MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

March 9, 1967

ST. LOUIS ENCEPHALITIS IN DALLAS - 1966

In the late summer of 1966, an epidemic of encephalitis caused by the St. Louis encephalitis virus occurred in Dallas County. 179 confirmed or suspected cases were documented, of which 134 had clinical encephalitis. As has been true of St. Louis encephalitis epidemics, there was an age-specific attack rate, increasing from less than 20 cases/100,000 population under the age of 50 to 70/100,000 in individuals 70 or over. Nineteen deaths were recorded, with all but two deaths in individuals over the age of 50. The first case was observed during the second week in July. An abrupt increase in incidence was noted during August, followed by a sharp decline in September.

The mosquito responsible for spread of this virus to man was Culex quinquefasciatus, which made up 96% of all mosquitoes caught by special teams during the time of study. Virus isolation was made from 62 of these mosquitoes prior to aerial spraying (infectivity rate of 1:167). Local control measures were initiated on August 15, and aerial spraying with malathion was undertaken from August 19 through August 27. Only two viral isolations of SLE virus were obtained post-spray, both collected 27 days after the spraying (infectivity rate 1:57,300). These data, along with the rapid fall in cases approximately 14-21 days post-spray, give strong support to the effectiveness of this massive spray program.

Ninety-one patients with laboratory-confirmed clinical cases of St. Louis encephalitis were seen at Parkland Memorial Hospital. Sequential prospective clinical studies were performed on these individuals and on 29 patients with cerebrospinal fluid pleocytosis not due to SLE. In addition, a number of special studies were performed to evaluate various system involvement as a consequence of this infection.

Clinical Features

	SLE	CNS Other Than SLE
Age (median)	53 years	23
Sex	51 M/49 F	61 M/39 F
Race - Cau/N/LA	39/49/3	17/10/2
Mortality	15%	3%
Significant underlying disease	35%	21%
(Mortality)	22%	
Duration - Stay	13 d	7 d

	SLE	CNS Other Than SLE
Symptoms		
Fever	99%	66%
Myalgia	16%	31%
Photophobia	13%	37%
Urinary Symptoms	10%	6%
Signs		
Altered Sensorium	69%	20%
Age > 40	84%	—
Nuchal Rigidity	66%	44%
Tremor	56%	20%
Age > 40	81%	—
Nystagmus	(48%)	(24%)
Suck and Snout Reflex	42%	6%
Plantar Extensor Response	28%	0
Cranial Nerve VII	20%	6%
Convulsions	12% (Mortality 55%)	0
Laboratory		
Hematocrit (<40)	40%	[illegible]
WBC > 12,000	28%	14%
< 4,000	1%	4%
BUN (> 25)	24% (Mortality 50%)	10%
Pyuria	44%	34%
Urine Cultures (Neg.)	84%	84%
SGOT (> 40)	25%	29%
EMG abnormal	4/6	—
Muscle Biopsy	Neg.	—
CSF		
Cells < 10	5%	0
> 100	37%	34%
> 500	2%	6%
Protein > 100	12%	6%
> 40	53%	69%
Sugar < 50 or 50%	0	0

Virus Isolation

10 Autopsies: 7 isolates, brain; 1 isolate (?), kidney

Special Studies

Cerebral Blood Flow Studies (Shapiro and Eisenberg): Five patients were studied, with one follow-up study. The most consistent finding was a normal cerebral blood flow in the presence of a moderate degree of hypocapnea, widened A-V O_2 and CO_2 differences, and normal to elevated cerebral O_2 uptake (conscious patients). The one comatose patient studied had a disproportionately high cerebral blood flow in relation to metabolic demand ("luxury-perfusion syndrome"). Hypoxia in these patients produced vasodilatation, but this was opposed by hypocapnea, giving a net effect of essentially normal flows which were high for the pCO_2 but too low for the hypoxia and/or metabolic demands.

Pituitary-Adrenal Axis: Nine patients were evaluated, selected because of the severity of their neurological involvement. Plasma 17-hydroxy corticoids were elevated in 3, and diurnal variation was reversed in 2. Urinary 17-OH corticoids were normal in all. Dexamethasone suppression (overnight) was absent in 2, only partial in 4, and normal in 3. A normal rise in 11-desoxycortisol occurred in 8 of 9 following the administration of metopirone. Plasma HOCS increased after IV insulin, whereas plasma growth hormone increased normally. Despite the severity of the CNS disease, no abnormality of the pituitary-adrenal axis was characterized. The findings reflect a normal response to stress.

ADH Secretion: Seventy-two patients were evaluated, 52 with SLE. Eighteen patients demonstrated hyponatremia and hypo-osmolality at the time of the study. There was no evidence of congestive heart failure, nephrosis, or cirrhosis. Renal function was normal in all but one. Six may have been salt depleted due to inadequate sodium intake. IV normal saline was administered to 12, but the hyponatremia persisted at a time that urine sodium concentration exceeded 35 mEq/L. Twenty other individuals with CSF pleocytosis not due to SLE had normal serum osmolality. The inappropriate secretion of ADH in these individuals may be due to hypothalamic involvement by the virus.

Hematology: Two individuals developed hemolysis secondary to G6PD deficiency in association with St. Louis encephalitis. No abnormality of platelet function or of clotting was noted.

General Reports and Reviews

1. Report on the St. Louis outbreak of encephalitis. Public Health Bulletin No. 214, January 1935.
2. Blattner, R. J., and Heys, F. M. Viral encephalitis. In: Advances in Pediatrics, Ed. by S. Z. Leirne. Year Book Medical Publishers, Inc., V. 12, 1962, pp. 11-119.
3. McAllister, R. M. Viral encephalitides. Ann. Rev. Med. 13:389, 1962.
4. Epidemic St. Louis encephalitis in Houston, 1964. A cooperative study. JAMA 193:139, 1965.

In 1932, an epidemic of encephalitis occurred in Paris, Illinois. The following summer, a similar epidemic of more than 1000 cases occurred in and around St. Louis and Kansas City, Missouri. The causative virus was isolated from human brain in 1933, and it was found to produce disease in monkeys and in mice. The virus was given the name St. Louis encephalitis agent; it is a member of the Group B arboviruses. Serological studies of this epidemic provided information that clinically inapparent infections were frequent. A mosquito vector was ruled out in the original report, but a PHS officer (Lumsden) concluded that either Culex pipiens or quinquefasciatus was the most likely vector. Study of later epidemics confirmed this astute observation. There is no apparent record of SLE infection prior to 1932.

The clinical characteristics were similar to Japanese B encephalitis, but not similar to the symptomatology of von Economo's encephalitis (encephalitis lethargica or "sleeping sickness"). During the 1933 epidemic, the age-specific attack rate was noted, as well as the increased mortality in the elderly (over 50% in cases > 70). Another epidemic occurred in St. Louis in 1937, during which more cases were noted in children.

Sporadic outbreaks have appeared in the past 30 years of SLE throughout the West and Central states. In the West, the disease is more rural and occurs in the same localities that have clinical cases of Western equine encephalitis (WEE). Males are affected more than females. In the South and Central states, it is an urban-suburban disease. The primary vectors in these areas are Culex pipiens and C. quinquefasciatus. These are domestic breeds and are preferentially "dirty water" breeders. Many outbreaks appear following a period of heavy rain which is followed by a drought, leaving collections of waste water in quantities adequate to result in the production of large populations of vectors. It also has been noted to present following unusually warm spring temperatures. The increase in cases in the rural West in 1965 was anticipated with this information.

St. Louis virus activity has been reported in Texas (Hidalgo County, Texas, 1954), Kentucky (lower Ohio River Valley, 1955), Trinidad (1955), Florida (1958), and Jamaica (1963). The Tampa Bay area of Florida experienced repeated outbreaks in 1959, 1961 and 1962. In 1964, an epidemic appeared in Houston, with the total number of cases confirmed or presumed due to SLE exceeding 200. Again, the progressing age-specific attack rate and high fatality rate in the elderly was noted. Pre-existing Group B arbovirus antibody was noted, presumably due to dengue infection in earlier years. Inhabitants of inadequately screened premises experienced a significant infection rate, whereas residents

of screened or air-conditioned premises were relatively protected. Evidence was obtained that general dispersion of SLE virus did not occur. Vector control was attempted with malathion spraying from trucks and by larviciding roadside ditches with diesel oil. Late summer rains reinforced mosquito breeding, but the number of older mosquitoes (presumably infected) markedly decreased.

Epidemiology

5. Kissling, R. E. The arthropod-borne viruses of man and other animals. Ann. Rev. Microbiology 14:261, 1960.
6. Sulkin, S. E., Sims, R. A., and Allen, R. Isolation of St. Louis encephalitis virus from bats in Texas. Science 152:223, 1966.

Research with mosquitoes has demonstrated that the culicine species have an 80% to 100% transmission efficiency, with an incubation period of from 12 to 19 days. Wild birds and chickens can become infected, but do not become ill. This is in favor of a long and close host-parasite association. The overwintering mechanism remains a problem. Mites have been postulated as such an overwinter host, but this cannot be confirmed. A recent report from Utah indicated that snakes are a possible overwintering host for WEE virus, but further work has not confirmed that they harbor SLE virus. Sulkin and others have reported the recovery of SLE virus from the blood of a Mexican free-tailed bat collected in the Houston area. Further work is underway to determine if Chiroptera may be the animal capable of filling the gap in the year-round transmission cycle of the SLE virus.

7. Bond, J. O., Quick, D. T., Witte, J. J., and Oard, H. C. The 1962 epidemic of St. Louis encephalitis in Florida. I. Epidemiological observations. Am. J. Epidemiology 81:392, 1965.
8. Quick, D. T., Serfling, R. E., Sherman, I. L., and Casey, H. L. The 1962 epidemic of St. Louis encephalitis in an epidemic area. III. A survey for inapparent infections in an epidemic area. Am. J. Epidemiology 81:405, 1965.
9. Phillips, C. A., and Melnick, J. L. Community infection with St. Louis encephalitis virus. JAMA 193:207, 1965.
10. Luby, J. P., Miller, G., Gardner, P., Pigford, C. A., Henderson, B. E., and Eddins, D. The epidemiology of St. Louis encephalitis in Houston, Texas, 1964. (Unpublished observations)

References 7 and 8 are part of a series of studies of the most severe of these epidemics in 1962 in the Tampa Bay area. Again, this was a late summer epidemic with cases occurring into the third week in October. In some areas, there occurred a larger than usual number of aseptic meningitis cases in which presumably enteroviruses were involved. Differences in chronological occurrences in the area suggested a radial spread of infection, although this was not proved. Inapparent infections were quite high, especially in the Negro, and the ratio of inapparent to apparent infections was 39:1. The serological study suggested widespread dissemination of the SLE virus in clear water, rather than focal concentration, data which correlated with multiple SLE virus isolations from mosquitoes collected in various parts of the town.

Studies of the 1964 Houston epidemic revealed 243 confirmed and presumptive cases, consisting of:

Encephalitis with paralysis	8%
Encephalitis	60%
Aseptic meningitis	18%
Febrile headache	14%

Almost all patients over 70 years of age and older had encephalitis. Aseptic meningitis was most common in the younger age groups. Sex incidence was similar, but a higher attack rate was noted in the non-white population. When the county was divided into geographical regions, attack rates within the various regions were similar in non-white and white groups. Furthermore, attack rates for varying socioeconomic areas within each region showed no significant differences. Although clinical attack rates progressively increased with advancing age, inapparent attack rates did not change.

Pathology

11. Suzuki, M., and Phillips, C. A. St. Louis encephalitis: A histopathologic study of the fatal cases from the Houston epidemic in 1964. Arch. Path. 81:47, 1966.

This is a study of 15 autopsy cases from the Houston epidemic. Cellular infiltrates were noted in the leptomeninges in all cases, but no severe suppuration or exudation was noted. Changes of the nerve cells varied from case to case, but common changes included loss of Nissl substance, swelling of nuclei, and invasion of cells by microglial phagocytes. Severe lesions were most frequently noted in the substantia nigra, and in the most severe instances, few neurons remained as phagocytes containing melanin replaced them. Changes in the thalamus were present in 12 of 15, but these were not as severe as in the substantia nigra. Less severe involvement was noted in the pons, cerebellum and cerebral cortex. Perivascular infiltration was noted throughout the brain substance, but thrombosis was not found.

Clinical Features

A. General Features (including neurological)

12. Kunin, C. M., and Chin, T.D.Y. St. Louis encephalitis in Hidalgo County, Texas: Clinical and pathological features. Public Health Reports 72:519, 1957.
13. Quick, D. T., Thompson, J. M., and Bond, J. O. The 1962 epidemic of St. Louis encephalitis in Florida. IV. Clinical features of cases reported occurring in the Tampa Bay area. Am. J. Epidemiology 81:415, 1965.
14. Barrett, F. F., Yow, M. D., and Phillips, C. A. St. Louis encephalitis in children during the 1964 epidemic. JAMA 193:131, 1965.
15. Riggs, S., Smith, D. L., and Phillips, C. A. St. Louis encephalitis in adults during the 1964 Houston epidemic. JAMA 193:284, 1965.
16. Phillips, C. A., et al. Dual virus infections. JAMA 197:101, 1966.

17. Southern, P. M., Smith, J. W., Barnett, J. A., Luby, J. P., and Sanford, J. P. Clinical features of epidemic St. Louis encephalitis. Abstract submitted and paper to be read before American College of Physicians, April 10-14, 1967.

The onset of the illness is generally abrupt with high temperatures during the first day or two of illness, occurring without rigors. In the most severely affected individuals, temperature elevations persisted with major spikes to 104° and 105° in the early afternoon. Temperature elevation persisting longer than 5 to 6 days carried a poor prognosis. Headache was the most frequent chief complaint, and many declared the headache to be the most severe and unremitting pain they had ever experienced. Little or no localization was observed. It usually diminished in intensity as the temperature declined. Nausea with or without vomiting occurred in half of the cases.

Altered level of consciousness was present in all individuals with encephalitis; confusion was commonplace, especially in regard to orientation to time and place. Drowsiness and stupor was present in one-half of encephalitis cases, and coma occurred in 16% of these. Sixty per cent of the individuals with coma died. Tremors were noted in two-thirds, consisting of a continuous, gross trembling of the hands and face. Abnormal reflexes (especially plantar extensor responses) were present in one-fourth. Convulsions occurred in 4% of the individuals with encephalitis.

Papilledema was not noted, and sensory changes did not occur. Renal involvement was strongly suggested by the frequent urinary tract symptoms (51%), microscopic hematuria and albuminuria without bacteriuria, and elevation of the BUN. They noted that this elevation was transient in all but one case, who died with uremia.

The routine laboratory studies were not abnormal. Spinal fluid pressures were seldom elevated. In a number of individuals, lumbar puncture performed early showed no cells, but repeat examinations 24 to 48 hours later revealed pleocytosis. Polymorphonuclear leucocytes were the prominent cell early, but by the eighth day, all CSF cells were lymphocytes. The CSF sugar was entirely normal, and cultures were negative. CSF protein was modestly elevated in most, but levels exceeding 90 were present in only 10%.

During the Houston epidemic, Dr. Yow and her group did a careful analysis of children admitted to the hospital with meningoencephalitis. Confirmed cases of SLE totaled 26, and non-SLE cases numbered 24. Severe encephalitis was more frequent in the SLE group, although there was no mortality in the 50 children. Males predominated in the SLE group. All but one of the SLE cases had an abrupt onset, whereas 7 (29%) of non-SLE cases had biphasic illnesses. There was no significant difference in neurological findings or laboratory findings in the two groups. They concluded that differences were not sufficient to permit an etiological diagnosis on clinical grounds alone. Dual infection was present in six (SLE antibody plus viral isolations from gastrointestinal tract), and five of these six had seizures (as opposed to two seizures in the remaining 44 patients).

B. Other Organ System Involvement

18. Shapiro, W., and Eisenberg, S. Cerebral blood flow and metabolism in epidemic St. Louis encephalitis. (Submitted for publication)
19. Drewry, J., Unger, R., Kaplan, N., and Sanford, J. The pituitary-adrenal axis in encephalitis. (Abstract)

Abstracts summarized under special studies.

20. Beisel, W. R., Burton, J., Anderson, K. D., and Sawyer, W. D. Adrenocortical responses during tularemia in human subjects. J. Clin. End. & Metab. 27:61, 1967.

This is a study of the adrenal steroid changes which were present in volunteers experimentally infected with Francisella tularensis (tularemia). With the onset of symptoms, 17 OHCS excretion increased progressively to approximately double the control values. Furthermore, the normal diurnal variation was obliterated as afternoon plasma 17 OHCS were equal to morning levels. Within one day after therapy (and before fever or symptoms remitted completely), urinary OHCS excretion became normal. A review of steroid response to stress is included.

21. White, M., Rector, F. C., Carter, N. W., and Seldin, D. W. The occurrence of the inappropriate secretion of antidiuretic hormone in an epidemic of St. Louis encephalitis. (Unpublished observations)

22. Carter, N. W., Rector, F. C., and Seldin, D. W. Hyponatremia in cerebral disease resulting from the inappropriate secretion of antidiuretic hormone. New Eng. J. Med. 264:67, 1961.

These articles review the intriguing syndrome of inappropriate secretion of antidiuretic hormone (ADH), the hallmark of which is the unrelenting secretion of ADH in spite of water retention and hypotonicity of the body fluids. This has been described in a variety of conditions, including bronchogenic carcinoma, subarachnoid hemorrhage, encephalitis, head trauma, metastatic tumors to the brain, primary myxedema, intermittent porphyria, and occasionally episodically on an idiopathic basis.

23. Feldman, S., Luttwak, E. M., and Carmon, A. Acute neurogenic activation of chronic duodenal ulcers. Arch. Int. Med. 115:140, 1965.

A description of three cases of activation of chronic duodenal ulcer as manifested by hemorrhage or perforation in individuals with acute cerebrovascular accidents. All three had successfully undergone surgery. The article reviews the common association of upper gastrointestinal hemorrhage and intracranial lesions.

24. Burka, E. R., Weaver, Z., and Marks, P. A. Clinical spectrum of hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency. Ann. Int. Med. 64:817, 1966.

This article summarizes the experience at the Columbia-Presbyterian Medical Center of 102 patients with erythrocyte G6PD deficiency. It was noted that frequently an illness acted to precipitate hemolysis. Hemolysis in association with bacterial or viral infection was present in 45 of 73 episodes of hemolysis in which an illness was involved. This was equal to hemolytic events presumably secondary to a drug.

25. Utz, J.P. Viruria in man. In Progress in Medical Virology. Karger, Basel/New York, Vol. 6, 1964, pp. 71-81.

This review notes that virus isolations have been obtained from urine in 12 viral infections, including mumps, measles, rubella, enteroviral infections, cytomegalovirus disease, vaccinia, Russian Spring-Summer encephalitis, rabies, and lymphocytic choriomeningitis. Although pathology of the kidney and urinary symptoms have been pointed out (1,13), no virus isolations have been reported. The one isolation from the kidney in the Dallas epidemic has not been absolutely confirmed. Urine cultures of active cases will be of interest.

26. Meyer, H. M., Johnson, R. T., Crawford, I. P., Dascomb, H. E., and Rogers, N. G. Central nervous system syndromes of "viral" etiology. Am. J. Med. 29: 334, 1960.

This represents a comprehensive review of 713 cases of CNS viral illness studied at military and V.A. hospitals from 1953 to 1958. Greater than 70% of all patients with either syndromes of aseptic meningitis, encephalitis, or paralytic poliomyelitis had a specific etiological diagnosis. Aseptic meningitis, of diverse etiology, was a uniformly benign syndrome. Encephalitis, which was caused by many of the same viruses producing aseptic meningitis, varied in severity. Mumps, LCM, arbovirus and herpes simplex were the most frequent agents, and severe sequelae were more frequent in herpes simplex and arbovirus disease. Seasonal variability of the respective agents was prominent.

Treatment:

27. Ledbetter, E. O., and Sanford, J. P. Encephalitis (viral, postinfectious and postvaccinal). In Current Pediatric Therapy, 1967-68. Ed. by B. Kagan and S. Gellis. (To be published)

No specific therapy is available. Symptomatic therapy remains. All the important numerous considerations in total patient care are summarized here. No vaccine is available, and it would be of little use. A hyperimmune serum is available, but it will be of significant benefit for laboratory personnel.

Sequelae:

28. Azar, G. J., Bond, J. O., Chappell, G. L., and Lawton, A. H. Follow-up study of St. Louis encephalitis in Florida. Ann. Int. Med. 63:212, 1963.
29. Nyhan, W. L., and Richardson, F. Complications of meningitis. Ann. Rev. Med. 14:243, 1963.

Follow-up studies with significant findings are difficult to come by, since no baseline in the elderly individuals is available. Most complaints post-encephalitis are neurasthenic in nature. One can only speculate on whether such complaints are from pre-existing lesions which might tend to increase the likelihood of SLE infection or from the basic disease itself.