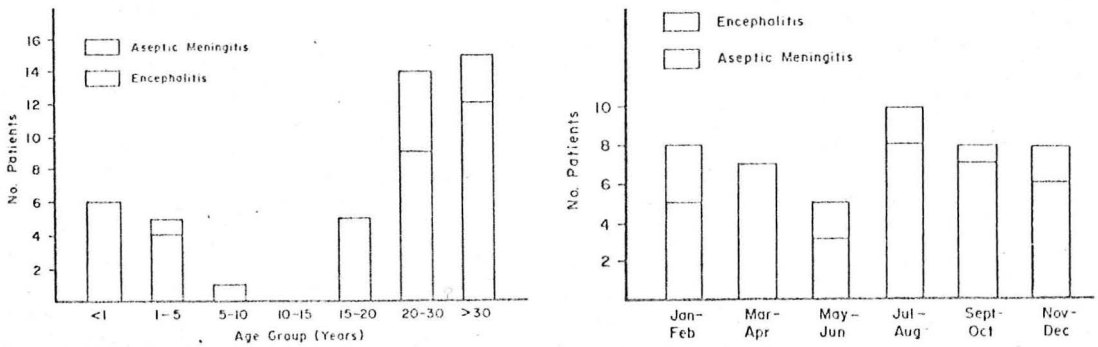
TABLE 8

Age-Frequency Distribution of Complement-Fixing Antibodies Against Herpes Simplex Virus

Age Group	Number of Sera Tested	Number Positive	Per Cent Positive	Titer Range
0-6 months	10	1	10	16*
7-12 mo.	7	1	14	8
1-3 years	22	4	14	4-16
4-6 years	30	5	17	8-32
7-9 years	30	2	9	8-16
10-14 years	20	4	20	4-16
15-19 years	20	5	25	8-16
20-29 years	32	14	44	4-32
30-39 years	20	11	55	8-16
≥ 40 years	20	16	75	4-32
Total	211	63	30	4-32

* Numbers are reciprocals of CF titers

The age distribution of herpesvirus associated CNS disease does not parallel the age periods when primary infection is most common. Cases of CNS disease occur throughout the year. Herpes simplex virus can induce aseptic meningitis or encephalitis (Figure 5) (41).



Age Distribution of Patients with Herpesvirus-Associated Central-Nervous-System Disease.

Seasonal Incidence of Herpesvirus-Associated Central-Nervous-System Disease.

FIGURE 5

Pathogenesis: In experimental animals, herpesvirus can reach the CNS either by neural (contiguous spread by infection of endoneural and perineural cells), olfactory (infection of respiratory mucosal and submucosal cells and direct penetration of the arachnoid at the cribriform plate or by infection of endoneural and perineural cells) or hematogenous routes. In man, only the hematogenous and olfactory routes appear probable (Table 9) (42).

TABLE 9

Pathways of Spread of Viruses to Central Nervous System in Animals and Man

Pathway of Spread	In Experimental Models	In Man*
Neural	Herpes simplex, B virus, rabies, and poliomyelitis viruses	Rabies, B virus and possibly poliomyelitis viruses
Olfactory	Herpes simplex and some arthropod-borne viruses	Possibly herpes simplex virus in adults
Hematogenous	Herpes simplex, lymphocytic choriomeningitis, and arthropod-borne viruses	Poliomyelitis, Coxsackie, ECHO, lymphocytic choriomeningitis and mumps viruses; herpes simplex virus in children; rubella and cytomegaloviruses in fetuses

* Probable

Neonatal infections with herpesvirus are usually generalized. The virus is disseminated via the hematogenous route and at autopsy can be isolated from many viscera, including the brain. The clinical course is overwhelming and usually fatal (43-45). In severely malnourished children, primary herpesvirus infections can also become disseminated and lead to fatality (46). Pathogenetic mechanisms, however, in most instances of herpesvirus associated CNS infections are not clear. The tendency for the localization of herpetic encephalitis to the orbital frontal and temporal lobes is consistent with spread along an olfactory pathway (42).

In non-neonatal cases, where the virus is localized to brain, it is probable that CNS disease can result both from extension of primary infection in a susceptible host and reactivation of a latent infection. The relative contribution of each mechanism is not clear. Evidence in favor of the extension of primary infection follows: 1) Concurrent herpetic gingivostomatitis is present in some cases. 2) Some cases of encephalitis have low or no initial antibody titer. 3) The rise in antibodies in these cases occurs slowly, as in primary infection, in contrast to the very prompt rise that can be seen with recurrent herpes labialis (47). Evidence favoring reactivation of a latent infection can also be presented: 1) Definite

histories of recurrent herpes labialis can be obtained in some (3/18) cases of herpetic encephalitis. 2) Cases of encephalitis can have elevated CF antibody titers early in the course of illness. 3) The age distribution of herpetic CNS illnesses does not parallel the age distribution of primary herpesvirus infections (48).

That herpesvirus can be latent in nervous tissue and produce recurrent disease seems clear from the following lines of evidence: 1) The production of latent infection and recurring encephalitis (induced by anaphylaxis or epinephrine) in the brains of experimentally infected rabbits. 2) The observation that disturbing the posterior sensory root of the fifth cranial nerve by operation results in herpetic vesicles in the areas innervated by the second and third peripheral divisions of the nerve in a highly significant number of patients, provided the ganglion has not been destroyed and the peripheral divisions are intact. 3) The occasional demonstration of virus in the spinal fluid of patients who show neither evidence of encephalitis nor herpetic eruptions (49-51).

Pathology: The most characteristic pathological picture found in patients with herpes encephalitis is an acute necrotizing encephalitis with Type A Cowdry inclusion bodies. Exceptions to this usual pattern have been observed (29). Perhaps the most definitive study on the pathology of herpes encephalitis is the one performed by Haymaker, Smith, Van Bogaert and De Chenar, who studied 37 cases of acute encephalitis with nuclear inclusions in adolescents and adults (52). Virus isolation and serological studies (neutralization and CF tests) established herpes simplex virus as the specific etiology in 8 (another case was probable). These authors noted that a striking and characteristic feature in all the cases was necrosis of the temporal cortex accompanied by tissue breakdown, often unilateral. The insular cortex was consistently affected. The hippocampal formation, the corpus callosum, the superior frontal gyrus shared in the necrosis. In 9/37 cases, there were lesions in frontal, parietal and/or occipital cortex, and in most of them the cortical lesions were most pronounced in regions adjoining the temporal lobe.

Hemorrhages, usually perivascular, and often extending into the adjacent necrotic nervous tissue, were very common. In some instances (5/37), these hemorrhages were large. Miller, Hesser and Tompkins pay particular importance to these areas of hemorrhage as a possible clue to the early diagnosis of herpes encephalitis. They state that these accumulations of erythrocytes ("erythrocyte lakes") often abut on the arachnoid membrane and are reflected in CSF changes (presence of erythrocytes and xanthochromia) (47).

Most instances of acute necrotizing encephalitis are probably due to herpes simplex virus. A retrospective, electron-microscopic study of 7 cases of acute necrotizing encephalitis revealed that 6 cases had particles resembling herpes simplex virus (53).

Clinical: The clinical and laboratory findings in series of herpetic CNS infections with 5 or more patients (excluding those primarily related to neonatal cases or disseminated infection) have been analyzed (Table 10) (29,41,47,48,52, 54-59). In instances where the clinical protocols are insufficiently detailed to reach a conclusion as to the per cent of patients involved, the appropriate space in the table has been left empty. For example, localizing neurological findings are extremely common in herpetic encephalitis. Most of the studies, however, do not contain enough information to state whether these were present or specifically sought after in the cases presented. Much of the clinical information in the

series analyzed is retrospective (chart review).

TABLE 10

Clinical and Laboratory Features of Herpes Simplex Virus Infections of the Central Nervous System

Ref.	No. of Patients	Diagnosis (% of Patients)*			Age Distribution % ≥ 30	% of Patients with AM‡	Case Fatality Ratio (%)	Sequelae in Survivors (% of Patients with E)
		V or V+S	Serological (S) Only	Pathological (Only)				
29	12	33	63	0	42	0	42	-
41	49	43	57	0	31	20	70	-
47	20	30	60	10	68	0	50	-
48	52	17	83	0	22	12	21	6/11= 55%
52	37	19	3	78	57	0	-	-
54	7	14	29	57	57	0	86	1/1 =100%
55	10	-	-	-	-	0	-	-
56	5	40	60	0	100	0	40	3/3 =100%
57	5	100	0	0	60	0	-	-
58	5	100	0	0	80	0	-	-
59a.	6 (IDU Rx)	-	-	0	-	0	33	0/4 = 0%
b.	7 (No IDU)	-	-	0	-	0	43	3/4 = 75%

TABLE 10 (Continued)

Ref.	Hallucinations (% of Patients With E)	Convulsions During Course (% Patients With E)	Localizing Neurological Findings (% Patients With E)	Papilledema (% Patients With E)	EEG (Pts. with E)	
					# Patients Examined	Abnormal (%)
29	-	-	-	-	-	-
41	-	64	78§	-	12	100
47	0	65	-	3/9=33%	-	-
48	-	-	-	-	-	-
52	1/18=6%	65	-	-	-	-
54	-	43	-	-	3	100
55	-	-	-	-	-	-
56	-	60	-	-	1	100
57	20	-	-	-	-	-
58	20	100	100	0	4	100
59a.	-	54	-	-	13	100
b.	-		-	-		

TABLE 10 (Continued)

Ref.	CSF						Radiologic Exams			
	Pleocytosis		RBCs or Xanthochromia		↑ Pressure		Brain Scan		Arteriogram	
	Pts.**	Abnormal (%)	Pts.	Abnormal (%)	Pts.	Abnormal (%)	Pts.	Abnormal (%)	Pts.	Abnormal (%)
29	-	-	12	33	-	-	-	-	-	-
41	43	91	-	-	43	16	-	-	12	17
47	-	-	20	55	-	-	-	-	-	-
48	18	94	-	-	-	-	-	-	-	-
52	37	100	37	30	-	-	-	-	-	-
54	7	86	7	43	-	-	-	-	5	80
55	-	-	-	-	-	-	-	-	-	-
56	5	80	5	0	5	0	-	-	-	-
57	-	-	-	-	-	-	-	-	-	-
58	5	100	-	-	-	-	-	-	2	100
59a. b.	13	69	13	0	- -	- -	6	50	6	17

* V or V+S. Diagnosis established by viral isolation or viral isolation + four-fold increase in CF antibody titer.
S. Diagnosis established by four-fold increase in CF antibody titer.
Pathological. Acute clinical course with acute necrotizing encephalitis and Type A Cowdry inclusion bodies.

‡ AM = aseptic meningitis. E = encephalitis.

§ Focal paralysis, focal seizures or both and asymmetric deep tendon or abdominal reflexes.

** Number of patients examined

Thus, although herpes simplex virus infections of the CNS can present as aseptic meningitis, the more common clinical presentation is that of a severe, often asymmetric encephalitis. Many of the cases are in mature adults ($\geq$ 30). Features in common with other encephalitides are fever, nuchal rigidity and disturbances in consciousness. The diagnosis of herpetic encephalitis may be suggested by the gravity of the illness in association with a history of hallucinations (usually related to smell or taste) and the presence of localizing neurological abnormalities on examination. Convulsions, focal and generalized, are common. Some of the patients may have papilledema. In a few, there is evidence of rapidly increasing intracranial pressure. Cerebrospinal fluid abnormalities are present in almost every case; lymphocytic pleocytosis with a normal glucose concentration are almost invariable findings. Erythrocytosis and xanthochromia in the CSF are suggestive. A characteristic mode of presentation is that of an expanding temporal lobe lesion.

Electroencephalograms in patients with encephalitis are invariably abnormal with either focal or generalized findings (58,60). Brain scan (61), ventriculography and arteriography can be abnormal, suggesting the presence of an intracerebral mass; however, these tests can be normal. The disease is highly lethal and survivors often have significant permanent sequelae.

Diagnosis: Exact etiologic diagnosis is dependent upon virus isolation, CF or neutralizing antibody titer rise in paired serum specimens and/or characteristic pathological findings (Table 11) (29).

TABLE 11

Virological Evidence of Herpes Infection in 12 Cases of Encephalitis

Age (years)	Sex	Herpes simplex isolation Brain	CSF	Herpes particles in brain (Electron microscopy)	CF serum titers for herpes simplex (1st/2nd serum)	Day of illness when sera collected (1st/2nd serum)
3	M	-	ND	ND	2048/2048	40/52
8	M	ND	-	ND	64/512	4/13
9	M	ND	-	ND	64/256	5/17
13	M	+	-	+	32/512	7/22
14	F	ND	ND	ND	2048/2048	23/30
17	F	+	-	+	<8/ND	7/ND
18	M	+	-	+	16/≥512	5/16
34	F	ND	ND	+	32/ND	5/ND
35	M	ND	-	ND	32/256	8/32
43	F	ND	-	ND	512/512	21/35
45	M	+	-	ND	<8/256	7/15
48	M	ND	-	ND	512/1024	22/33

ND = Not Done

In non-neonatal cases of encephalitis, herpes simplex virus is almost always restricted to brain. Virus isolations from CSF are extremely rare. The demonstration of virus in sites such as the nasopharynx is of doubtful etiologic significance. Since antibody titers rise slowly during the course of illness, rapid and reliable diagnosis depends on brain biopsy. Since these patients are often critically ill and tolerate any procedure poorly, the decision to perform this procedure must be carefully considered. Neurological and neurosurgical consultations are essential.

The site of biopsy should involve the most affected area. This can best be determined by the presence of localizing neurological abnormalities, electroencephalogram, brain scan, ventriculogram or arteriography. If localizing abnormalities are absent, biopsy from the anterior part of the non-dominant temporal lobe has been advocated (29).

Once obtained, the specimen should be submitted to the pathologist who then can search for the presence of Type A Cowdry inclusion bodies or herpes-like virus particles by electron microscopy. Immunofluorescence studies should be performed where these facilities are available. The biopsy should be submitted for viral culture. The characteristic cytopathic effect (CPE) associated with herpes simplex virus should become manifest within 2 to 7 days. A tentative diagnosis can be made at this time. Definitive identification of the virus by specific neutralization tests requires a longer period of time. Herpes simplex virus grows readily in a variety of cell cultures: rabbit kidney and human embryonic fibroblast cultures are among the most suitable and widely available.

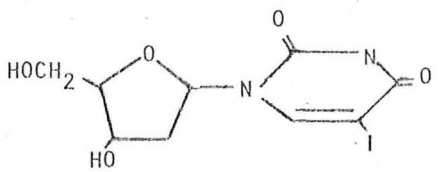
Positive viral cultures are dependent on the following factors: 1) Site of biopsy. Herpetic encephalitis is a localized process and the biopsy may miss the area where virus is present. 2) Time when biopsy is obtained. Late in the course of illness, virus may be absent. The virus can also be neutralized if the antibody content in the extracellular fluid is high.

Due to necessity for early and reliable diagnosis and the reluctance to perform brain biopsies on critically ill patients, there has been a search for alternative methods to establish a rapid diagnosis. Determination of neutralizing antibody titers, complement and non-complement dependent (C'+ and C'-) and calculation of the enhancement with C' addition, has been suggested as an approach (59,62,63). This is presently being evaluated.

Therapy: Intravenous fluid therapy is complicated by the following considerations: 1) Salt and water deficits due to excessive loss (fever) and diminished intake can be present. 2) Inappropriate antidiuretic hormone (ADH) secretion can occur (64,65). 3) Rarely, diabetes insipidus can ensue (65). 4) The elderly patient may have occult heart disease. Gastrointestinal tract ulceration has been reported and preventive measures, in this regard, should be considered (41).

If there is evidence of increasing intracranial pressure, intravenous hypertonic solutions should be tried. Corticosteroids probably should be held in abeyance because of uncertain effect on virus multiplication and natural recovery processes (interferon, antibody) (66). Neurosurgical decompression procedures may be necessary if the increase in intracranial pressure is progressive (67-69).

5-Iodo-2'-Deoxyuridine (IDU, IDUR)



IDU

Originally synthesized for use in tumor chemotherapy, this compound soon became recognized for its ability to inhibit the replication of DNA viruses. It acts as a thymidine analogue being successively converted to its mono-, di- and triphosphate and then incorporated into both host cell and viral DNA in place of thymidine. Electron microscopy of herpesvirus infected cells after IDU addition reveals large numbers of defective particles. Partially assembled capsomeres, filamentous material and ragged, irregularly sized particles without envelopes

result (70). The best explanation for these findings is that the DNA, resulting after IDU addition, is "fraudulent" and cannot code for processes related to assembly or for synthesis of structural proteins (71,72). Host cell DNA is also affected. In the intact organism, rapidly proliferating tissues (bone marrow, gastrointestinal tract, hair) are particularly involved (73).

IDU is a weak acid. It is poorly soluble; the pH of the solution must be adjusted to 8.2-8.6 before the compound can be brought into solution. IDU is prepared for intravenous use in 5% dextrose-water solutions (3-8 gm/1000 ml D5W). IDU is destroyed by autoclaving; hence, the solution must be filter sterilized before use.

In man, IDU is both rapidly excreted and metabolized (73). Four hours after completion of a 2-hour infusion of I^{131}-labeled IDU in 2 volunteers with terminal cancer, 44% of injected radioactivity had been collected in the urine; after 24 hours, approximately 90% had been excreted. During the 2-hour period of infusion, half the radioactivity excreted was in the form of IDU. After this period, progressively more radioactivity was found in metabolic products (5-iodouracil and iodide).

Side effects include leucopenia, thrombocytopenia, stomatitis, alopecia, and fingernail loss. Toxicity is dose related. 6/6 patients receiving a total of 600 mg/kg developed leucopenia (WBC < 4000), stomatitis and alopecia. Maximal leucocyte depression occurred 9 to 14 days after onset of therapy. Nausea and vomiting can be seen during infusion. A reasonable course of therapy has been outlined: (Total IDU dose = 430 mg/kg, administered intravenously over a 5-day period. 3 gm IDU/1000 ml D5W.) (59).

Individual case reports of IDU therapy have been encouraging (29,74-76). In a series of 6 patients with herpetic encephalitis treated with IDU, 2 died during the treatment course. The 4 survivors recovered without significant sequelae (Table 10) (59).

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St. Louis Encephalitis in Dallas: Status Report

In Dallas, after the 1966 epidemic (168 confirmed cases and 20 deaths), a mosquito control and surveillance program was initiated at approximately $100,000/year. Since 1966, there have been no confirmed human cases of SLE in Dallas. In 1968, one mosquito pool was positive for SLE virus, another for WEE virus. Hemagglutination inhibition tests in nestling birds and serially in sentinel chicken flocks placed throughout the city regularly reveal conversion to both SLE and WEE (~ 10% of chickens tested). Reported cases of SLE from other parts of the country since 1966 have been infrequent.

Etiologic Workup of the Patient With an Acute Viral Infection of the Central Nervous System:

Cases of encephalitis and paralytic poliomyelitis should be assigned priority. Since there is a promising agent for therapy of herpes simplex encephalitis and since practical means exist (conventional mosquito control procedures, aerial spray of insecticide) for the prevention of further cases of arboviral encephalitis (SLE and WEE), laboratory documentation of infection should be pursued in those patients whose clinical illnesses suggest these diagnoses. Cases of encephalitis in patients ≥ 35 years of age occurring in urban areas during summer and early autumn, in particular, should suggest SLE. Specific etiologic diagnoses should be sought, at the least, in some cases of aseptic meningitis, particularly if the incidence of this disorder is increased. In this way, the prevailing enterovirus types can be ascertained by year for a given locality. Viral agents infrequently associated with CNS infection should be considered in the individual clinical setting (infectious mononucleosis, lymphogranuloma venereum, influenza, etc.). A list of specimens to be submitted and recommended serological tests for each clinical syndrome is included (Texas) (Table 12) (84).

TABLE 12

Etiologic Investigation of Cases of Acute Infections of the Central Nervous System

Clinical Syndrome	Specimens Submitted for Viral Isolation*	Recommended Serological Tests‡
Paralytic poliomyelitis	CSF (≥ 3 ml) Stool (4-8 gm) or rectal swab (2 in BSS)§ ± Throat swab (2 in BSS) Autopsy specimens	CF tests for poliovirus, types I, II, III
Encephalitis	CSF (≥ 3 ml) Stool (4-8 gm) or rectal swab (2 in BSS) ± Throat swab (2 in BSS) Autopsy specimens	Neutralization tests against specific enterovirus isolated CF tests for herpes simplex virus,** ± mumps HAI tests for SLE, WEE (In rural East Texas--CEV, EEE)

TABLE 12 (Continued)

Clinical Syndrome	Specimens Submitted for Viral Isolation	Recommended Serological Tests
Aseptic meningitis	CSF (≥ 3 ml) Stool (4-8 gm) or rectal swab (2 in BSS) ± Throat swab (2 in BSS)	Neutralization tests against specific enterovirus isolated CF tests for herpes simplex virus, mumps

* Specimens should be kept frozen (-20°C) and shipped by fastest transportation, preferably on dry ice. If wet ice is used, specimens must be in watertight containers.

‡ Acute (collected at or near onset of illness) and convalescent (2-3 weeks after onset) sera

§ BSS (balanced salt solution)

** Further diagnostic tests considered in text of this review