THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
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INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH MASSIVE DOSES OF SYSTEMIC PENICILLIN

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PURULENT MENINGITIS IN THE ADULT

The therapy of meningitis began its modern era with the study of Dowling and associates who treated pneumococcal meningitis with "massive" doses of parenteral penicillin and published their report in 1949. They achieved a 38% case fatality rate with 1,000,000 units of penicillin given every two hours. This amounted to 12,000,000 units of penicillin per day and is the definition of high dose penicillin. Their study compared historical controls and the prior usage of 200,000 to 1,000,000 units of penicillin intravenously per day in conjunction with daily intrathecal injections of 10,000-20,000 units of penicillin. In patients treated in this manner the case fatality rate was 62%.

In the antibiotic era, there have been several excellent reviews on the etiologies of purulent meningitis in the adult. Particularly notable are the experiences of Carpenter and Petersdorf in Seattle, Washington who accumulated data during the Fifties and Swartz and Dodge in Boston, Massachusetts who accumulated data during the Sixties (Table 1, Figure 1, Figure 2). These two classic contributions stressed the importance of the

Table 1

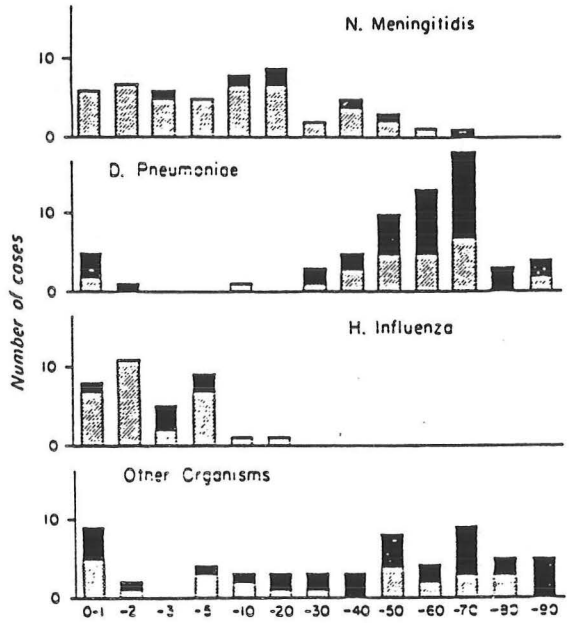
CAUSATIVE PATHOGENS IN BACTERIAL MENINGITIS

Etiologic Agent	No. Cases	No. Positive Cerebro-spinal Fluid Culture	No. Fatal Cases
Meningococcus	53	46	7 (13%)
Pneumococcus	63	59	37 (59%)
Hemophilus influenza	35	34	6 (18%)
Other	58	34	33 (57%)
Unknown agent	22	...	6
Mixed infections	9	9	9
Escherichia coli	9	9	7
Staphylococcus	8	6	5
Pseudomonas	3	3	1
Streptococcus	3	3	1
Paracolon	2	2	2
"Diphtheroid"	2	2	2

Am J Med 1962;33:262-275

pneumococcus and the meningococcus as the major pathogens in adult meningitis. Hemophilus influenzae was an uncommon pathogen being seen in only one adult patient in the Seattle series and only in four adults in the Boston series. In both of these reports Listeria monocytogenes was not noted as a significant pathogen and a clear distinction was not made between gram-negative meningitis in the adult medical patient and gram-negative meningitis that occurred in patients having had trauma to the central nervous system or a prior neurosurgical procedure. Staphylococcal infections also were not analyzed as patients who might present on the Medical Service or who

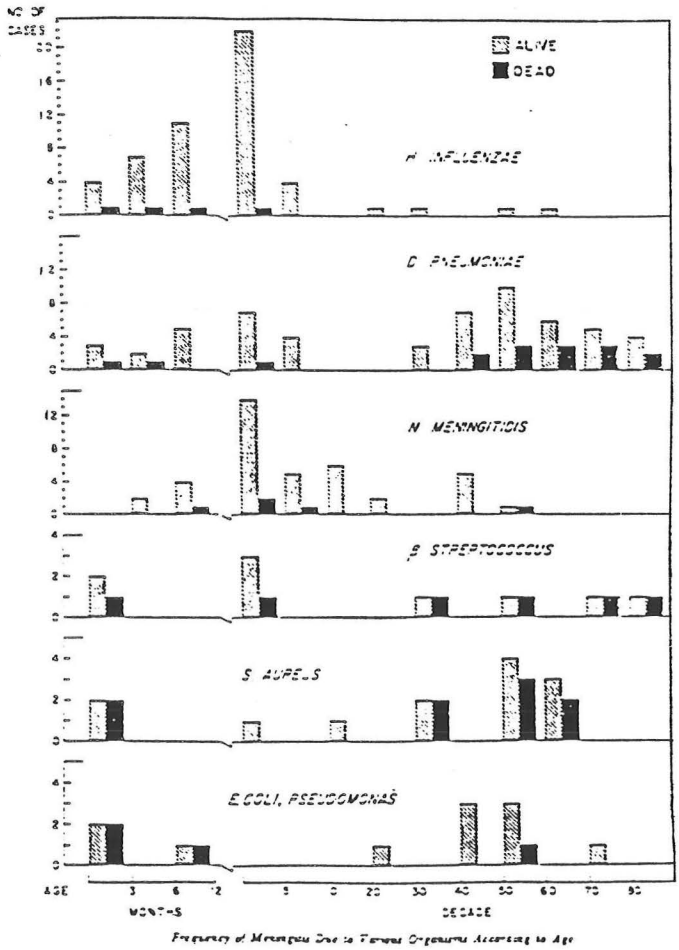
Figure 1



Relationship of age to etiologic organisms in bacterial meningitis.

Am J Med 1962;33:262-275

Figure 2



N Engl J Med 1965;272:725-731

were clearcut complications of trauma or neurosurgical procedures. These two series also were remarkable in pointing out the predominance of Hemophilus influenzae as a pathogen of younger childhood and the high mortality of pneumococcal meningitis in the adult, particularly with advancing age. The reasons underlying this high mortality were thought to be the age of the patient, the state of consciousness on arrival to a medical facility, the length of time between onset of the disease and the initiation of therapy, the presence of underlying disease, bacteremia and associated manifestations of pneumococcal sepsis like pneumonia or endocarditis.

It has only been since the early part of the 1970's that Listeria monocytogenes began to emerge as a major adult pathogen in pyogenic meningitis. In this decade also there were several papers that delineated the clear distinction between adult medical patients who developed gram-negative bacterial meningitis from adult patients who developed gram-negative bacillary meningitis after trauma or a neurosurgical procedure (Table 2).

Table 2

Etiologic Agents in Meningitis Caused by Gram-Negative Bacilli

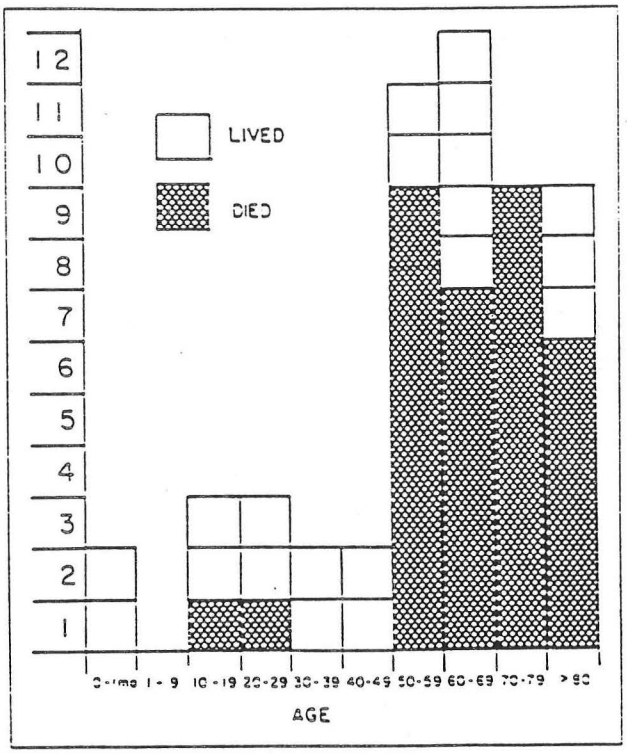
Organism	Postneuro-surgical	Spontaneous	Total
Escherichia coli	3 (1)*	7 (4)	10 (5)
Klebsiella pneumoniae	6 (2)	0	6 (2)
Acinetobacter calcoaceticus var. *anitratus*	4 (0)	1 (0)	5 (0)
Haemophilus influenzae	0	4 (0)	4 (0)
Pseudomonas aeruginosa	1 (0)	1 (1)	2 (1)
Citrobacter diversus	1 (0)	0	1 (0)
Salmonella type B	0	1 (0)	1 (0)
Proteus mirabilis	0	1 (1)	1 (1)
Total	15 (3)	15 (6)	30 (9)

* Number of patients (number who died).

Ann Intern Med 1980;93:253-260

In a study from New York City by Cherubin and associates based upon all cases reported to the New York City Health Department during 1972-1979, it was concluded that Listeria monocytogenes and gram-negative bacteria independent of trauma or surgery were not uncommon causes of meningitis in the adult (Figure 3). A single paper pointed to the occurrence of Hemophilus influenzae as a spontaneous pathogen in adult meningitis and commented upon its relative infrequency before that report. Gram-negative meningitis in the adult medical patient that originates without a known focus or that results from a urinary tract infection or gram-negative bacterial pneumonia has been shown to have a high case fatality rate in contrast to gram-negative bacillary meningitis that occurs on the neurosurgical service where the case fatality rate usually is less. All recent series have commented upon the fact that about 15-25% of patients presenting with frank signs and symptoms of bacterial meningitis have had negative cerebrospinal fluid and blood cultures. The exact etiologies of these cases have not been ascertained although it has generally been accepted that they represent the same spectrum of etiologic agents that occurred in the rest of the series.

Figure 3



Age. Distribution of 53 cases of meningitis due to Listeria monocytogenes.

Am J Med 1981;71:199-209

In the last 10 years at Parkland Memorial Hospital, at least 100 episodes of bacterial meningitis have been accumulated with a known etiology occurring in 98 patients (Table 3). An approximate additional 15 patients also had bacterial meningitis but did not have an identified specific etiologic agent. All of these patients presented to the Medical Service as cases of purulent meningitis. In the last 5 years, 25 episodes of known etiology in 24 patients of purulent meningitis following trauma, neurological or ENT surgery have also been accumulated. The predominant pathogen of purulent meningitis on the Medical Service at PMH in the last 10 years has been Streptococcus pneumoniae, accounting for 56% of the episodes. One patient, a man with CSF rhinorrhea had 3 episodes of meningitis. The first was with a group B streptococcus; following a surgical procedure to repair a cholesteatoma, he developed CSF rhinorrhea and had two subsequent episodes of pneumococcal meningitis. Neisseria meningitidis accounted for 16% of the episodes. Listeria monocytogenes was the third most frequent pathogen accounting for 7% of the episodes. Listeria monocytogenes was the single most important agent producing purulent meningitis on the Renal Transplant Service and also occurred in patients with lymphoma. It, however, was a significant pathogen in the aged patient and in alcoholic persons. Hemophilus influenzae occurred in 5% of the episodes. It was not possible to predict which patients might have had this organism as the pathogen based

Table 3

Etiology of Purulent Meningitis
on the Medical Service*

	Number, %
S. pneumoniae	56
N. meningitidis	16
L. monocytogenes	7
H. influenzae	5
S. aureus	5
Streptococci	
viridans streptococci	2
Enterococcus	2
Group B streptococcus	1
Gram negative bacteria (E. coli, K. pneumoniae)	5
N. gonorrhea	1

* One hundred episodes with known etiology in 98 patients

upon their identifying features. It occurred in a 20-year-old man, a 30-year-old woman with a middle ear infection, a middle-aged alcoholic man with lobar pneumonia and in two elderly patients, one of whom had a middle ear infection. The isolates were both type B and other types and were ampicillin sensitive and resistant. Staphylococcus aureus accounted for 5% of the episodes and generally did so in the setting of bacterial endocarditis or a focus like an abscess elsewhere in the body. One patient developed staphylococcal pneumonia following laboratory proven influenza and subsequently developed staphylocccal meningitis. Streptococci, including viridans streptococci, enterococci and Group B streptococci accounted for 5% of the isolates. The patient with the group B streptococcus has been mentioned previously. The other patients had underlying endocarditis but presented primarily as patients with purulent meningitis. There were 5 adult patients who had gram-negative bacterial meningitis, 4 had E. coli infections and one had a Klebsiella pneumoniae infection. The four patients with E. coli infections had underlying urinary tract infections. The single patient with Klebsiella pneumoniae had this organism isolated only from the cerebrospinal fluid. These patients with gram-negative bacterial meningitis had protracted clinical courses and poor outcomes. Neisseria gonorrheae was the pathogen in one of the cases. This series derived from patients at Parkland stresses the importance of the pneumococcus and meningococcus as pathogens but emphasizes that Listeria monocytogenes, Hemophilus influenzae, staphylococci, streptococci and gram-negative bacteria can contribute to the etiology of purulent meningitis on the Medical Service. These latter cases were clinically important because of their severity and because they were unexpected. Mistakes were made in the interpretation of the Gram stained CSF. At least two patients with Hemophilus influenzae meningitis were not

diagnosed as having that infection. In one case, the gram-negative bacilli were interpreted as gram-positive diplococci. The patient with staphylococcal pneumonia following influenza had the Gram stain of the CSF interpreted as showing pneumococci. The patient with Klebsiella pneumoniae meningitis was originally treated with penicillin alone. Delay in appropriate therapy for the last two patients resulted in adverse outcomes.

The advent of the third generation cephalosporins has virtually eliminated the need for chloramphenicol as an antimicrobial agent utilized in the therapy of purulent meningitis in the adult. Most infectious disease authorities would use chloramphenicol only as a transient maneuver awaiting the outcome of desensitizing the patient either to pencillcin or to a third-generation cephalosporin. Although the definition of high dose penicillin is 12,000,000 units per day, most physicians treat pneumococcal meningitis with 3 or 4 million units of penicillin q4h for a total of 14 days. If the patient is allergic to pencillin, an alternative drug like cefotaxime or ceftriaxone whould be utilized. In the therapy of adult meningitis, cefotaxime and ceftriaxone are considered to be equivalent antibiotics. On the Medical Service at Parkland, cefotaxime given as 3gms q6h is less expensive than ceftriaxone given as 2gms q12h, and this includes the cost of administering the antimicrobial. The meningococcus is also best treated with pencillin with cefotaxime used as a second line drug if the patient is allergic to penicillin. Therapy for meningococcal meningitis needs to be given only for 7 days. Penicillin therapy does not eradicate the meningococcus from the nasopharynx of the infected person, and it is necessary to give rifampin at a dose of 600mg twice a day for two days in order to eradicate carriage. Listeria monocytogenes is not susceptible to third generation cephalosporins; it is most susceptible to ampicillin followed by penicillin, vancomycin and sulfatrimethoprim. In the immunosuppressed host, meningitis due to Listeria monocytogenes should be treated longer than the usual 14 days. At least 28 days of therapy is necessary for cure. This is most probably because Listeria monocytogenes has the capacity to form small abscesses in brain and protracted therapy in the immunosuppressed patient is necessary in order to eradicate these residual foci. Hemophilus influenzae initially is best treated with cefotaxime but a change to ampicillin should be made if the isolate is beta lactamase negative. Staphylococcal infections are best treated with nafcillin or vancomycin. Viridans streptococci and enterococci should be treated with penicillin and ampicillin, respectively. Enterococci encountered in this present series have been ampicillin sensitive so that ampicillin and gentamicin to treat the coexisting endocarditis have been sufficient to cure the meningitis. In gram-negative bacterial meningitis other than H. influenzae, patients have had poor outcomes. In one patient, the cerebrospinal fluid glucose remained low until at least three weeks of cefotaxime had been given. Most authorities recognize that gram-negative bacterial meningitis in the aged adult has a poor prognosis and that prolonged therapy with a drug like cefotaxime is necessary. The case of Neisseria gonorrheae meningitis was treated successfully with penicillin. Initial therapy at the present time would have utilized cefotaxime or ceftriaxone because of the present prevalence in the community of penicillinase producing strains of Neisseria gonorrheae.

A well done Gram stain is necessary in the initial assessment of the patient with purulent meningitis. Latex agglutination tests for the antigens of Neisseria meningitidis, groups A and C, Hemophilus influenzae type B, and pneumonococci are helpful adjuncts, however, they are only as sensitive as the Gram stain and less specific. If a specific agent is not seen on the Gram stain at the time of the original assessment, that stain or an unstained slide of CSF should be saved so that an experienced microbiologist can assess the results later. This can be helpful in that the Gram stain can be positive although the culture may be negative. If the Gram stain is negative, and before the results of the cultures become available, it seems most logical to initiate therapy with a combination of drugs. Many authorities would utilize ampicillin at 12gms a day plus cefotaxime at the same dosage or ceftriaxone. If staphylocci are suspected on epidemiological or clinical grounds, nafcillin or vancomycin plus cefotaxime would be acceptable empiric therapy. It should be remembered that vancomycin has an effect against Listeria monocytogenes whereas nafcillin does not. Vancomycin and cefotaxime are more expensive than ampicillin and cefotaxime and so if staphylococci are not suspected, cost considerations favor the use of the latter combination. After cultures return antibiotics can be changed. If no etiologic agent is uncovered, many authorities would utilize either penicillin or ampicillin and treat for a 14 day course as though they were treating pneumococcal meningitis.

Many patients with meningitis are treated with antimicrobial agents before they finally come to the hospital and have a diagnosis of meningitis made by lumbar puncture. There are problems in dealing with these patients. Generally, in most patients the antimicrobial therapy has been in low dose and for only a short time before the definitive diagnosis of meningitis has been made. It is generally thought that such antimicrobial therapy may have no effect or may render blood and CSF cultures artifactually negative (Table 4). The latter may be particularly true as pertains to meningococcal

Table 4

EFFECT OF PRIOR TREATMENT ON THE RECOVERY OF SPECIFIC AGENTS OF BACTERIAL MENINGITIS

Complaint	Treated		Untreated	
	No.	%	No.	%
Neisseria meningitidis	10	6.6	31	19.6
Diplococcus pneumoniae	21	13.9	34	21.5
Haemophilus influenzae	42	27.3	46	29.1
No organisms isolated	63	41.6	19	12.0
Miscellaneous, including enteric Bacillus, Pseudomonas, Streptococcus, Staphylococcus, Listeria	16	10.6	28	17.8
Total	152	100.0	158	100.0

Am J Clin Pathol 1968;49:410-413

meningitis. Some studies have demonstrated that prior antimicrobial therapy in patients with purulent meningitis at low dosages and for a short period has no effect on white cell number, glucose or protein concentrations (Table 5). However, other studies have disputed this. The best evidence

Table 5

EFFECT OF PRIOR TREATMENT ON THE SPINAL FLUID CELL COUNT, GLUCOSE, AND PROTEIN CONCENTRATION IN BACTERIAL MENINGITIS

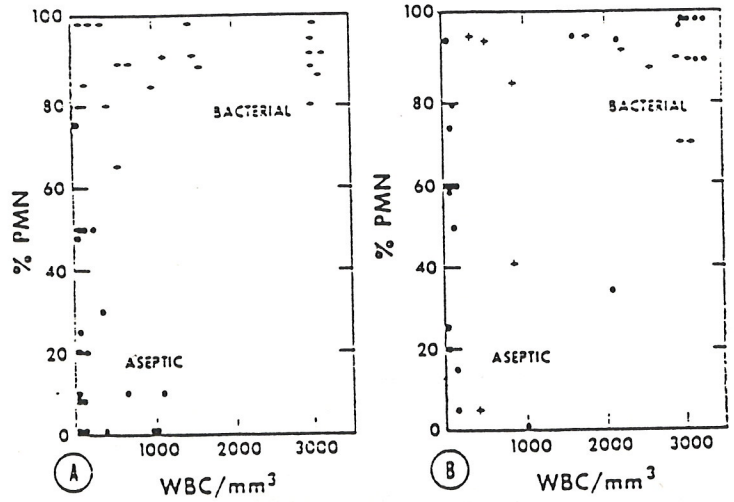
	W.B.C. Count		Protein Concentration		Glucose Concentration	
	Treated*	Untreated*	Treated†	Untreated†	Treated*	Untreated*
Haemophilus influenzae	3559 ± 864	5170 ± 471	97 ± 11	160 ± 24	27	27
Diplococcus pneumoniae	2283 ± 191	2788 ± 566	236 ± 63	376 ± 56	31	27
Neisseria meningitidis	5570 ± 1525	9122 ± 3037	188 ± 52	256 ± 36	27	26
No organisms isolated	3318 ± 593	3523 ± 736	126 ± 14	259 ± 47	35	35

* Average.
† Average in mg./100 ml.

Am J Clin Pathol 1968;49:410-413

that the white blood count and the percent of neutrophilic leukocytes in the differential can be affected in such a way to make bacterial meningitis appear like aseptic meningitis is demonstration in one study that two pretreated patients were found who had positive CSF bacterial cultures but had white blood cell counts and peripheral percentages of neutrophilic leukocytes like those occurring in aseptic meningitis. These two patients, however, both had CSF glucose concentration less than 45mg/dl (Figure 4). If antimicrobial therapy affects CSF parameters, another study indicates that

Figure 4



Multifactorial analysis of initial spinal fluid findings. + = Positive culture. ● = negative culture. *A*, Untreated patients. *B*, Partially treated patients.

J Pediatr 1973;83:220-225

the CSF protein concentration remains at 150mg/dl for at least 60 hours after onset of therapy. In managing pretreated patients, one method that appears logical, particularly when there may be a high incidence of aseptic meningitis occurring in the community at the same time, is to assess the patient clinically and perform a lumbar puncture. If the patient has been treated less than 48 hours and if the lumbar puncture has a cerebrospinal fluid formula that is consistent with aseptic meningitis (WBC<1200/mm^3, >40% plasma glucose, protein <150mg/dl) and the patient does not have an impairment in consciousness, is not hypotensive, does not have petechiae, or, in fact, does not appear particularly ill, then admit the patient into the hospital and repeat the lumbar puncture in 6-8 hours. It has been found in viral meningitis, that the initial neutrophilic leukocytosis that may occur early in its course has changed to a lymphocytic predominance at the end of 6-8 hours (Tables 6 and 7). If the patient does not improve, or worsens,

Table 6

Serial CSF Findings in Viral Meningitis

Laboratory Studies	Normal Values	Values at Initial and Subsequent Examinations: Admission (n = 16)	18-48 hr (n = 10)	5-12 Days (n = 11)	2-6 wk (n = 7)
WBCs/cu mm	0-5	201.00 ± 178.50	210.00 ± 165.3	92.00 ± 73.20	2.70 ± 0.70
Polymorphonuclear cells, % of total	0-1	41.75 ± 29.00	8.60 ± 8.78	9.00 ± 22.29	0.00
Protein concentration, mg/dL	14-45	48.38 ± 13.60	38.50 ± 18.24	34.50 ± 12.22	26.67 ± 4.99
Sugar level,† mg/dL	44-100	66.22 ± 8.61	73.20 ± 11.58	60.81 ± 10.81	68.67 ± 7.63

Arch Neurol 1979;36:581-582

Table 7

Clinical and Laboratory Characteristics of Patients with Aseptic Meningitis.

Interval between Lumbar Punctures*	Duration of Illness before Initial Lumbar Punctures	Initial Lumbar Puncture: Total Cells	Initial Lumbar Puncture: Polymorphonuclear Leukocytes	Repeat Lumbar Puncture: Total Cells	Repeat Lumbar Puncture: Polymorphonuclear Leukocytes
hr	*days*	*per mm³*	%	*per mm³*	%
6-8(31)†	1.7 ± 1.4‡	197.4 ± 224.7	71 ± 16	166.5 ± 171.7	27.5 ± 29.5
12(5)	1.5 ± 0.7	168.2 ± 86.5	68.4 ± 13.5	85.4 ± 86.4	21.0 ± 26.5
24(4)	2.1 ± 2.6	59.8 ± 42.7	76.3 ± 21.4	102.5 ± 121.3	26.5 ± 42.5
48-72(8)	1.5 ± 1.4	443 ± 336	87 ± 16	203 ± 136	3.6 ± 6.9

*Interval between initial & repeat lumbar punctures.
†Figures in parentheses represent no. of patients sampled.
‡Mean ± 1 SD.

N Engl J Med 1973;289:571-573

another lumbar puncture can be performed and appropriate empiric therapy initiated. Many physicians who deal with the problem of partially treated bacterial meningitis do not feel that routine treatment of these patients with antibiotics is indicated. An alternative course of treating the patient

until the cultures are determined to be negative and them stopping therapy does not appear reasonable since pretreatment can cause the Gram stain and the culture to become negative. If the patient has been pretreated for longer than 48 hours, then the safest way to proceed may be to place the patient on an antibiotic like ampicillin and treat for 10-14 days.

Meningitis in pediatric patients continues to be impressive because of the numbers of patients and because major changes and advances have occurred with the disease. Because of the high colonization rate with methicillin resistant Staphylococcus aureus in the Special Care Nursery, the usual etiology of neonatal meningitis (Group B streptococci, Listeria monocytogenes and gram-negative bacilli) has changed to reflect the fact that MRSA is now the major pathogen causing neonatal sepsis and meningitis in infants who have been through this facility. Another new factor in pediatric meningitis is the availability of potent vaccines against Hemophilus influenzae, type B. This will lead to a decrease in incidence of this form of meningitis in the future. A series of studies performed at Children's Medical Center and Parkland Hospital by Dr. George McCracken and his associates recently has demonstrated that hearing loss in Hemophilus influenzae meningitis can be prevented by the administration of dexamethasone concomitantly with antibiotic or, more effectively, before the antimicrobial is begun. The efficacy of dexamethasone in preventing deafness leads to the question of whether steroids could be used beneficially in a lethal disease like adult pneumococcal meningitis. Several studies have addressed this question, the first one of which took place at Parkland Memorial Hospital, was written by Drs. Ribble and Braude and published in an 1958 American Journal of Medicine article (Table 8). In adults treated with ACTH and hydrocortisone and penicillin, they reported only one death in 12 cases of pneumococcal meningitis. However, utilizing the same protocol a subsequent study at this

Table 8

	Treatment		
Day	Penicillin, Intravenously (millions of units)	ACTH, Intravenously (units)	Hydrocortisone, Intravenously (mg.)
0	30	60	60
1	30	60	160
2	30	60	100
3	30	40	100
4	30	60	90
5	30	60	90
6	15	60	75
7	15	60	75
8	15	60	45
9	10	60	0
10	0	40*	0

* Intramuscularly.

Am J Med 1958;24:68-79

hospital found a very high case fatality rate in the next nine patients. Lepper and Spies published an article on intravenous hydocortisone as supplemental treatment in acute bacterial meningitis. The dose of hydrocortisone used was 250 mg per 24 hours for 5 days in adults and older children. All ages were included in the study and the results on 57 patients with Hemophilus influenzae meningitis, 49 patients with meningococcal meningitis and 23 patients with pneumococcal meningitis were reported. They found an increase in frequency of subdural effusions in Hemophilus influenza meningitis in the hydrocortisone treated group but deafness was not studied. The routine use of hydrocortisone was more likely to be detrimental in patients with meningococcal meningitis. The number of patients with pneumococcal meningitis was too small to reach any statistically valid conclusions. A recent study at the U.S. Naval Hospital in Cairo, Egypt demonstrated efficacy with the use of steroids in pneumococcal meningitis but there were few patients who were elderly included in the study. In Spain, in a non-blinded, non-randomized study assessing dexamethasone therapy with phenytoin and bolus mannitol, the efficacy of the combination was demonstrated but historical controls were used, there were not many elderly persons and there was a relatively high number of patients with CSF rhinorrhea, an underlying condition which predisposes to pneumococcal meningitis but which has a usual good prognosis. At the present time, there is no evidence that the routine use of steroids has a beneficial effect in the therapy of adult bacterial meningitis.

The sequelae of meningitis due to the principle bacterial pathogens has been studied, both in the pediatric population and in adults. Unilateral or bilateral deafness appears to be the most common with seizures and mental defects next in frequency (Table 9).

Table 9

Neurologic Sequelae of Meningitis Due to Principal Pathogens.

Pathogen	Patients with Follow-up Data	Patients without Follow-up Data	Patients with No Residua	Patients with Mental Defect	Patients with Seizures	Patients with Hemiparesis or Tetraparesis	Patients with Bilateral Deafness	Patients with Hydrocephalus	Patients with Other Sequelae
D. pneumoniae:									
Pediatric	16	2	12	1	1	0	2	0	Deafness in 1 ear; 2d-degree trauma (2 cases).
Adult	17	4	12	0	1†	1	0	0	Anosmia (1 case); peripheral nerve lesion (2 cases).
H. influenzae:									
Pediatric	37	7	30	1	2	1	1	1	Vestibular disturbance (2d degree); streptomycin (1 case).
Adult	4	0	3	0	0	0	0	0	Deafness in 1 ear (1 case).
N. meningitidis:									
Pediatric	18	5	17	1	0	0	1‡	0	"Neurotic" (1 case)
Adult	7	1	4	0	0	0	0	0	Deafness in 1 ear (1 case); monocular blindness (2 cases).
Totals	99	19	78	3	4	2	4	1	

N Engl J Med 1965;272:1003-1010

The etiology of purulent meningitis following trauma or surgery was assessed at Parkland in 25 episodes of known etiology in 24 patients Table 10). Staphylococcus aureus was the predominant pathogen with one of

Table 10

Etiology of Purulent Meningitis
Following Trauma or Surgery*

	Number
S. aureus	
Methicillin sensitive	4
Methicillin resistant	1
S. epidermidis	4
Enterococcus	1
viridans streptococci	1
P. aeruginosa	4
S. marcescens	3
K. pneumoniae	3
E. cloacae	2
E. coli	1
H. influenzae	1

* Twenty-five episodes with known etiology in 24 patients

the isolates being methicillin resistant. Staphylococcus epidermidis was the second most common isolate followed by gram-negative bacteria, Pseudomonas aeruginosa, Serratia marcescens, Klebsiella pneumoniae, Enterobacter cloacae and E. coli. Hemophilus influenzae occurred as a single isolate in a patient with a recent epidosde of head trauma. Enterococcus and viridans streptococci each occurred in a single patient. Although purulent meningitis in this setting occurs with virulent pathogens, it usually has a reasonable prognosis. This may be because the disease is discovered early or that the patients have underlying good medical health. The therapy of S. aureus infections is with nafcillin while methicillin resistant S. aureus, coagulase negative staphylococci and enterococcal infections require vancomycin. With methicillin resistant S. aureus and coagulase negative staphylococci, the addition of rifampin may be necessary.

The introduction of the third-generation cephalosporin, ceftazidime has made the treatment of gram-negative bacterial meningitis much easier. This drug can be given at 2-3 gm q8h and has efficacy against most of the gram-negative bacteria that have occurred in this series. The drug has been utilized in the hospital for a 3-year period of time and unfortunately, there has been an increasing tendency for enterobacter isolates to have become resistant. At the present time, about 30% of Enterobacter cloacae isolates at PMH are resistant to ceftazidime. In the patient with gram-negative

bacterial meningitis occurring after trauma or neurosurgery, a reasonable empiric regimen would be ceftazidime intravenously and an aminoglycoside intrathecally along with the systemic administration of the aminoglycoside. The aminoglycoside could be gentamicin given daily at 8 mg intrathecally. A special gentamicin preparation without a preservative must be utilized. Amikacin could also be utilized and would have a broader gram negative rod coverage. The usual dose of amikacin to be administered intrathecally for the average adult is 20-30 mg. As soon as susceptibility studies have been performed demonstrating that the etiologic agent is susceptible to ceftazidime, the aminoglycoside can be discontinued. The length of treatment has been debated but a reasonable period of time would be 14 days after the culture becomes negative. Intrathecal aminoglycoside administration results in high lumbar space drug levels but little or no penetration into the ventricles. In gram-negative bacterial meningitis there is almost always an associated ventriculitis. However, even before third-generation cephalosporins, it was possible to obtain cures on a regular basis with the use of systemic and lumbar space gentamicin plus the administration of a drug like ticarcillin which was able to penetrate into the cerebrospinal fluid. The most difficult cases to treat have been methicillin resistant Staphylococcus aureus meningitis which has required therapy for as long as a month and patients in whom ceftazidime cannot be given because of drug resistance or hypersensitivity reactions.

Occasionally, sulfatrimethoprim can be used suscessfully when ceftazidime cannot be given but the patient has to be followed closely because of the possibility that the meningitis may recur. Imipenem may be able to be used but a high frequency of seizures has been noted in one series in which usual cases of meningitis were treated with the drug.

SUPPURATIVE INTRACRANIAL INFECTIONS

In this section, brain abscess, epidural abscess and subdural empyema will be examined. A major contribution to the knowledge of the etiology of brain abscesses was made by Drs. Heineman and Braude in 1963 in an article in which they clearly delineated the importance of anaerobic bacteria. These anaerobic bacteria emanated from underlying disease processes like chronic sinusitis and otitis media and chronic respiratory tract infections. Prior to this article, many brain abscesses had been found to be sterile. Now, in fact, most abscesses have specific bacterial etiologies. A second major advance in the management of brain abscesses occurred with the introduction of better antimicrobial agents like nafcillin, metronidazole, and the third-generation cephalosporins. Metronidazole was particularly important because it is usually bactericidal to many anaerobic bacteria and is a small molecule that can cross the blood brain barrier easily. The third advance in brain abscess management came with better imaging techniques. CT and MRI scans of the head, with and without contrast can be performed recurrently in patients and the size of brain abscesses and the associated edema can be assessed and therapy can be also gauged.

Brain abscesses arise from areas of infection around the face like otitis media, paranasal sinue infections and dental infections (Table 11). They can result from metastatic infection as in cases of sepsis or bacterial

Table 11

Etiology of Intracranial Infection in 42 Patients

Etiology		Patients (no.)
Otitic/paranasal sinus infection		8
Metastatic infection		19
Sepsis	5	
Pulmonary	7	
Congenital heart disease	7	
Trauma		9
Penetrating wounds	6	
Surgery	3	
Miscellaneous (postmeningitic)		1
Etiology unknown		5

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endocarditis, or from chronic pulmonary suppuration or in congenital heart disease where there is a right to left shunt or in some patients where there is a patent foramen ovale. Brain abscesses can also arise from trauma due to penetrating wounds or after surgery. Occasionally, brain abscess may result after meningitis and in some instances, a specific origin for the brain abscess is never found. The organism in brain abscesses reflect the underlying cause. For acute sinusitis, the major organisms are Streptococcus pneumoniae, Hemophilus influenzae, Moraxella catarrhalis, group A streptococci and anaerobic bacteria. In chronic sinusitis, the major pathogens are Staphylococcus aureus and anaerobic bacteria. In chronic otitis media, anaerobic bacteria and gram-negative bacilli predominate as the etiologic agents. In dental infections, viridans streptococci, especially Streptococcus intermedius (milleri) can be found. In chronic suppurative infections in the chest, anaerobic bacteria predominate.

Patients with brain abscesses commonly present with fever, headache, history of a recent seizure, mild obtundation and with a mild hemiparesis. Moderate papilledema may be seen on examination of the eye grounds whereas it is hardly ever seen in acute bacterial meningitis. The course is usually subacute but three quarters of the cases assembled in the Parkland series had symptoms of less than 14 days, a period shorter than seen in other series. The diagnosis of a brain abscess is critical to its management. CT scan of the head with contrast should be performed to delineate the extent of the abscess. The CT scan or sinus films can outline foci of suppuration like paranasal sinus infection. If a brain abscess is suspected, lumbar puncture should not be done because of the risk of herniation with asymmetrical intercranial hypertension and because this procedure is of limited diagnostic import since the CSF findings represent a sympathetic outpouring to the pyogenic process occurring in the parenchyma of the brain. After delineation of the brain abscess and its extent and the underlying probable source, antimicrobial therapy can be initiated on an empiric basis. Usually this consists of nafcillin or penicillin plus metronidazole. If an otitic focus is found or there is complicated sinus disease, particularly in immuno-suppressed patients like those with diabetes mellitus, gram-negative bacterial coverage should be initiated and would involve the addition of a third-generation cephalosporin like cefotaxime. Phenytoin can be given to control seizure activity. Dexamethasone is often given to control

intracranial hypertension. Of diagnostic importance is sampling the brain abscess and its source to obtain material for culture which can be processed for aerobic and anaerobic bacteria. Gram stain and culture simplify antimicrobial therapy. A large abscess or its presence in the posterior fossa may necessitate immediate surgery for drainage. After bacterial cultures have returned and susceptibilities are available, antibiotics can be shortened to a combination that may simply consist of high dose penicillin and metronidazole. Chloramphenicol is no longer utilized in brain abscesses because of the availability of metronidazole and third-generation cephalosporins which have better potential to kill the involved microorganisms. With recurrent CT scanning, it may be possible to treat the patient medically and let the brain abscess close completely. This usually requires a 4-6 week period of time. Medical therapy of brain abscess was not deemed possible before the advent of metronidazole or the better imaging techniques.

Epidural abscesses usually occur in the spine in the epidural space between the bone and the dura mater. Occasionally, they occur in the skull. Factors underlying epidural abscesses include hematogenous spread of an organism like Staphylococcus aureus, vertebral osteomyelitis, and other contiguous sources such as a paraspinus abscess. Patients with a spinal epidural abscess clinically have fever, local pain, tenderness at the site of the abscess, a sensory level, paraparesis or paraplegia and loss of control of bladder and bowel function. The major etiologic agents involved include Staphylococcus aureus, gram-negative bacteria, Streptococcus pyogenes, other streptococci and sometimes anaerobic bacteria (Table 12). Empiric antibiotic therapy might necessitate the use of a drug like nafcillin or vancomycin to cover Staphylococcus aureus and streptococci and also an agent to cover gram-negative bacteria like gentamicin or cefotaxime. At Parkland Hospital, a major problem in spinal epidural abscesses is the fact that Mycobacterium tuberculosis must also be included as an etiologic consideration (Pott's disease). It is impossible to distinguish tuberculosis definitively from a spinal epidural abscess of usual bacterial origin. The next step in

Table 12

Bacteriology of Spinal Epidural Abscess

Organism	No. of Patients
Staph aureus	21
Streptococcus pyogenes	1
Streptococcus (nonhemolytic)	1
Streptococcus (anaerobic)	1
Esch coli	3
Pseudomonas aeruginosa	2
Diplococcus pneumoniae	1
Mixed cultures:	
Bacteroides melaninogenicus, veillonella, anaerobic streptococcus	1
Staph albus, nonhemolytic streptococcus	1
Staph aureus, *S pyogenes*	1
Anaerobic propionibacterium, alpha-hemolytic streptococcus	1
No growth	5

N Engl J Med 1975;99:539-544

management is sampling the disease process, either the vertebral body or a contiguous abscess, to obtain material for culture and for pathologic examination. A tuberculin skin test should be placed. If a neurologic deficit is present, neurosurgical consultation is essential to effect decompression of the abscess and to prevent further neurological injury. Since many bacteria can be involved in the process it is mandatory to obtain sufficient material for culture. Major problems in the care of these patients relate back to the fact that empiric antibiotic therapy may not have covered the organisms actually present in the disease process. After surgery therapy of an epidural abscess consists of at least 4 weeks of appropriate antimicrobial drugs and at least 6 weeks of therapy if vertebral osteomyelitis is present.

Even in the era of the CT scan, the rapid diagnosis of a subdural empyema may be difficult. MRI is preferable for imaging. Arteriography used to be the best way to make the diagnosis. Subdural empyemas can occur in the spine but most commonly occur within the skull spreading in the subdural space that lies between the dura and the arachnoid. It is easy to dissect along this space and hence a subdural empyema has a large surface area but may not be thick so that it could be missed by a routine CT scan. The common diseases underlying subdural empyema are paranasal sinusitis, otitis media and mastoiditis, meningitis, intracranial surgery, head trauma and infrequently bacteremia and hematogenous spread. A classic syndrome consists of a young person, usually a male, with frontal sinusitis, who develops progressive obtundation and hemiparesis. Specific etiologic agents include Staphylococcus aureus, streptococci, Hemophilus influenzae, and anaerobic bacteria (Table 13). If a subdural empyema should eventuate after intracranial surgery or head trauma, gram-negative bacteria should be suspected. After MRI documentation of the presence of pus in the subdural space, empiric antibiotic therapy is initiated. This usually consists of the combination of nafcillin plus metronidazole with or without the addition of a third- generation cephalosporin like cefotaxime to cover gram-negative bacteria. Craniotomy on an emergency basis is essential to remove the pus in the subdural space. Lumbar puncture is contraindicated because of the presence of asymmetrical intracranial hypertension and because the CSF findings are similar to those of a brain abscess and reflect only a sympathetic pleocytosis in the presence of pus within the subdural space. The subdural space is drained as well as possible, cultures are taken and processed for aerobic and anaerobic bacteria. A second look, that is a craniotomy performed one or two days after the first, may be necessary in order to remove pus that has been left behind. Antimicrobial agents are simplified according to results of the culture and therapy is continued for a least a month. A subdural empyema represents an emergent neurosurgical situation in which there must be rapid evacuation of subdural pus otherwise the process can extend rapidly to involve other areas.

Table 13

Bacteriology of Subdural Empyema

Etiology	Cases	Organisms Cultured from Intracerebral Infection			
		Aerobic Isolates		Anaerobic Isolates	
Para-nasal Sinusitis	42	Streptococcal sp. (alpha hemolytic)	15	Streptococcal sp.	13
				Staphylococcal sp.	1
		Streptococcal sp. (beta hemolytic)	3	*P. acnes*	2
		Staphylococcal sp.	2		
		Hemophilus influenzae	1		
		Streptococcus pneumoniae	1		
		Other species	4		
Otitis Media and Mastoiditis	11	Streptococcal sp. (alpha hemolytic)	3	Streptococcal sp.	1
		Streptococcal sp. (beta hemolytic)	1	*B. fragilis*	1
		Staphylococcal sp.	3		
		Streptococcus pneumoniae	1		
Meningitis	8	*Hemophilus influenzae*	3		
		E. coli	1		
		Streptococcus pneumoniae	1		
Intracranial Surgery or Head Trauma	8	*S. aureus*	4		
		Enterobacteriaceae	3		
		Streptococcal sp.	1		
		Streptococcus pneumoniae	1		
Hematogenous	5	Streptococcal sp.	2	Streptococcal sp.	1
		Staphylococcal sp.	1		

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GRANULOMATOUS MENINGITIS

This particular section focuses on patients with tens to hundreds of cells in the CSF, with a glucose concentration less than 40mg/dl or 40% of the simultaneous plasma glucose and an elevated protein concentration. Although granulomatous meningitis and chronic meningitis have been used to describe this entity, each term has drawbacks. Meningeal carcinomatosis produces these findings and has no granulomas associated with it. Chronic meningitis, by definition, lasts for 4 weeks but many cases of tuberculous or cryptococcal meningitis come to medical attention after only a short course. Despite problems with terms, this CSF formula designates a particular class of patients who have significant disease, with the majority of cases being infectious in origin and requiring antimicrobial chemotherapy. The only benign conditions occurring within this differential diagnosis include mumps, lymphocytic choriomeningitis, some instances of varicella zoster virus infection, a stage in the evolution of a subarachnoid hemorrhage and chemical meningitis where a colloidal substance has been injected into the CSF. When hypoglycorrhacia occurs with herpes simplex virus infection, it usually connotes significant and advanced disease and necessitates specific therapeutic intervention (Table 14).

Table 14

The Differential Diagnosis of Granulomatous Meningitis

1. Cryptococcal meningitis
2. Tuberculous meningitis
3. Carcinoma, lymphoma
4. Other fungal etiologies
   Histoplasmosis, coccidioidomycosis, candidiasis, sporotrichosis, blastomycosis, mucormycosis, aspergillosis
5. Toxoplasmosis
6. Syphilis
7. Cysticercosis
8. Sarcoidosis
9. Brucellosis
10. Listeriosis
11. Whipple's disease
12. Nocardiosis
13. Evolution of SAH
14. Chemical reaction ususally to injection of a colloid into the CSF
15. Mumps, LCM, HSV, VZV

The differential diagnosis of granulomatous meningitis as defined is large and at Parkland hospital most commonly includes cryptococcal meningitis, tuberculous meningitis, carcinoma or lymphoma, other fungal causes, toxoplasmosis, syphilis, cysticercosis, sarcoidosis, brucellosis, listeriosis, Whipple's disease, and nocardiosis as well as the conditions already mentioned. The diagnosis involves a complete history and physical examination as well as laboratory studies to assess involvement of other organ systems. A lumbar puncture necessitates determination of the CSF glucose in relationship to a simultaneous plasma glucose, a CSF protein concentration, cell number and cell type by cytospin. The cytospin preparation should be looked at directly by the physician or by capable technologist; if any suspicion of abnormal cells are found a hemato-pathologist should be asked to examine the slide. Routine other tests on the CSF include an IgG synthetic rate, cryptococcal antigen determination, immunodifusion and complement fixation antibody studies for histoplasmosis, coccidoidomycosis, and blastomycosis, a VDRL and cultures for tuberculosis, fungi and aerobic bacteria. If indicated, a toxoplasma IFA, cysticercosis ELISA or lymphocyte marker studies should also be done on the CSF specimen. Serum cryptococcal antigen, fungal, brucella, and toxoplasma serological tests should be performed. If the CSF formula is as stated and benign conditions excluded, a CT and/or a MRA image of the head with contrast should be obtained to assess ventricular size and patency and to find an abnormal area for biopsy. It is probably not useful to do a blind biopsy without evidence by imaging of involvement of some portion of the brain. A tuberculin skin test with at least three controls should be applied. Consider repeating the tuberculin skin test in two weeks if negative because by the time there may be a boost in delayed type hypersensitivity by the first skin test or that therapy might have eliminated anergy. If complement fixation tests are sent to the State Health Laboratory, the laboratory should be called and asked to perform these test as soon as possible and to call you

with the specific results once they are done. Performing an angiotensin converting enzyme assay, a diffusion capacity for carbon monoxide, antinuclear antibody determination, are helpful additional tests. If lymph nodes are enlarged or if there is hepatic dysfunction, consider biopsying the lymph node or doing a bone marrow or a liver biopsy. If diarrhea is present, do a stool exam for acid fast organisms and consider a small bowel biopsy because Whipple's disease can present such a CSF formula. An HIV antibody test can lead to an emphasis on some diagnoses rather than others.

It may be necessary to biopsy an abnormal area of the brain if it can be reached. If the diagnosis has not been reached at this point in time and the patient has not improved or has had a downward course, an empiric therapeutic trial is indicated. The therapeutic trial should be initiated with isoniazid and rifampin. With the exception of mucomycocis and aspergillosis, the new antifungal agent fluconazole can be expected to have ameliorative effect on the other fungal meningitides and can be considered as an additional agent for therapeutic trial. Prior to fluconazole amphotericin was necessitated; this, in itself, did not cover meningitis due to coccidiodomycosis since intraventicular amphotericin was also needed. Occasional patients with central nervous system tumors have presented this CSF formula and the abnormal cells were not apparent on cytospin. Tumor markers such as α-fetoprotein or β-HCG might be obtained. It is usually inappropriate to use steroids without a specific diagnosis because they may exacerbate fungal diseases. There is a syndrome of granulomatous meningitis of unknown etiology. It is poorly characterized; several of these patients have come to postmortem examination and have had an underlying fungal disease. Others get better spontaneously without specific therapy. This last entity is a disease of exclusion and it is best to concentrate on specific causes that can be treated.

CASE REPORT. The patient was a 40-year-old white man employed at an oil company and who lived in Odessa, Texas. In the preceding 10 years, he had traveled around the world including several trips to Africa. He was well until the first of February when he developed a headache, malaise and mild confusion. He was seen by his personal physician and treated for 7 days with oral ampicillin. There was no improvement in his status and he had an episode of syncope for which he was hospitalized for 4 days but released without a specific diagnosis. On the 22nd of February, he was readmitted into the hospital with worsening confusion. A CT scan of the head was interpreted as being normal but a lumbar puncture showed 400 nucleated cells, 100% of which were lymphocytes, a glucose of 12mg/dl, and a protein of 130mg/dl. Cultures for aerobic bacteria were negative. He developed a right sixth nerve palsy and was treated for 7 days at the hospital with intravenous acyclovir. On February 26, he developed bilateral blindness.

He was transferred to Parkland Memorial Hospital on March 1 with a temperature of 38.5°, a right sixth nerve palsy, evidence of papilledema and a CT scan which showed an increase in the size of the ventricles. Lumbar puncture revealed 234 nucleated cells, 89% of which were lymphocytes, 8% of which were neutrophilic leukocytes and 2% monocytes. The opening pressure was 220mm of saline. The glucose was 19mg/dl and the total protein was 139mg/dl. Blood and cerebrospinal cultures were obtained and he was started on ampicillin and cefotaxime intravenously. On questioning, it was found

that he had apparently lived with someone who had tuberculosis in his 20's. A tuberculin skin test was positive. On ampicillin and cefotaxime, he continued to do poorly and then was started on intravenous amphotericin B along with isoniazid, rifampin and pyrazinamide. From his admission into the hospital on March 1 and his death on March 17, he had an unrelenting downhill neurological course. He became nonresponsive and developed seizure activity. On the 7th hospital day a right frontal ventriculostomy was performed. Serial CT scans of the head and an MRI scan revealed evidence of basilar meningitis, a communicating hydrocephalus and infarcts in the left caudate nucleus and then again in the right thalamus. A postmortem examination was performed.

VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEMS

Aseptic meningitis will not be considered in this section. An important differentiation needs to be made between primary infections of the central nervous system producing encephalitis and post-infectious encephalitis. The best comparison of these entities was made by Johnson and associates and focused on Japanese encephalitis and encephalitis occurring during the course of rubeola infection as examples (Table 15). In Japanese encephalitis, virus is present in brain causing acute pathological changes consisting of perivascular inflammatory changes, cell necrosis and microgleal nodules. The condition is associated with fever, cerebral dysfunction, and often times with nuchal rigidity. Virus can be demonstrated directly by culture or by any one of multiple techniques for the demonstration of viral antigens. In the encephalitis associated with rubeola, perivenous demyelination is seen, but virus is not present by culture or by any antigen detection techniques, like RNA-RNA hybridization or the use of immunofluorescence. The polymerase chain reaction was not used. In this classical post-infectious encephalitis, it is conceived that rubeola virus acts as an inciting agent for an immunological attack on the central nervous system which is severe but not associated directly with the presence of virus in the brain. Another classical post-infectious encephalitis can be seen during the course of varicella or during or after herpes zoster infection. Understanding the difference between primary infectious encephalitis and post-infectious encephalitis is important because of implications in terms of therapy.

The major problems encountered with severe infections of the central nervous system that are present in the central part of the country include herpes simplex encephalitis, St. Louis encephalitis and encephalitis of undertermined etiology. Herpes simplex encephalitis is important because acyclovir is effective therapy. Therapy with acyclovir has changed slightly because of the fact that it is now thought that to prevent the post-infectious encephalitis that may result after herpetic infection, a longer course of acyclovir (14-21 days), may be needed rather than the 10 day course previously considered optimal. St. Louis encephalitis is an important problem because it periodically manifests itself as an urban epidemic in the central and southern areas of the county and in Florida. Occasionally epidemics are found in the western part of the country usually in association with Western Equine encephalitis. The present lack of cases of St. Louis

Table 15

Comparison of Japanese encephalitis and postmeasles encephalomyelitis

Characteristic	Japanese encephalitis	Measles encephalomyelitis
Pathology	Acute perivascular and parenchymal inflammation (predominantly gray matter), neuronophagia	Acute perivenular inflammation (predominantly white matter), demyelination
Pathogenesis	Neurotropic virus, acute lytic infection of neurons	Lymphotropic virus, disruption of immunoregulation, virus not found in brain
Antibody	Early intrathecal synthesis of IgM and IgG antibody related to recovery	No intrathecal synthesis of antibody
Cellular response	T cells predominate in brain and spinal fluid (helper-to-suppressor ratio of 4-5:1), probably involved in clearance of virus-infected cells	Peripheral lymphocytes responsive to myellin basic protein possibly act as effector cells in demyelination.

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encephalitis is no indication that the problem has ceased because in the past, there were periods with an absence of cases which were followed by the occurrence of large epidemics. In 1976, for example, there were estimated to be at least 1850 laboratory documented cases of St. Louis encephalitis in the country and these occurred in a wide region from Texas in the south to Ontario in Canada in the north. The last entity to be considered is encephalitis of undetermined etiology. It has a specific epidemiology and constitutes by number one of the most common forms of encephalitis that is seen in certain regions of the country. Encephalitis of undertemined etiology is common in Texas and in the east and west south central portions of the country. It is also common in California and in the upper midwest. It occurs most commonly in the late summertime, and early autumn involves all ages but most commonly involves men in their 20's and 30's. It has a case fatality rate of 10%.

In order to illustrate the differences in St. Louis encephalitis, herpes simplex encephalitis and encephalitis of unknown etiology, three cases will be presented, but not necessarily in the order above so that certain specific points can be made.

CASE REPORT. This 63-year-old man was admitted into Parkland Memorial Hospital on August 10. He had fever, headache and malaise for three days. He had been previously healthy. Physical examination revealed a blood pressure of 160/80, a pulse rate of 100 and a temperature of 39°. He was disoriented to time and place. Rigidity of his extremities on passive motion was noted. He was diffusely tremulous. When his attention could be directed toward the performance of tasks, an increase in his tremulousness was noted. The hemoglobin was 12.8gms/dl, the white blood count was 6300. A urinalysis revealed 0-4 white blood cells per high power field. A lumbar puncture showed 156 nucleated cells per mm^3 consisting of 69 neutrophilic leukocytes and 87 lymphocytes. The glucose was 66 with a simultaneous plasma glucose of 86. The total protein concentration was 72mg/dl. The patient remains persistently febrile up to 40°. A second lumbar puncture performed the following day revealed an open pressure of 120cm, of H_2O with 67 nucleated cells of which were 61 lymphocytes and 6 neutrophilic leukocytes. On the 3rd hospital day he was hallucinating, a stiff neck was noted and there was weakness of the left arm. On the 4th day, pneumonia developed in the left lower lobe and the white blood count increased to 19,500/mm^3 with 67% neutrophilic leukocytes. The patient expired on the 5th hospital day.

CASE REPORT. The patient was a 35-year-old white man who was admitted on September 28. He had been previously healthy but had had a headache for 3-4 days. He then noted left sided weakness and slurred speech. When originally examined, he was able to follow commands. However, his mental state rapidly deteriorated. On physical examination he had a right gaze preference, a left facial nerve palsy and a left sided hemiparesis. He had sensory deficits on the left upper and lower extremities. Bilateral Babinski responses were noted. The admission white blood count was 17,200/mm^3. The differential included 88 neutrophilic leukocytes, 5 lymphocytes and 7 monocytes. Lumbar puncture was performed which revealed 44 red blood cells, 15 nucleated cells including 66% neutrophilis leukocytes, 9% lymphocytes and 25% monocytes. A MRI of the brain was obtained which revealed swelling of the white matter on the right, widening of gyri on the right and a right to left shift, consistent with cortical white matter edema vs. demyelination. An area of edema was noted in the cerebellum. The patient had a brain biopsy. Thirty-two days after hospital admission he had remarkedly improved, was sitting in bed reading, listening to the radio and was subsequently discharged to the care of his private neurologist.

CASE REPORT. The patient was a 15-year-old woman in the last month of her pregnancy. She was admitted on February 18th with a 1-2 day history of fever, chills, nausea, sore throat and headache. The temperature upon admission into the hospital was 38.6°. There was no clear source of fever but she was admitted into the hospital because of the late stage of her pregnancy. The estimated fetal weight was 6 lbs and the estimated fetal age was 35 weeks. The white blood count was 10,200/mm^3 with 89% neutrophilic leukocytes and 11% lymphocytes. The next day the temperature was 38.8°, no localizing manifestations for fever were apparent but the fetal heart rate had increased to 190 and the patient was placed into Labor and Delivery for close observation. The next day the maximum temperature was 39.2°, the fetal heart rate was again noted to be 190. The patient continued to complain of a headache but had no nuchal rigidity. The third day after admission at 8:00 in the morning, the patient was combative and dioriented. She had nystagmus

on right lateral gaze and began to have focal seizure activity originating in her right face and hand and which then became generalized. A lumbar puncture was done which revealed 398 cells, 7% neutrophilic leukocytes, 84% lymphocytes and 9% monocytes. The CSF glucose was 53 and the protein concentration was 181mg/dl. A CT scan of the head without contrast showed a low density area present in the right temporal lobe. Following ascertainment of the viability of the fetus, the patient had the induction of labor and subsequently underwent brain biopsy. Fifteen days after her entrance into the hospital she was alert, had no neurological defects and left the hospital with a normal infant.

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