Inf. Disease
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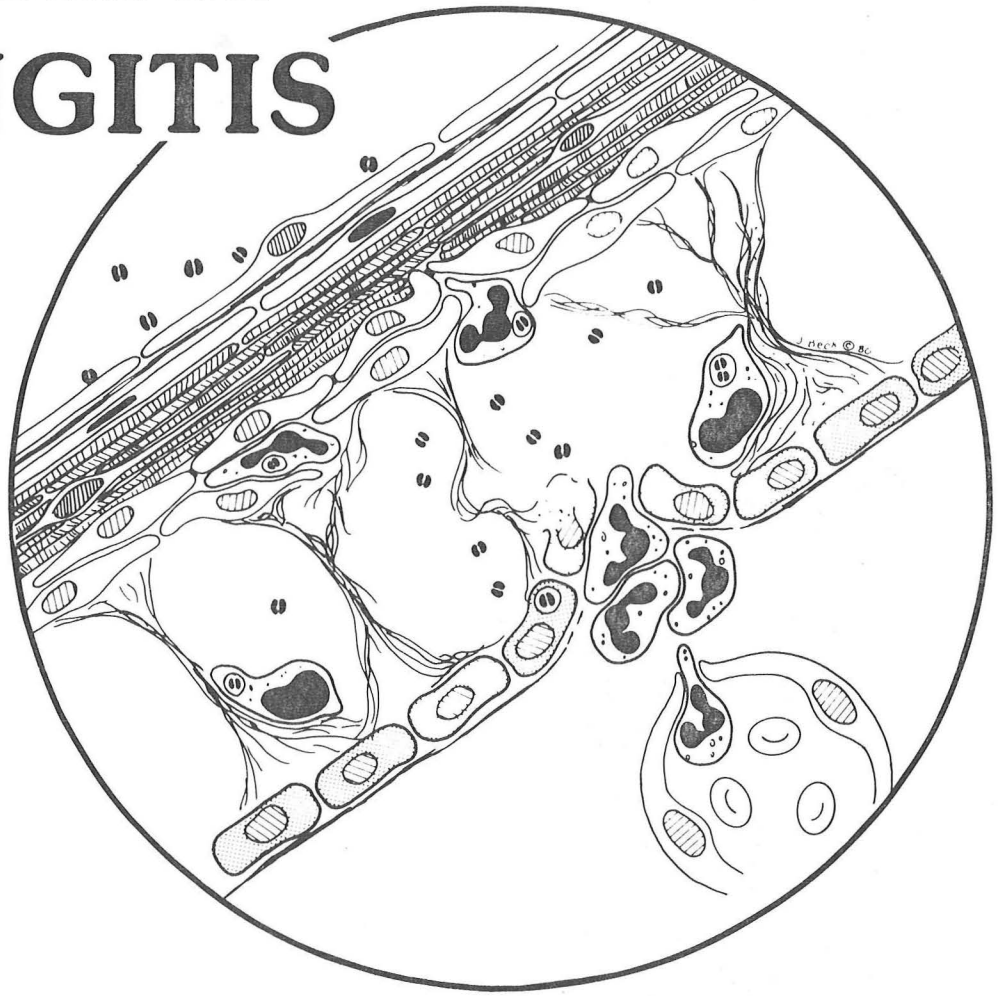
Medical Grand Rounds

BACTERIAL MENINGITIS



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ACUTE BACTERIAL MENINGITIS IN THE ADULT

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BACTERIAL MENINGITIS

I. History

Meningitis was probably first described by the Egyptian surgeons who authored the Edwin Smith Papyrus (Mettler, 1947), when they wrote of penetrating wounds of the skull followed by "stiffness of the neck" (ca. 2500 B.C.). For all their preoccupation with febrile disorders, medical writers failed for the ensuing four millenia to clearly describe non-traumatic meningitis. In medical writings from ancient times to the enlightenment, neurologic diagnoses were required to fit into a small number of fixed nosologic categories based on symptoms. Consequently a case of meningitis might be called phrenitis (febrile delirium), lethargy (febrile coma), opisthotonus, tetanus or, later, hydrocephalus (Mettler, 1947). Paul of Aegina, the seventh Byzantine physician, wrote of phrenitis as a febrile delirium due to "an inflammation of the membranes, the brain sometimes also being inflamed with them"; he apparently knew this without reference to necropsy material; de Meyserey described an "epidemic phrenitis" or "brain fever" in French military camps in the early 18th century (Mettler, 1947), which may have been meningococcal meningitis.

Thomas Sydenham (1686) may have been describing meningococcal meningitis, when he wrote of a "new fever" that appeared in London in the early spring of 1685:

> ...the patient has chills and flushes in turn; frequently complains of pain in his head and joints. There is also pain in the neck and in the fauces, less than in quinsy; and it comes on when the disease first makes its attack ...with young and sanguine subjects there will be purple blotches. Sometimes the so-called miliary eruptions are scattered over the body, not unlike measles, except that they are redder, and that when they go off they leave no such branny scales as may be seen after the departure of measles...of all the fevers I have ever seen, this attacks the brain most, and cannot be detached from it without great trouble and danger...at length when matters have been so mismanaged that the spirits are wholly thrown into confusion, an inordinate pulse sets in. With this there is jerking of the limbs and then death takes place speedily.

However credit for the description of bacterial meningitis is generally accorded to Gaspard Vieusseux who reported a spring epidemic of "malignant contagious fever" in Geneva in 1805, beginning "in a most peculiar and terrifying manner...in a district inhabited by poor people, dirty, and in whom the manner of life favored the development of every contagious disease". Two large neighboring families became ill in rapid succession, all dying in 14-24 hours.

> As a consequence, all the furniture and clothing of the two families were burned. The individuals were transported elsewhere and their dwellings...white-washed and disinfected with the greatest care.
>
> At the end of 15 days a young man living in the house nearby was also attacked by the same disease and died between evening and morning, having a purple body even to the tips of his fingers...

> There appears a violent pain in the head, especially over the forehead; then there come pains of the heart, or vomiting of greenish matter, or stiffness of the spine, and in infants, convulsions.

Between 1805-1850 numerous accounts of malignant epidemics of "spotted fever" or "cerebrospinal fever" appeared in American and European medical literature with emergence of distinctions between "simple" (sporadic) and "epidemic meningitis", and the term "hydrocephalus" ceased to be applied to the disease. Horner (1829) on the basis of autopsy studies, considered meningitis to be an intrinsic part of the alcoholic syndrome. Rilliet subsequently enunciated the first "law of meningitis" in 1846 with his distinction between the basilar meningitis of tuberculosis and involvement of the convexities or generalized arachnoid involvement in "simple meningitis". Karl Georg Lange, was responsible for separating syphilitis meningitis from "simple" purulent meningitis in 1872. By the time the first edition of Osler's textbook appeared in 1892, bacterial meningitis was understood as a distinct pathologic and clinical entity. In 1880 Eberth described diplococci in subarachnoid pus; Gram in 1884 described both his stain and the staining characteristics of the "pneumoniemikrokokken" (White, 1938). Albert Fraenkel, in stormy competition with Friedländer's laboratory, was first to demonstrate the presence of pneumococci in subarachnoid pus in 1886. The following year Weichselbaum demonstrated a Gram-negative diplococcus in CSF. Osler himself describes an infant with fatal coliform meningitis following surgery for imperforate anus. The subsequent history of the pathogenesis of bacterial meningitis is rich with the names of illustrious investigators: Councilman & Mallory (1898), Flexner (1907), Wollstein (1911), Weed (1920) and Goodpasture.

II. Pathogenesis of Bacterial Meningitis

The Route of Invasion.

An otic focus of infection is found in 29-34% of cases of bacterial meningitis, recent head trauma in 5-7%, remote head trauma in 6%, sinusitis in 2% (Waring & Weinstein, 1948; Carpenter & Petersdorf, 1962; Swartz & Dodge, 1965). About 28% of cases have a distant docus of infection, e.g. pneumonia* (25%), endocarditis* (6%), urinary infection (2%), or cellulitis (6%) (Carpenter & Petersdorf, 1962; Waring & Weinstein, 1948). *Hemophilus influenzae* meningitis is most closely associated with otitis or pharyngitis; *S. pneumoniae* with pneumonia, and *N. meningitidis* with pharyngitis (Table 1). Cases associated with prior head trauma were most often due to the pneumococcus (52% of post-traumatic meningitis), however *S. aureus* and aerobic Gram negative rods are more common agents after three days in the hospital (Hand & Sanford, 1970). In an era when the

*The syndrome of pneumococcal meningitis, pneumonia and endocarditis is variously termed Austrian's triad or Osler's triad. It was first described by Colomiatti: Arch. Ital. Biol. 1:397, 1882.

natural course of untreated disease could be observed, Osler (1892) found meningitis in 8% of 100 autopsied cases of pneumonia and 12% of cases of "ulcerative endocarditis".

Table 1. Causative Organism and Associated Lesions in Bacterial Meningitis

Associated Condition	*S. pneumoniae* (63 cases)	*N. meningitidis* (53 cases)	*H. influenzae* (35 cases)
Otitis and/or Mastoiditis	22%	23%	60%
Pharyngitis	10	68	54
Head Trauma	19	2	6
Pneumonia	56	2	3
	100%	100%	100%

Of 209 cases reported by Carpenter & Petersdorf from King County Hospital, Seattle (1962)

In conformity with these observations, the routes of invasion of the subarachnoid space are classically said to be:

1. Hematogenous from a remote source;
2. Direct invasion through a traumatic, surgical or congenital dural defect; or
3. Spread from a contiguous focus.

But how does a meningotropic organism gain access to the subarachnoid space from the blood? How does an organism cross an intact dura into the subarachnoid space from an adjacent extradural site?

Spread from a contiguous focus. A standard medical textbook (Beeson & McDermott, 1975) suggests as a route of transit from an adjacent extradural site:

"that bacteria enter through a rent in the leptomeninges or that infection in a neighboring focus may render the meninges more permeable to microorganisms".

The organization of the dura mater probably precludes this explanation, unless inapparent congenital defects are present in 34% of cases of bacterial meningitis adjacent to the extradural suppurative focus. As illustrated in Fig. 1 and schematically

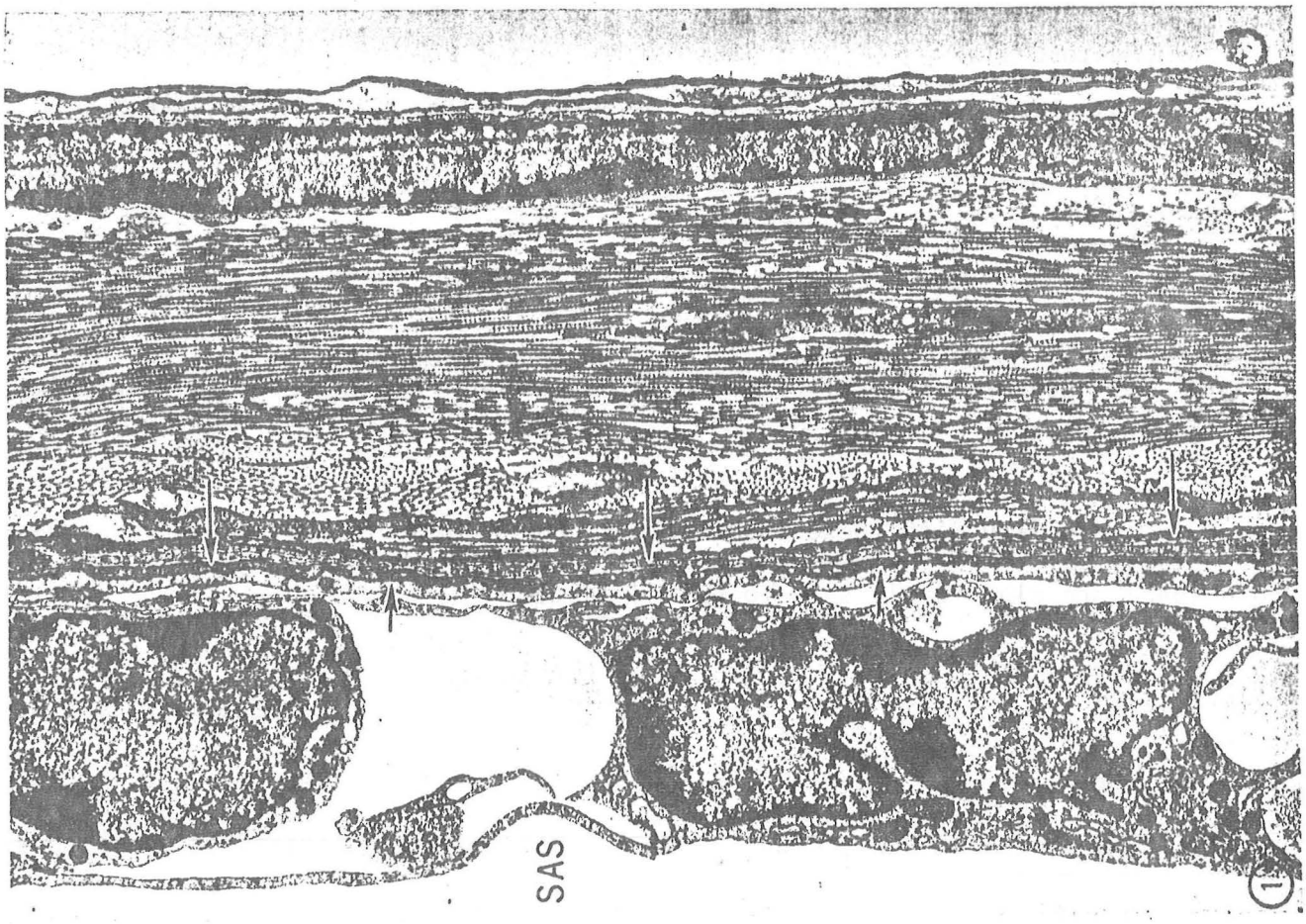


FIG. 1. Survey view of dura and adjacent arachnoid, spinal meninges. Both peripheral (far right) and medial (long arrows) dural borders consist of flattened cells indistinguishable from fibroblasts. Collagen and elastic fibers form the major bulk of the central core. Arachnoidal cells contain less dense cytoplasm. The dura-arachnoidal interface is readily identified (short arrows). Subarachnoid space (SAS) is noted on the left. Guinea pig; × 18,000, reduced.

in the cover figure, the dura consists of dense interlacing bundles of collagen arranged in transverse, longitudinal and oblique layers in a repeating pattern; elastic fibers composed of fine closely packed filaments are interwoven among the collagen (Waggener & Beggs, 1967). In addition the inner and outer borders are covered with thin overlapping sheets of attenuated cells displaying tight junctions. The outer cell layer of the arachnoid, which is adherent to the dura is also bound together by tight intercellular junctions (zonulae occludentes). The outer surface of the dura is fused to the cranial periosteum. The dura seems to present a formidable barrier to bacterial transit.

Table 2. Emissary Veins (E.V.)
Connecting Extracranial Sites with Dural Sinuses

Emissary	From	Sinus
Mastoid e.v.	Mastoid air cells Posterior auricular v. External occipital v.	Transverse (Lateral)
Parietal e.v.	Scalp veins	Superior sagittal
Condyloid foramen e.v.	Deep neck veins	Transverse
Hypoglossal canal e.v.	Deep neck veins	Marginal (occipital)
Ophthalmic v.	Angular vein of the face	Cavernous
Foramen ovale e.v.	Pterygoid plexus	Cavernous
Middle meningeal v.	Pterygoid plexus	Superior sagittal
Unnamed (foramen cecum)	Nasal veins	Superior sagittal

In earlier otolaryngologic literature it was suggested that infection might spread along sheaths of the cranial nerves VII and VIII or via the cochlear aqueduct between ear and subarachnoid space (Crowe, 1934; Perlman & Lindsay, 1939). However cranial nerves as they exit the subarachnoid space receive an investment of dura that becomes continuous with the nerve sheath. The cochlear aqueduct is no longer believed

to communicate with the subarachnoid space (Ballenger, 1977), and indeed its perilymph fluid differs substantially in composition from CSF (Table 3).

Table 3. Composition of Perilymph and CSF

	Perilymph	CSF
K	5.5-6.3	2.9 meq/l
Glucose	104	67 mg/dl
Protein	200	30 mg/dl
LDH	127-155	2 IU/ml

Ballenger, 1977.

On the other hand, meningeal veins coursing through the subarachnoid space (Fig. 2) present only a thin venous endothelium and an investment of arachnoid as barrier (Frederickson & Low, 1969). These veins drain the superficial cortex and arachnoid, piercing the dura to enter cerebral venous sinuses. No valves are present to prevent regurgitation of venous sinus blood into the tributary veins. The cerebral venous sinuses or dural veins are surrounded by an investment of dura and also receive blood from extradural sites via emissary veins (Table 2). Emissary veins drain such potentially infected sites as the mastoid air cells, ears, diploe of the skull, orbits, central portion of the face, and the paranasal sinuses.

Present in the dural venous sinuses and some tributary veins are arachnoid villi, microsopic transdural invasions of arachnoid into the sinuses, through which cerebrospinal fluid is discharged from the subarachnoid space. Their physiologic function is well established, i.e. to clear CSF essentially unfiltered, except particles more than 7 μ in diameter (Davson, 1967). The controversy over their precise anatomy and means of CSF clearance began with a debate between Harvey Cushing and Lewis Weed and remains contested. Several investigators have described a network of coapted tubules, penetrating the stroma of the villus and lined with "endothelium" continuous with venous

endothelium; they become progressively distended as CSF pressure rises above venous pressure, and collapse when the pressure difference falls below 2 cm of H_2O (Welch & Friedman, 1960; Shabo & Maxwell, 1968, Gomez, Potts & Deonarine, 1974). Others have noted that giant vacuoles form in "mesothelial" villus cells (Fig. 2) in proportion to the CSF/venous pressure ratio, and seem to incorporate tracers from the CSF side and discharge them into the sinus (Tripathi & Tripathi, 1974).

Whether CSF discharge is transcellular or intercellular, the arachnoid villus may represent a vulnerable site of bacterial invasion, although regurgitation of bacteria into CSF from blood would ordinarily be prevented.

Figure 2.

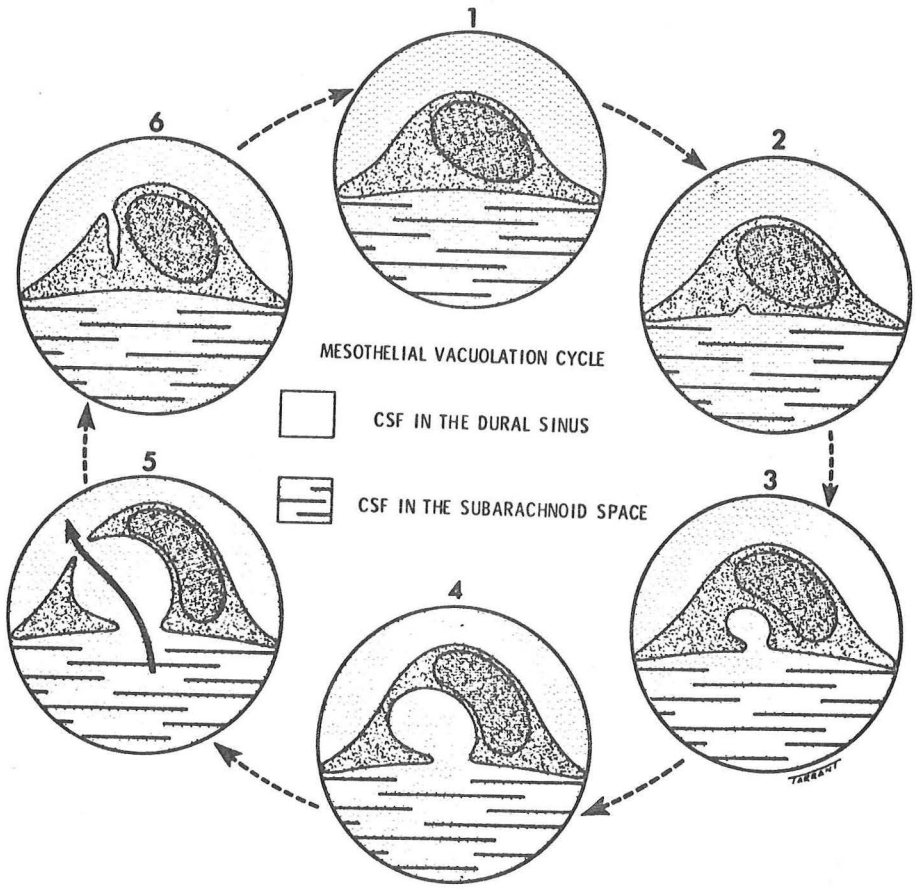


Diagram of drainage of aqueous humour or CSF across endothelium of canal of Schlemm or of arachnoid villus with a giant vacuole (3), a continuous channel (5), and exocytosis into venous blood (6). [Reproduced by permission of the Physiological Society 1978 from Tripathi and Tripathi (1974)]

Throughout an extensive literature on experimental meningitis beginning with Flexner (1907), investigators have found it difficult to produce meningitis by intravenous inoculations (Harter & Petersdorf, 1960). Most experimental models have relied on direct inoculation of bacteria into the cisterna magna or injuring the arachnoid by puncture during or shortly before induced bacteremia (Harter & Petersdorf, 1960; O'Donohughe, Schweid & Beaty, 1974; Petersdorf, Swarner & Garcia, 1962). In classic experiments at the Rockefeller Institute, Weed et al. (1920) observed that bacteremic cats did not develop meningitis, but when bacteremic cats were subjected to jugular venous compression, intravenous hypertonic infusions or an episode of cardiovascular shock, meningitis developed. Each of these procedures would be expected to produce either reduced flow in cerebral venous sinuses or frank regurgitation of dural venous blood into the tributary meningeal veins.

Recently Moxon et al. (1974) have produced a model of *Hemophilus influenzae* type B meningitis in infant rats by intranasal inoculation with 10^5 organisms. Bacteremia occurs rapidly and precedes meningitis; inflammation appears first in the dorsal longitudinal and lateral dural sinus walls, followed by meningitis. A similar pattern was demonstrated in a later study in which meningitis was defined as a positive CSF culture (Fig. 3). At 48 hours, 68% of the animals were bacteremic and

Cumulative incidence of bacteremia and meningitis after intranasal inoculation of 10-day-old rats with 10^7 *Haemophilus influenzae* type b. The rats were sacrificed at regular intervals, and blood and cerebrospinal fluid were cultured. Each point represents the number of positive cultures X 100/total number of blood (●) and cerebrospinal fluid (○) cultures.

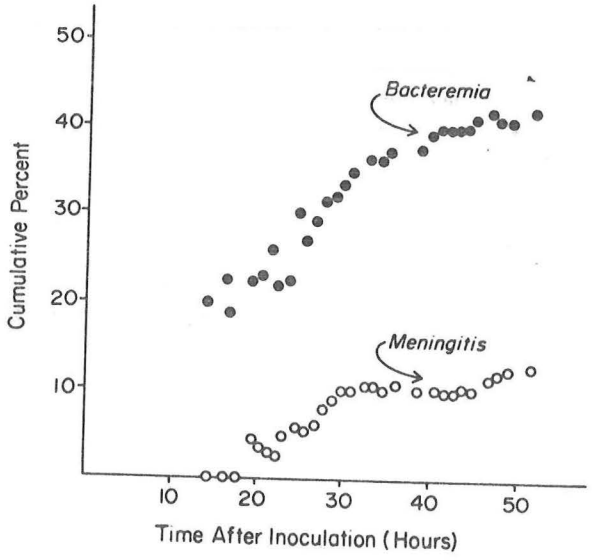


Figure 3.
Moxon & Murphy, 1977.

78% of these had meningitis. No animals without bacteremia had meningitis, and development of meningitis was directly related to the magnitude of bacteremia (Table 4; Moxon et al., 1977). Only 5% of animals developed leptomeningitis without pachymeningitis, but 19% had pachymeningitis alone. No rats developed ventriculitis. Studies using a direct fluorescein-conjugated anti-*H. influenzae* antiserum, demonstrated organisms in the nasal submucosa within hours, and concentration of organisms in the dural vein walls at 48 hours in all ten animals with leptomeningitis. Organisms were also found in the dural vein wall of animals who did not have leptomeningitis. Interestingly several rats developed otitis interna with or without meningitis.

Illustrating the importance of *portal of entry* is a subsequent study in this model (Moxon et al., 1977), in which infant rats were inoculated with either E. coli K1, a major agent of neonatal human meningitis, or *H. influenzae* type b. When *H. influenzae* was administered, via an orogastric tube only 15% became bacteremic, whereas 56% became bacteremic when E. coli K1 was administered by this route (Table 5).

Table 4. Relation of Bacteremia to Occurence of Meningitis: *H. influenzae* in Infant Rats

Bacteremia (cfu/ml)	% with Meningitis
Undetectable	0/95 = 0
10^2 - 10^3	0/4 = 0
10^3 - 10^4	2/13 = 16%
10^4 - 10^5	8/20 = 40%
10^5	12/12 = 100%

Moxon, Glode, Sutton & Robbins, 1977.

Table 5. Effect of Portal of Entry on Bacteremia

	Intranasal	Intragastric
E. coli K1	15%	56%*
E. coli K100	-	1.4%
H. Influenzae type b	56%	15%

*26% of those inoculated developed meningitis.
Moxon et al., 1977.

A non-K1 strain E. coli (Easter, K100) was less able to colonize the animals and rarely produced bacteremia (1.4%). *H. influenzae* produced bacteremia in only 11% when administered intragastrically.

Adherence to specific body surfaces has been shown to determine the ecological niche for many bacteria (Gibbons, 1977). Species that commonly cause endocarditis, i.e. enterococci, viridans streptococci and *S. aureus*, have the unique ability to attach to endocardium (Gould et al., 1975). Among strains of E. coli at least three different ligands in fimbria for intestinal cell surface determinants have been described, one attaching via mannose, one by β-D-galactosyl and one by N-acetyl glucosamine moieties; such a ligand seems to be required by enterotoxigenic E. coli to produce traveler's diarrhea and by K88 and K99 antigen-bearing E. coli to produce enterocolitis (Ober & Beachey, 1980). The attachment characteristics of meningotropic bacteria strains with respect to dural vein endothelium have not been examined, but it is intriguing that the K1 capular polysaccharide is identical to that of the group B meningococcus. Out of 250 capsular and somatic antigens, K1 is associated with 84% of infant meningitis (Robbins et al., 1974). Adherence characteristics of an organism may determine in the first instance whether it can establish itself at an epithelial surface in sufficient numbers for bacteremia to occur, and in the second instance, where it will enter tissue. Buddingh & Polk (1939) inoculated 15 day chick embryos

with meningococci and found that, regardless of the site of inoculation, bacteria consistently localized in three specific sites: dural sinuses, meninges and lungs. Similar observations have been made following chorioallantoic membrane inoculation of *H. influenzae* (Gallavan, 1937).

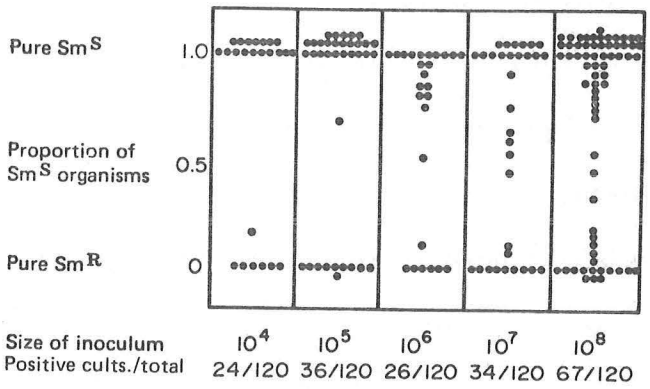
Moxon and Murphy (1978) have further shown that at low inocula, which may resemble natural infection more closely, the establishment of nasopharyngeal colonization by *H. influenzae* is dependent on the probability of a single organism persisting at the mucosal site. They inoculated infant rats with an equal mixture of streptomycin-sensitive (Sm^s) and streptomycin resistant (Sm^r) organisms (Table 6). If less than

Table 6. Rates of Recovery of Single Variants of *H. influenzae* After Inoculation of Mixed Sm^s and Sm^r Strains

Inoculum	Nasopharynx*	Blood*
10^2	42%	-
10^5	0.0	97%
10^8	0.0	68.7%

Moxon & Murphy, 1978, *% single variants among positive cultures

100 organisms were inoculated, only 40% of the animals had positive cultures 24 hours later; 42% of these were pure cultures of a single variant, Sm^r or Sm^s. At higher inocula ($>10^3$), which produced bacteremia (Fig. 4), again a single variant was uniformly recovered from blood at lower inocula, even when nasopharyngeal cultures were mixed. At higher inocula (10^8), 69% of blood isolates were still single variants. When the blood culture contained mixed variants, CSF cultures contained a single variant in 68% of animals with positive CSF cultures. When blood cultures contained a single variant, 98% of positive CSF cultures contained the same organism (Table 7). Thus the effect of inoculum size at each barrier along the route of invasion is to increase the likelihood that a single organism will breach the barrier.



Proportion of Sm^S and Sm^R variants of *H. influenzae* type b recovered from blood cultures. Groups of 40 rats each received inocula of 10^4–10^8 intranasal organisms. Cultures were obtained 2, 3, and 5 days after inoculation.

Figure 4. Moxon & Murphy, 1978.

Table 7. Comparison of CSF and Blood Cultures From Infant Rats Inoculated with Mixed Strains of *H. influenzae* (Sm^r + Sm^s)

CSF Culture	Sm^s	Sm^r	Mixed
Sm^s	25	0	7
Sm^r	0	14	6
Mixed	1	0	6

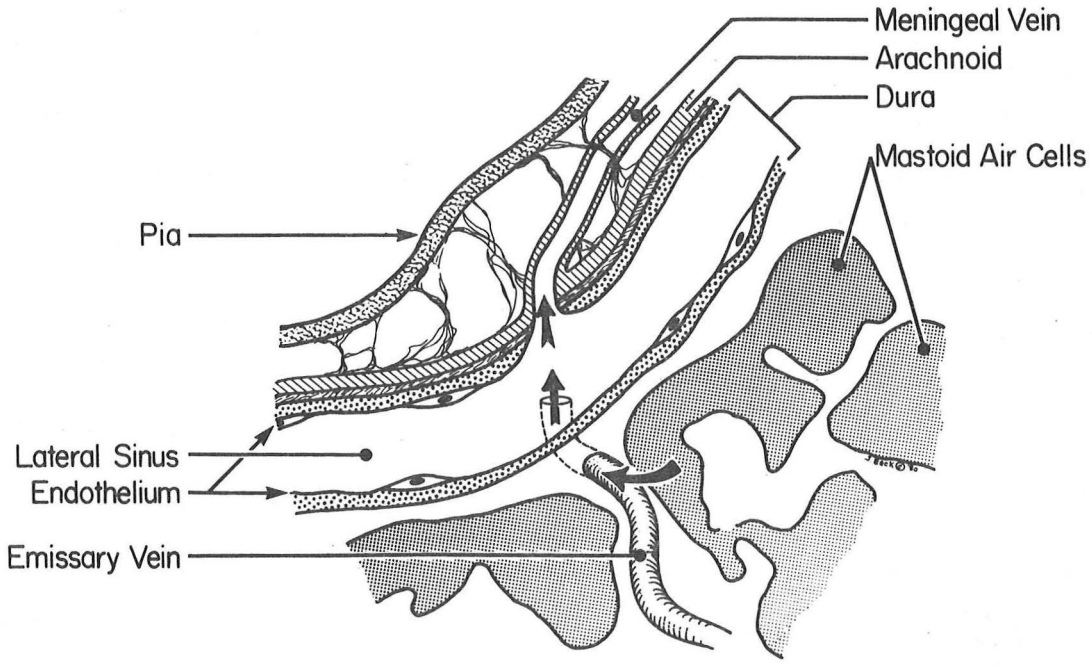


Figure 5.

A pathogenetic hypothesis. Speculating on these observations, the pathogenetic events in patients with meningitis and "contiguous" focus may be something like the following: Infection in the site of origin, for example a mastoid sinus, leads to bacteremia in an emissary vein considerably in excess of systemic bacteremia (Fig. 5). The larger the number of organisms delivered to this slow-flowing, low-pressure channel, the greater the likelihood of margination, regurgitation into tributary veins, and the endothelial attachment. Without attachment organisms would be swept back into the dural sinus. Attachment would similarly be required for invasion through arachnoid villi to occur.

Once in the subarachnoid space an organism faces a division of the mononuclear phagocyte system whose clearance capacity has not been studied. However, draped from the trabeculae of the subarachnoid space are phagocytic cells that also wander over and into both the pia and arachnoid membranes (Morse & Low, 1972). Phagocytosis in normal deficient CSF must take place without opsonins. Wood, Smith & Watson (1946), in classic studies with the pneumococcus, showed that phagocytosis and killing is efficient in the absence of opsonins, if the phagocyte is provided a surface against which to trap the organism. Pia cells are also phagocytic (cover figure), becoming very active in the first 2-4 hours after subarachnoid inoculation of bacteria (Nelson, Blinzinger & Hager, 1962). It is not inconceivable that during bacteremia, this system routinely, and successfully in most instances, clears bacteria that wander into the CSF, aided by outward bulk flow.

Fishman's observation that bulk flow is increased in canine pneumococcal meningitis (1968) suggests that this may be an important early response to facilitate bacterial clearance; however as CSF protein content rises, clearance of macromolecules is relatively impeded in proportion to size. So as meningitis progresses, bacterial clearance too may be impeded. Nevertheless substantial clearance of CSF pneumococci to blood can be demonstrated during experimental meningitis. Schelde et al. (1979) sampled CSF, superior saggital sinus and femoral artery of intracisternally infected dogs every 30 minutes for the first two hours and hourly thereafter. The disappearance of pneumococci during the first 90 minutes was in excess of that expected from dilution alone and was associated with demonstrable phagocytosis in the subarachnoid space. Bacteria appeared in the saggital sinus 1.5 hours before systemic bacteremia and persisted at a ten-fold higher concentration than in systemic blood; in turn concentration in CSF persisted at 10^3-fold higher than in sinus blood (Fig. 6). The lower systemic bacteremia is attributable to dilution. The time required to saturate lung clearance mechanisms accounts for the delay.

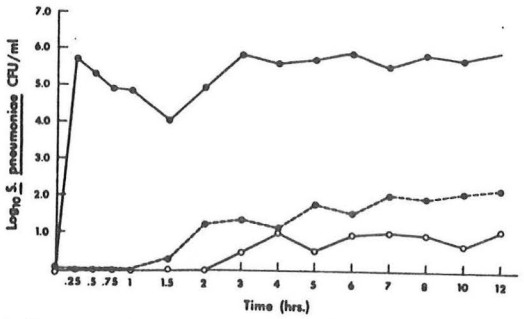


FIG. 1. *Change in bacterial titer with time after intracisternal inoculation. CSF (●——●), superior saggital sinus (●- - -●), femoral artery (○——○). Each point represents the mean of seven animals.*

Figure 6. Schelde et al., 1979

This study seems to vindicate Feldman's (1977) notion that the clinical bacteremia detected at the time of diagnosis of bacterial meningitis is secondary. He had observed that the proportion of cases with bacteremia was directly related to the number of bacteria in CSF.

Hematogenous infection from a remote source. Intravenous administration of bacteria has consistently failed to produce meningitis in experimental animals. However Gregorius et al. (1976) inoculated rabbits per carotid artery with 10^8-10^9 *S. aureus*. This resulted in a transient increase in permeability of meningeal vessels, exhibited by extravasation of fluorescein, and the production of bacterial arachnoidits, choroid plexitis and ependymitis. Cellular exudate around meningeal capillaries was found within 15 minutes. Ordinarily the surface of the choroid plexus is monitored (Fig. 7) by phagocytic cells called epiplexus or Kolmer cells which are probably able to contain intermittent breaches of the epithelium by bacteria. Nevertheless meningitis that accompanies pneumonia and endocarditis may resemble the Gregorius model.

The organisms that account for 70-72% of cases of meningitis, *S. pneumoniae* *N. meningitidis*, and *H. influenzae* are all encapsulated. The two major agents of neonatal meningitis, the K1 strain of E. coli and serotype III of group B streptococci (S. agalactiae) are similarly encapsulated. The effect of the certain bacterial capsules in resisting phagocyte attachment is well known (Robertson & Sia, 1927;

Dri et al., 1976), so that opsonization is required. Patients deficient in opsonins, such as alcoholics (Tapper, 1980), seronegative children, and those with sickle cell anemia (Pearson, 1977), and hypogammaglobulinemia or complement disorders are more likely to have bacteremia of greater magnitude. This increases likelihood of spill into tributary veins of cerebral venous sinuses, as well as entry directly through meningeal capillaries. Once in the subarachnoid space these organisms meet the uniformly opsonin-deficient environment of the CSF. An additional factor is the mode of opsonization. The alternate complement pathway is an important host defense against bacteremia in the absence of type-specific antibody. Patients with diminished alternate pathway activity appear to be at greater risk of pneumococcemia (Coonrod & Rylko-Bauer, 1977). Virulent (Group II) strains of E. coli K differ from less virulent (Group II) strains in their resistance to the alternative complement pathway; Group II strains specifically require classical pathway for opsonization, in proportion to the quantity of K1 polysaccharide in their capsule (Bortolussi et al., 1979). Disorders in which the bacteremic potential of encapsulated bacteria is enhanced are listed in Table 7.

Table 7. Bacteremia with Encapsulated Bacteria

Organism	Deficiency associated with increased risk of bacteremia
S. pneumoniae	Splenectomy C3 C3b inactivator Opsonins
N. meningitidis	C3 & C3b inactivator Components of terminal complement sequence (C5-C8) Opsonins
H. influenzae type b	Opsonins Splenectomy C3b inactivator
E. coli K1	Complement deficiencies ?

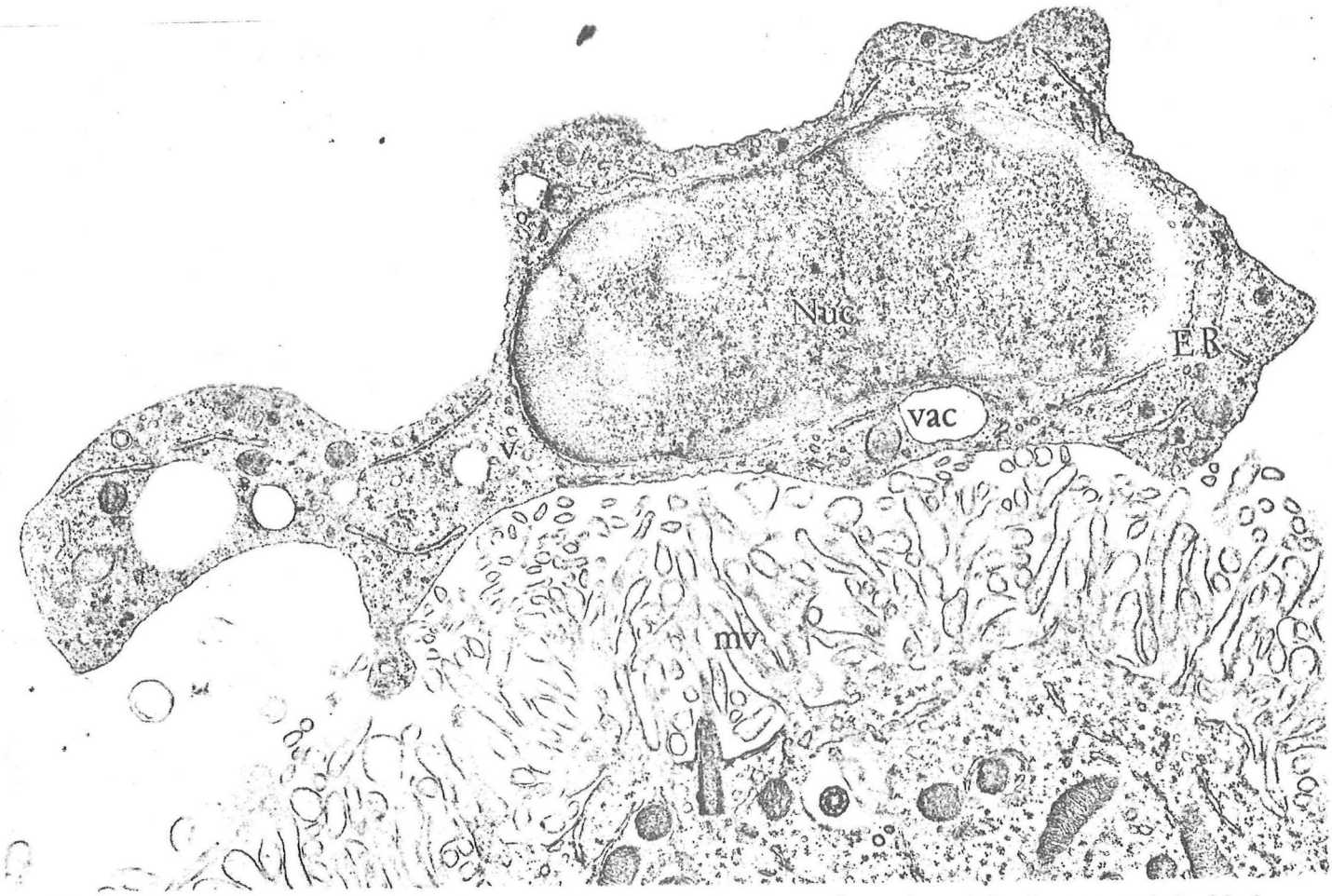


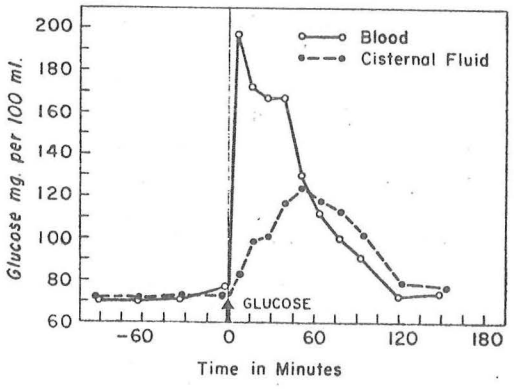
Figure 7. Kolmer cell grazing on the brush border of a choroid plexus epithelial cell (Peters, Palay & Webster, 1976).

Hypoglycorrhachia.

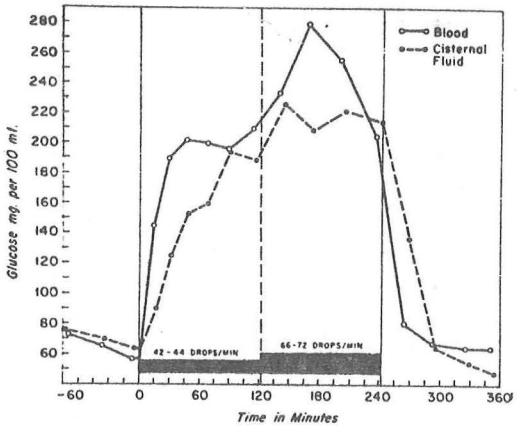
Definition and Interpretation. In 1893, only two years after Quincke's description of the lumbar puncture, Lichtheim published an account of the low cerebrospinal fluid glucose (hypoglycorrhachia; ραχισ: spine) in bacterial meningitis, an observation quickly confirmed by Quincke himself (1895). Since that time considerable clinical importance has been attached to this finding in the diagnosis of acute and chronic inflammation of the brain and its coverings. The concentration of glucose in human cerebrospinal fluid (CSF) obtained from the lumbar space is maintained at 60-90% of the blood glucose under fasting steady state conditions or about 50-80 mg/dl. CSF glucose decreases slightly with advancing age, particularly above age 50; Pryce, Grant & Saul (1970) have described a higher mean lumbar CSF glucose in women than men, but this observation has not been confirmed by others (Greenawald et al., 1973).

Human CSF is produced at a rate of 0.25-0.5%/min or 20-25 ml/hr and requires 6 to 8 hours to turn over completely (Cutler, Lorenzo & Barlow, 1968). Consequently changes in solute composition at the ventricular secretory site are not rapidly reflected in lumbar CSF. Furthermore as CSF flows caudad, it exchanges freely with

relatively glucose-deficient extracellular fluid from surrounding neural tissue. About 12% of CSF volume is derived from brain metabolic water, which is essentially glucose-free (Rapoport, 1976). As a consequence, lumbar CSF glucose is 6 to 18 mg/dl or a mean of 11 mg/dl lower than ventricular fluid glucose (Merritt & Fremont-Smith, 1937; Marks, 1960). Cisternal fluid glucose is intermediate in concentration. The flow and mixing of CSF below the cisterna magna is not uniform and depends on changes in posture and in fluctuation of venous pressure related to respiration and Valsalva maneuvers (DuBoulay et al., 1972; Williams, 1976). This further contributes to the unpredictability of lumbar CSF glucose except under steady state conditions. An oral glucose load in a non-diabetic person produces a minor elevation in CSF glucose after a 1-4 hour lag (Merrit & Fremont-Smith, 1930; Goodwin & Shelley, 1925). In studies of lumbar CSF glucose during glucose tolerance tests, Goodwin & Shelley (1925) found only a 10-15 mg% rise in CSF glucose after peak blood sugars of 150-225. No steady state studies of human CSF glucose during hyperglycemia have been done. In the dog sustained hyperglycemia produces more rapid CSF glucose equilibration at a higher level than does an intravenous bolus (Fig. 8: Myers & Netsky, 1962). The time to equilibration seems to depend on the degree of hyperglycemia, the duration of hyperglycemia, the site of CSF sampling, and the baseline blood glucose. In contrast the fall in CSF glucose in response to hypoglycemia is rapid and equal to the drop in blood sugar (Fig. 9).

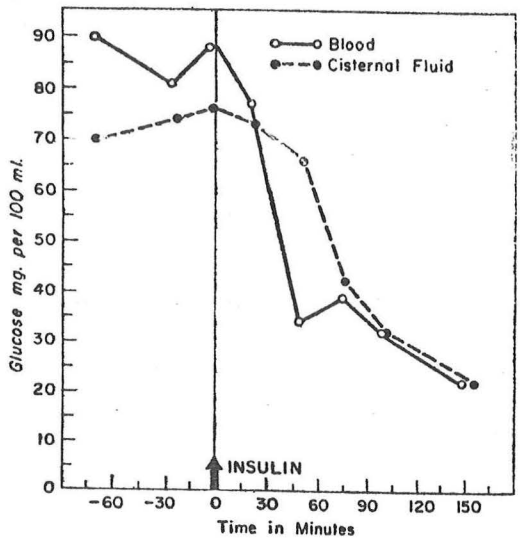


(Dog 7).—Chart demonstrating effect of 8 gm. of glucose given intravenously within 2 minutes. The level of glucose in the cisternal fluid lags considerably behind the high blood concentrations. The declining blood levels then exceed the fall in cisternal glucose until equilibrium is reached.



(Dog 12).—Chart showing effect of infusion of intravenous glucose first at slow, then faster rate. The glucose concentration in CSF more readily approaches that of blood at the slower rate.

Figure 8. Myers and Netsky, 1962.



(Dog. 4).—Chart showing effect of 17 units of insulin given intramuscularly. The glucose in blood falls more rapidly than in cerebrospinal fluid, but an equilibrium is reached after 1 hour.

Figure 9. Myers & Netsky, 1962.

Unlike human subjects, there is little difference between fasting blood and CSF glucose values in the dog; however during sustained hyperglycemia, the equilibrated ratio of cisternal CSF glucose to plasma glucose concentration falls for increasing values of plasma glucose. This is associated with saturation of glucose transport at 210-240 mg/dl in CSF (Fishman, 1964; Myers & Netsky, 1962). An elegant study of glucose concentration in nascent CSF at the rabbit choroid plexus (Welch & Saler, 1967) has shown that there is a sharp drop from 60% to 43% in the ratio of CSF/plasma glucose concentration when the plasma sugar exceeds 250 mg/dl (Fig. 10).

There are obviously difficulties in predicting CSF glucose during hyperglycemia, especially in the lumbar sac, even under controlled experimental conditions. In the clinic or on the ward, where steady state conditions are achieved only with fasting, and serial blood sugar values prior to lumbar puncture are not available, no attempt should be made to interpret a CSF/blood sugar *ratio* in the hyperglycemic patient. This is not usually a problem in the patient with acute meningitis, unless the physician has initiated intravenous hydration with dextrose-containing fluid rather than saline. Patients with subacute or chronic neurologic symptoms who do not require emergency lumbar puncture should fast for 4 to 6 hours before the procedure.

A CSF glucose concentration less than 40 mg/dl may be regarded as abnormal even the fed state unless the patient has been hypoglycemic in the previous three hours. However the CSF glucose should not be considered in isolation. In the absence of pleocytosis, glucose concentrations of 40 mg/dl or less are occasionally seen without hypoglycemia, particularly in children below the age of 5 years. Feinbloom and Alpert (1969) collected 32 such patients, of whom none had or subsequently developed meningitis. When blood is present in the CSF or is introduced by procedural trauma, the CSF glucose may be lowered, especially if the specimen is allowed to incubate for a period before the determination; at room temperature, glucose concentration in blood will fall at the rate of 7 mg/dl per hour. Values of 40 to 60 mg/dl may usually be considered abnormal, if the fasting blood sugar is high and the ratio less than 40%. The increasing substitution of plasma glucose for blood glucose determination in clinical laboratories may result in more borderline ratios, since plasma glucose is 14-15 mg/dl higher than blood glucose concentration. Nevertheless a CSF/plasma glucose ratio less 40% should generally be considered abnormal in the patient with a normal blood sugar.

Pathophysiology of Hypoglycorrhachia. The concentration of glucose achieved in CSF results from the operation of several balancing forces: (1) clearance of glucose from CSF to dural venous blood by "*bulk flow*" through arachnoid villi (Fig. 11), (2) the consumption of glucose by surrounding nervous tissue, (3) the simple and *facilitated diffusion* of glucose across the choroid plexus, (4) *active transport* of glucose from ventricular fluid mediated by a Na, K-activated membrane ATPase, and probably (5) the rate of plasma flow through the choroid plexus as well.

Cerebrospinal fluid exits through arachnoid villi into dural venous sinus blood (p. 6-7). Additional arachnoid villi may penetrate spinal veins (Welch & Pollay, 1963), but their functional significance is controversial (Dayson, 1967). In vitro it was shown that particles up to 7μ passed the villi unidirectionally without appreciable filtering

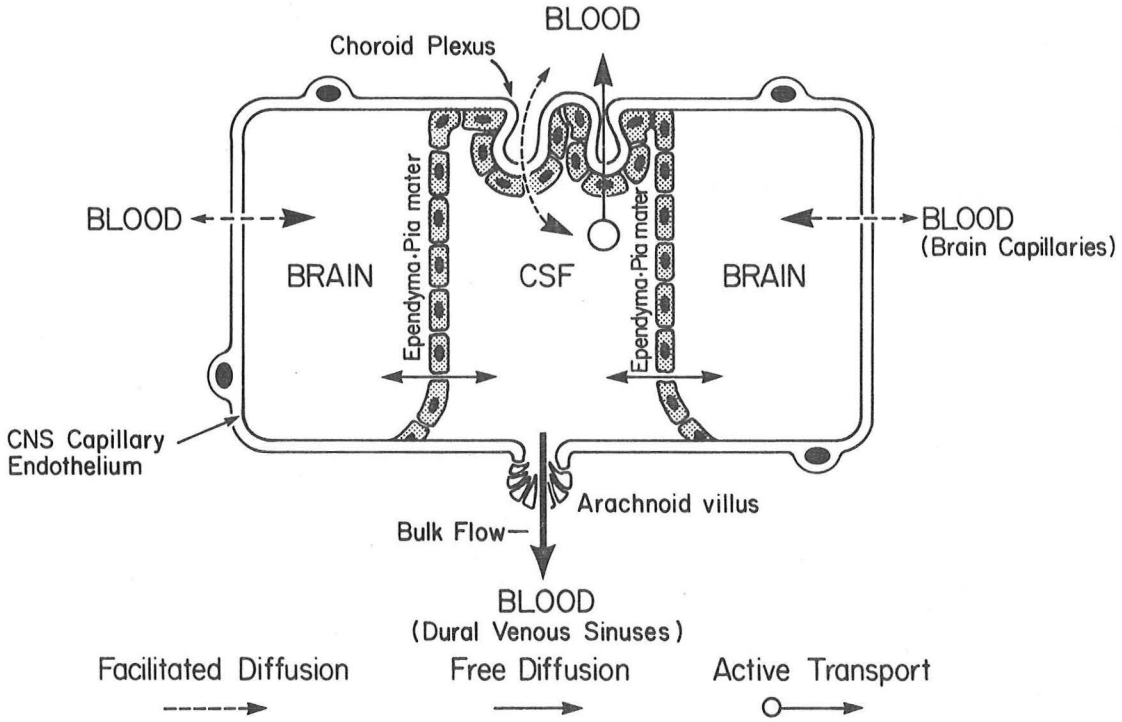


Figure 11. The concentration of glucose in the CSF is determined by facilitated diffusion into the CSF at the choroid plexus and into brain at the capillary endothelium, utilization by brain, bulk unfiltered flow out through arachnoid villi and removal by active transport at the choroid plexus.

and that passage was pressure dependent but independent of colloid osmotic pressure (Welch & Friedman, 1960; Welch & Pollay, 1961). In normal animals, all CSF solutes are cleared continuously at this site at equal rates without regard to size, charge, lipid solubility or gradient across the villus.

In addition solutes are cleared by *simple diffusion* across choroidal and ependymal membranes. Back diffusion of glucose across choroid plexus is limited by its insolubility in the lipid membrane, whereas diffusion into the brain across ependyma and pia is governed only by the Gibbs-Donnan equilibrium. Since a steep gradient is generated by rapid *glucose utilization* by brain, diffusion of glucose from CSF is favored (Fig. 12). The mean fasting glucose concentration of brain tissue is approximately 25 mg/dl, and intracellular glucose is as low as 5 mg/dl

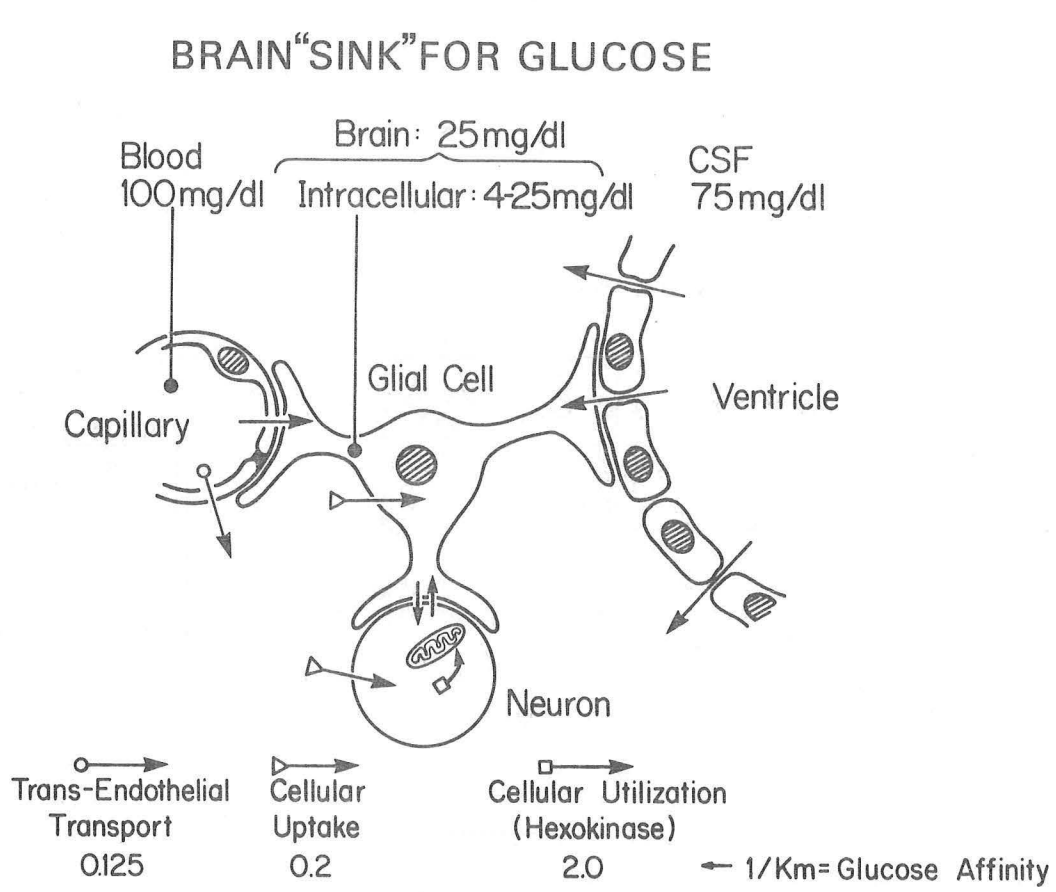


Figure 12. Rapid utilization of glucose by brain maintains a large net flow of glucose across the brain capillary endothelium into neuronal, as well as out of CSF. (Data from Sokoloff, 1960; Pappenheimer & Setchell, 1973; Betz, 1973; Rapoport, 1976).

(Rapoport, 1976). Accordingly the affinity for glucose (1/Km) increases stepwise at each compartmental barrier: 0.125 mM at the capillary endothelium, 0.2 mM at the brain cell plasma membrane and 20 mM for incorporation into metabolism (Betz et al., 1973). This sequential increase in glucose affinity maintains a large net flow of glucose from plasma into cerebral metabolism (Pappenheimer & Setchell, 1973); it also creates a "sink" for CSF glucose.

Transport of glucose between CSF and blood is another major determinant of CSF glucose concentration. Opposing entry of glucose into CSF is its polarity, which makes it relatively insoluble in lipid membranes. These barriers stand between blood and brain at the brain capillary endothelial cell and between blood and CSF

at the choroidal epithelial cell (Dayson, 1976). Consequently simple diffusion from blood accounts for only 3% of CSF glucose, although it may be up to 10% during extreme hyperglycemia (Fishman, 1964). The remainder is derived from *facilitated diffusion* (carrier-mediated transport), such as characterizes glucose transport across the membranes of erythrocytes, and across brush border membranes of proximal renal tubular cells (Silverman, 1976) and jejuno-ileal epithelial cells (Gray, 1975). The characteristics of facilitated diffusion are 1) saturation of the carrier (Fig. 13), 2) sterospecificity of binding to the carrier, 3) competitive inhibition of carrier binding, and 4) bidirectional transport. Each of these criteria has been met for both blood-CSF (Fishman, 1964) and blood-brain transport of glucose (Bradbury, 1979).

In the dog, saturation is achieved at a CSF glucose concentration between 200-250 mg/dl (Fishman, 1964). Analysis of the relative affinity of monosaccharides for the carrier (Table 8), shows that the hydroxyl groups at C-1, C-3, C-4 and C-6 and the ring oxygen are preferred binding sites, and the C-1 chain conformation of α-D-glucose is the preferred sugar configuration (Betz, Gilboe and Drewes, 1975). Competitive inhibition of transport by a glucose analog is of clinical importance in galactosemia in which high plasma concentrations of galactose reduce brain uptake of glucose, producing a "functional hypoglycemia" (Nadler, Inouye & Hsia, 1969).

The bidirectional characteristic of facilitated diffusion implies a carrier binding and releasing glucose on either side of the membrane; net flux depends on the firection of the glucose gradient across the membrane. The carrier is conceived to be either (1) a protein or glycoprotein that oscillates back and forth through the lipid bimolecular layer (Fishman, 1964), or (2) a transmembrane protein (Silverman, 1976) that dislocated glucose from one side to the other by a conformational change in response to binding. The transmembrane protein is variously considered to be a tubular structure through which glucose passes along a sequence of binding sites or a kind of merry-go-round, taking on riders on one side of the membrane and discharging them on the other. Functionally more than one species of glucose carrier may exist in the same membrane (Honegger & Semenza, 1973).

Active transport of glucose at the choroid plexus has been described in the sheep, dog, horse and cat, although not in amphibians (Czaky & Rigor, 1968; Bronsted 1970; Deane & Segal, 1976). In all cases the transport has been unidirectional from CSF to blood, ouabain-sensitive and both sodium and potassium dependent. These studies suggest that as much as 25% of glucose transport out of CSF is mediated by a Na-K activated membrane ATPase. By analogy with the intestinal epithelial cell (Crane, 1965) the proximal renal tubular cell (Kokko, 1973; Silverman, 1976), one would expect that active transport of glucose at the choroidal epithelial cell is supported by the Na pump. According to this model, glucose is transported in the direction of the sodium gradient, by a carrier with dual affinity for sodium and glucose (Fig. 14).

Table 8. Order of Affinity for Glucose Carrier at Blood-Brain Barrier

FROG	RAT	DOG
D-glucose	2-deoxy-D-glucose	α-D-glucose
3-O-methyl-D-glucose	D-glucose	2-deoxy-D-glucose
2-deoxy-D-glucose	3-O-methyl glucose	3-O-methyl-D-glucose
D-mannose	D-mannose	β-D-glucose
D-ribose		D-galactose
D-galactose	D-galactose	D-mannose
D-xylose		D-xylose
L-arabinose		D-ribose
		L-arabinose

Non-binding Monosaccharides

L-glucose

D-fructose

From Rapoport (1976); Betz et al. (1975); Bradbury (1979); Oldendorf (1971).

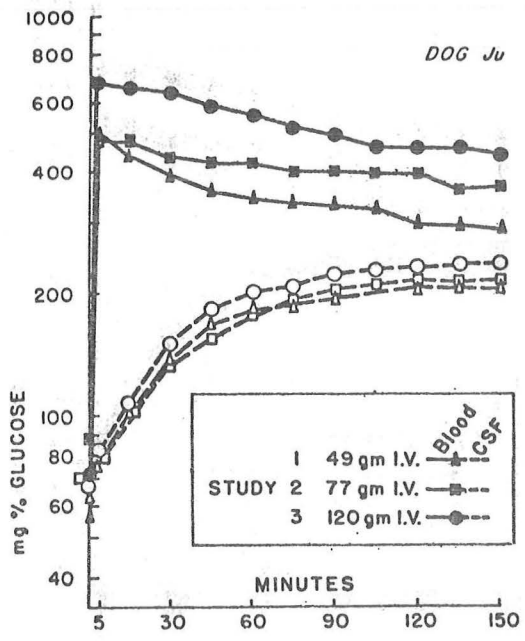
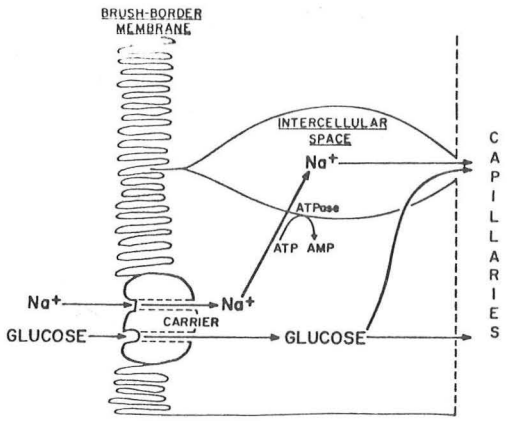


Figure 13. Sustained hyperglycemia was obtained by rapid infusion of a loading dose @ 50% glucose followed by constant infusion of 5% glucose, at 3 dosage levels. Steady state ratios of CSF/blood glucose do not rise with increasing blood concentrations, illustrating saturation of the diffusion mechanism (Fishman, 1964).



Mechanism for Intestinal Glucose Transport Based on the Hypothesis of Crane.

Glucose and Na^+ are bound at separate specific sites on the carrier macromolecule. Uphill movement of Na^+ from the interior of the cell into the intercellular space is facilitated by energy derived from ATP hydrolysis. Active glucose transport occurs by virtue of the coupling with Na^+ at the carrier step.

Figure 14. Crane, 1965; Gray, 1975.

In the choroidal epithelial cell, the Na, K-ATPase pump is located at the luminal (CSF) side, rather than the stromal or basal-lateral side as in the absorptive cells of the intestine or renal tubule. Accordingly Na is secreted into, rather than absorbed from CSF (Fig. 15). This is a major mechanism for delivering water and

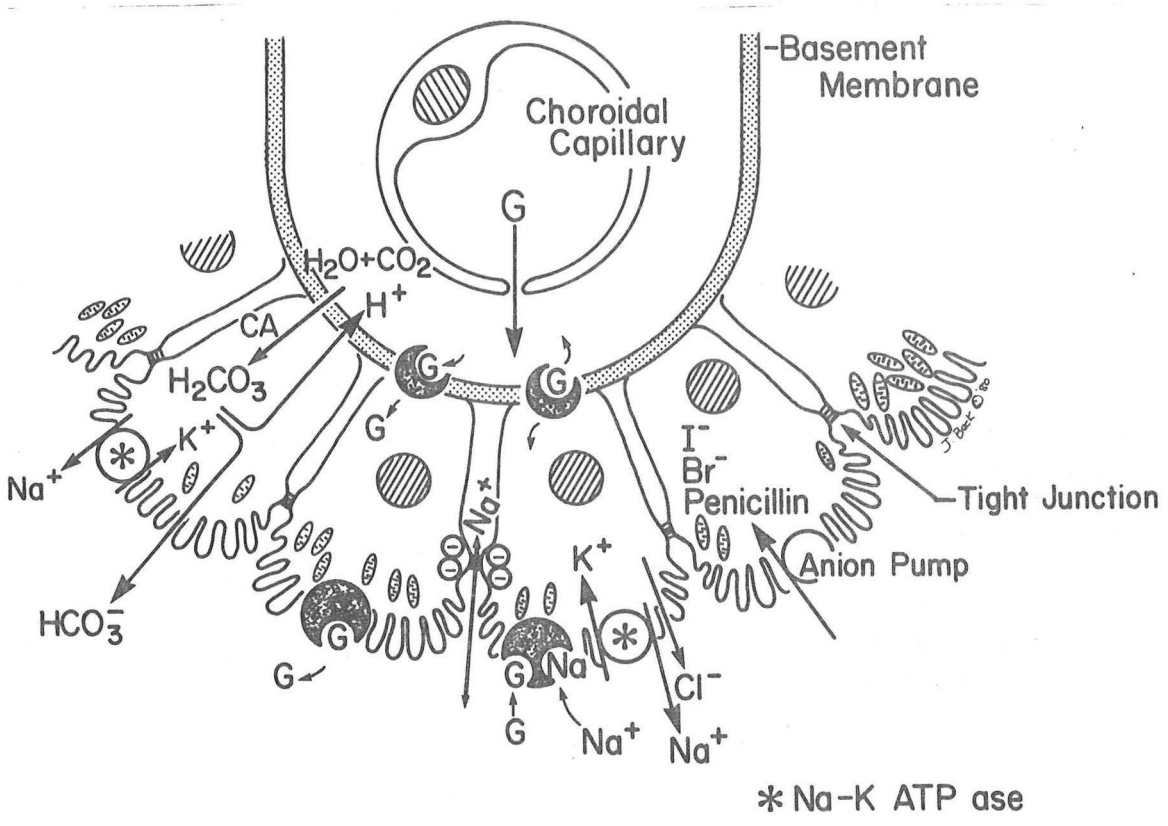
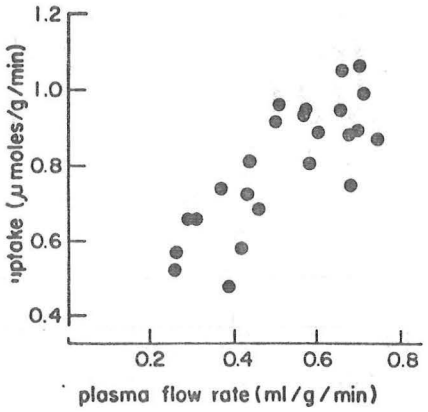


Figure 15. Choroid plexus. Illustrated (1) facilitated diffusion of glucose at basal-later and brush border membranes of the choroid epithelial cell, (2) active transport of glucose by a glucose-Na^+ carrier into CSF at the brush border, (4) anion pump, (5) carbonic anhydrase system required with the Na^+ pump for H_2O transport, (6) passive diffusion of Cl^- with Na^+ into CSF against the anion pump, (7) tight junctions retarding macromolecules.

chloride into the ventricle. Since a sodium gradient is created by this mechanism, a sodium-glucose carrier in the luminal brush border would account for energy dependent removal of glucose from CSF. Active transport of glucose in the central nervous system is probably limited to the choroid plexus epithelium (Bradbury, 1979).

Plasma flow also affects glucose extraction from blood (Fig. 16); accordingly conditions such as purulent meningitis that depress cerebral blood flow (Paulson, 1974) will favor lower rates of glucose transfer into brain (Betz et al., 1973). If choroid plexus arterial flow is also diminished in proportion to cerebral blood flow, decreased extraction of glucose from plasma by the choroid plexus would be expected.



. Plot of rate of unidirectional glucose uptake vs. plasma flow rate when glucose concentration has been kept constant. [Reproduced by permission of American Physiological Society from Betz *et al.* (1973)]

Figure 16.

CSF chemical alterations in meningitis. Cohen (1927), noting the behavior of CSF proteins and ions in meningitis (Table 9), formulated a "law of meningitis" to the effect that in meningitis the concentrations of substances in CSF tend toward plasma concentration. CSF concentrations in excess of e.g. calcium, magnesium and chloride, plasma fall; substances with a CSF/plasma ratio less than 1.0, e.g. protein, potassium and phosphorus rise. The behavior of glucose clearly defies Cohen's law (Table 10).

When meningeal inflammation results in hypoglycorrhachia, it may do so in four ways: (1) by increasing local parameningeal brain utilization of glucose, (2) by masking or impairing the mobility of the glucose carrier in the choroidal epithelial

Table 9. Distribution of Solutes in Human Lumbar CSF and Plasma

Solute	Normal CSF/Plasma Ratio	Change in Bacterial Meningitis
Na	0.98	±
Cl	1.1	↓
Mg	1.4	↓
Ca	0.49	↑
K	0.62	↑
HCO_3	0.87	↑
P	0.73	↑
Protein	0.004	↑
Glucose	0.6 - 0.8	↓

Table 10. Hourly Glucose Consumption

100 ml CSF with 6,000 PMN/mm^3 and 10^8 pneumococci	25-37.5 mg
100 gm normal brain	330 mg
100 gm inflamed brain	1320-3300 mg

Calculated from the data of Petersdorf, Swarner & Garcia (1960); Sokoloff (1960); Bachelard et al. (1974); and Collins, Posner & Plum (1970).

A standard explanation for the hypoglycorrhachia of meningitis has been that bacteria or neutrophils consume glucose.

Goldring and Harford (1950) showed that quantities of pneumococci (10^8-10^9/ml) condierably in excess of the number found in meningitic CSF were required to produce a detectable glucose consumption in CSF in vitro. The same was true of leukocytes incubated in CSF. Petersdorf & Harter (1961) re-examined this question, showing that detectable glycolysis occurred in four hour 1 ml cultures of CSF only if live pneumococci (10^8-10^9/ml) were incubated together with 6000 neutrophils/mm^3. Petersdorf, Swarner & Garcia (1963) later showed that this effect was associated with phagocytosis. Dogs made leukopenic by total body irradiation developed ten fold less CSF leukocytosis, higher CSF bacterial concentrations and almost no hypoglycorrhachia in response to pneumococcal meningitis as compared to unirradiated dogs (Petersdorf, Garcia & Swarner, 1959).

Nevertheless the contribution of glycolysis by phagocytic neutrophils in CSF to hypolycorrhachia is probably trivial. Normal brain glucose consumption is 55 µg/min/g of tissue (Sokoloff, 1960; Menkes, 1969). Under conditions in which the cerebral metabolic rate of oxygen (CMR_{O_2}) falls, as in head trauma, ischemia and seizure activity (Oleson, 1974), the brain is able to increase glucose consumption by as much as four to ten fold to support energy requirements (Holowach-Thurston & McDougal, 1969; Collins, Posner & Plum, 1970; Bachelard et al., 1974). In 14 patients with bacterial meningitis or viral encephalitis studied by Paulson et al.(1972), there was a mean decline in CMR_{O_2} to 40% of normal. In bacterial meningitis, the region adjacent to the CSF space is the site of greatest anaerobic glycolysis, so that local glucose consumption may theoretically exceed 500 µg/min/g of subependymal or subpial tissue. Comparing these rates of glucose consumption to that in a culture of actively phagocytic neutrophils and pneumococci (Table 10), neutrophils and

bacteria probably consume less than 1/100 of the glucose consumed by surrounding parameningeal brain. Definitive testing of this view awaits the measurement of the local parameningeal glucose metabolic rate by the elegant method of emission computed tomography recently described by Phelps et al. (1979).

The striking elevation of CSF lactate concentration in excess of pyruvate and depression of CSF pH in bacterial and tuberculous meningitis (Prockop, 1968; Yalaz, 1970; Bland et al., 1974), supports the notion of local anaerobic glycolysis in the depletion of CSF glucose. Lactate production by as many as 10^7 endotoxin-stimulated granulocytes/ml is trivial (Cohn & Morse, 1960). Blood lactate is effectively excluded from CSF (Crone & Sorenson, 1970; Posner & Plum, 1967), and CSF lactate and pH are known to approximate the values in adjacent brain (Plum & Posner, 1967; Tschirgi, 1960)

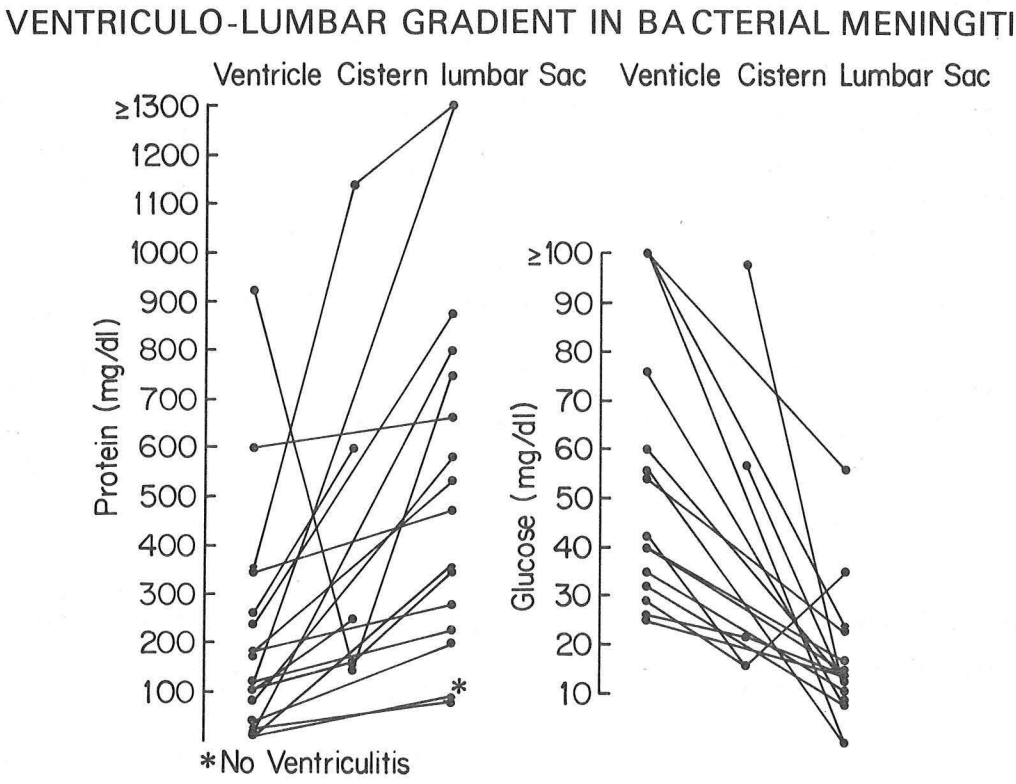


Figure 17. CSF protein and glucose concentrations in 20 patients with acute purulent meningitis. Derived from data of Merrett & Fremont-Smith, 1937.

This construction also explains the exaggeration of the ventriculo-lumbar gradient for glucose that is seen with meningitis (Figure 17). In other words, as CSF courses over an inflamed neuraxis, more of the increased rate of utilization is reflected in CSF reaching the lumbar sac than the relatively nascent CSF at the ventricle.

Prockop and Fishman (1968) have shown, determining CSF inulin and ^{125}I-albumin clearances in dogs with experimental pneumococcal meningitis, that early in the disease bulk flow is increased. As protein increases larger molecules are cleared relatively less well; however, the effect should be to "wash out" glucose, contributing to hypoglycorrhachia.

Diminished facilitated diffusion has likewise been demonstrated in this dog model by two different methods (Cooper et al., 1968; Prockop and Fishman, 1968). However, when bidirectional flux is considered the decrease in facilitated diffusion may not be sufficient to explain the degree hypoglycorrhachia in bacterial meningitis (Prockop and Fishman, 1968). The degree to which altered choroidal blood flow might contribute to reduced glucose entry has not been examined.

In summary, factors contributing to depressed CSF glucose values in meningitis cannot be compared directly and have not been fully studied. However, the most important appear to be increased brain glucose consumption, increased clearance of glucose through arachmoid villi and probably immobilization of carrier protein in the brush border, with impaired diffusion.

Clinical syndromes associated with hypoglycorrhachia are shown in Table 11. Although viral meningitis is not generally considered to induce hypoglycorrhachia, three agents regularly do: herpes simplex usually, mumps in 25% of cases, and lymphocytic choriomeningitis Meningovascular syphilis, meningeal involvement

Table 11

Meningeal Syndromes Associated with Hypoglycorrhachia

Usually	Frequently	Occasionally or Rarely
Bacterial meningitis	Intracranial hemorrhage	Herpes zoster meningitis
Tuberculous meningitis	Chemical meningitis	Leptospirosis
Fungal meningitis	Meningcal carcinomatosis	Mycoplasma meningo-encephalitis
Amebic meningoencephalitis	Viral encephalitis or meningitis due to:	In Infants:
Nonspecific granulomatosis (sarcoid)	Herpes simplex Mumps Lymphocytic chorio-meningitis virus	Coxsackie B Eastern equine encephalitis
	Meningovascular syphilis	
	Nocardiosis	
	Leaking cyst	
	Cysticercosis	

with carcinoma, lymphoma or leukemia and subarachnoid hemorrhage are particularly important causes to distinguish from early bacterial meningitis. Infants are unusually disposed to develop hypoglycorrhachia during coxsackie B meningitis (Avner, Satz and Plotkin, 1975; Lake et al., 1976) and eastern equine encephalitis (Winter, 1956) and following intracranial hemorrhage (Matthew et al., 1979).

Several investigators have attempted to derive diagnostic information from changes in the CSF glucose in response to IV glucose infusion. These studies (Table 12) have shown that depressed CSF glucose can be elevated by glucose administration even in tuberculous meningitis, but the alterations in pattern of response described defy analysis.

Table 12

Appearance of Glucose in CSF
After I.V. Glucose Loading

		Uncomplicated Meningitis	Spinal Block
Sifontes et al., 1953 1 gm/kg	Tbc Meningitis	Exaggerated cistern-lumbar difference (Lumbar ↑ less than controls)	Reverse cistern-lumbar difference (Lumbar ↑ greater)
Contoyiannis et al., 1975 0.1 gm/kg	Bacterial Meningitis	Greater increase in lumbar CSF glucose than controls	Little or no ↑ in lumbar CSF glucose
Williams et al., 1964 1 gm/kg	Bacterial Meningitis	Exaggerated cistern-lumbar difference (lumbar ↑ less than controls)	Hydrocephalus: no increase in lumbar glucose
Fishman, 1963 0.9 gm/kg	Carcinomatosis	Lesser increase in lumbar CSF glucose than controls	----

CSF Chloride and Bromide

Both chloride and bromide obey Cohen's law. Unlike other halides, Cl^- is concentrated in CSF relative to plasma and its concentration falls in meningitis. This is in spite of active transport of halides out of CSF by the anion pump (Figure 15), which is impaired in meningitis. However, the relative affinity of Cl^- for the anion pump mechanism is the weakest of the halides ($I^->Br^->Cl^-$). Thus, passive diffusion with Na^+ appears to be the more important transport mechanism (Bradbury, 1979); accordingly, when the Na^+ pump fails in meningitis, Cl^- entry is impaired and CSF Cl^- concentration falls.

Bromide on the other hand is efficiently removed from CSF by the anion pump (Figure 15), although fixed negative charges at intercellular tight junctions also must function to exclude bromide. Walter's bromide test which has recently been

revived in a more accurate form using oral ^{82}Br (Mandal et al., 1972) undoubtedly measures both injury to tight junctions and to the anion pump. Although patients with tuberculous (and bacterial) meningitis reliably have a serum/CSF ratio < 1.5, the test probably adds little diagnostic information to routine tests and requires 48 hours to perform.

Cerebrospinal Fluid Protein

The concentration of protein in CSF is highly restricted by tight junctions between choroidal epithelial cells that exclude protein, both by molecular size and charge (Rapoport, 1975), much as the glomerulus excludes protein from urine (Deen et al., 1975). Consequently, normal CSF protein is <0.8% (usually 0.4%) of the plasma concentration. Gamma globulin is relatively more exluded than albumin, but small amounts of IgG (3 mg/day) are produced in the CNS (Tourtellote, 1975) unlike CSF albumin, which is derived entirely from plasma (ratio 0.4-0.8%) (Tibbling, Link & Ohman, 1977). Accordingly, increases in CSF protein may be due (1) entirely to increased CNS production of IgG, as in subacute sclerosing panencephalitis, (2) entirely due to increased diffusion through impaired functional barriers, as in heavy metal poisoning, (3) obstruction to clearance by bulk flow through arachnoid villi, as in loculated subdural effusion or hydrocephalus. The CSF/plasma ratios of albumin and of IgG can be examined separately as an indication of which factor is the predominant cause of an elevated protein (Tibbling, Link & Ohman, 1977). In the case of bacterial meningitis, there is both increased diffusion of protein across choroid plexus cell junctions and increased production of local IgG. In the presence of very high CSF protein, there is usually relative obstruction to bulk flow through arachnoid villi as well (Prockop & Fishman, 1968).

As CSF circulates caudally and over the cerebral convexities, its protein concentration increases; the steepness of this concentration gradient is proportional to the lumbar CSF protein value (Hill et al., 1958) and is exaggerated in bacterial meningitis. Ventricular CSF protein concentration is 5-15 mg/dl, cisternal CSF protein 10-25 mg/dl and lumbar sac, 20-45 mg/dl (Krieg, 1979). Accordingly, if a number of tubes of sufficient volume are collected at lumbar puncture, the last tube will contain fluid of lower protein concentration than the initial tube (Bock, 1975). This ventriculo-lumbar protein gradient has been attributed to absorption of water from CSF (Krieg, 1979), but free diffusion of protein across pia and ependyma makes this unlikely. Futhermore, Hill et al. (1959) showed that all proteins are not concentrated uniformly along the gradient or below a spinal block; the concentration of pre-albumin decreases, while albumin concentration increases out of proportion to globulins, especially the γ fraction. Labelled protein introduced into brain parenchyma is cleared into CSF (Cserr, 1971). Intravenously administered labelled albumin appears more rapidly in lumbar than ventricular CSF (Fishman, Ransohoff & Osserman, 1958). Thus, free exchange of protein across the pia and ependyma results in a net increase in CSF total protein in proportion to concentrations in adjacent interstitial nervous tissue. This process is enhanced when CSF clearance is slowed or when CSF circulation is obstructed. Hence below a spinal arachnoid block, CSF protein concentration may be so high as to produce a fibrinoid clot (Froin, 1903).

The high CSF protein concentration (20-170 mg/dl) during the first three months of life is believed to reflect the permeability of the intercellular

junctions of immature choroidal epithelium and brain capillaries (Widell, 1958; Davson, 1968, Sarff, 1976). Beyond age 40 there is gradual increase of approximately 5 mg/dl per decade (Spina-Franca & Amar, 1963; Tibbling, Link & Ohman, 1977; Krieg, 1979). Mean male CSF protein concentration may be somewhat higher than that of women by 5-7 mg/dl (Dencker & Zethraeus, 1961).

III. Epidemiology and Clinical Patterns

General Considerations

The clearest picture of the epidemiology of endemic bacterial meningitis emerges from a careful study of a well characterized population of 280,000 in Charleston County, South Carolina, employing casefinding techniques that identified nearly 90% of cases in the county from 1961-1971 (Fraser et al., 1973). Blacks suffered a 3.4 fold greater incidence of bacterial meningitis than whites; similar racial differences were found for each agent (including Listeria, streptococcal species and miscellaneous agents), excepting only meningococcal

Table 13

Comparative Incidence of Bacterial Meningitis

	S. pneumonia	*H. influenzae*	*N. meningitidis*	All Agents
Race: Black	4.9	7.7	3.3	5.6
White	0.89	2.2	2.1	18.9

Charleston County, South Carolina (Fraser et al., 1973).

meningitis, which occurred with equal frequency in both groups (Table 13). The risk of acquiring pneumococcal meningitis for patients with sickle cell disease was 36 fold greater than for other Blacks and 314 fold greater than for whites. Data from Los Angeles suggest that the annual rate of pneumococcal meningitis for a defined prospectively studied population of sickle cell disease patients may be as high as 500, most of this risk accruing in the first five years of life (Overturf,

Powers & Baraff, 1977).

Analysis of National Center for Health Statistics data 1960-70 indicates that bacterial meningitis death rates for American Indians are three times those of Blacks and 5-7 times those of whites.

Table 14

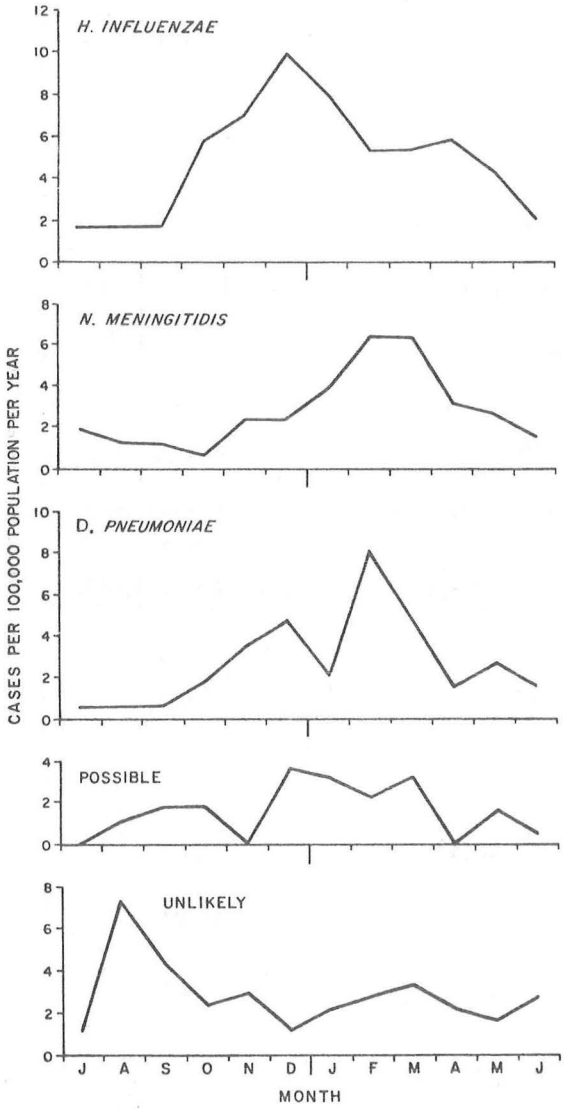
Age-adjusted National Incidence of Death Due to Bacterial Meningitis

	White	Black	American Indian
S. pneumoniae	0.2	0.82	1.53
H. influenza	0.16	0.3	0.72
N. meningitidis	0.17	0.33	0.81

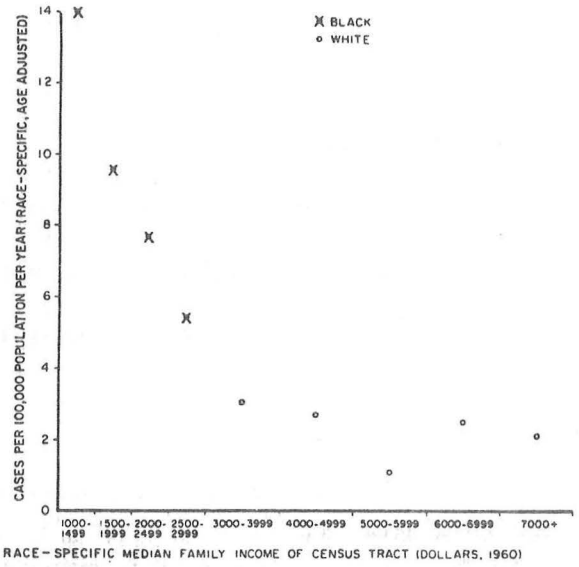
National Center for Health Statistics data (Feldman, Kochler & Fraser, 1976)

Among Blacks the incidence of bacterial meningitis was inversely correlated with income in Charleston County (Figure 18), although pneumococcal meningitis considered separately was not related to income. In Bernalillo County, New Mexico, where a broader range of income levels was found among whites, the incidence of both *H influenzae* and penumococcal meningitis was inversely correlated with income. However, income did not influence rates in groups with a high school education or more.

Incidence of all definite bacterial meningitis due to major agents peaked in the winter, *H. influenzae* in December, meningococcal and pneumococcal in February to March (Figure 19). There is remarkable difference between culture-negative partially treated meningitis (classified as "possible meningitis" by Fraser) and culture-negative meningitis. The latter was generally diagnosed as bacterial by the patient's physician on the basis of > 100 wbc and either > 50% granulocytes or glucose < 30 mg/dl, but was classified by Fraser et al. as "unlikely." The



Seasonal incidence of definite bacterial meningitis caused by *Hemophilus influenzae, Neisseria meningitidis,* and *Diplococcus pneumoniae* and of possible and unlikely bacterial meningitis (Charleston, South Carolina, January 1961–June 1971).



Incidence of definite meningitis due to *Hemophilus influenzae* among blacks and whites by median family income of census tract of residence.

Figure 18 (above) Fraser et al., 1973.

Figure 19 (left) . Fraser et al., 1973.

incidence of partially treated meningitis peaked in the winter, while culture-negative meningitis without prior treatment peaked in the summer, suggesting the majority to be viral meningitis.

Age-specific incidence of meningitis due to all three major agents peaked during the first year of life, between 6-8 months; *H influenzae* reached 250/100,000 of that age group, an incidence 2.5-3.0 fold higher than that of pneumococcal or meningococcal meningitis.

Table 15

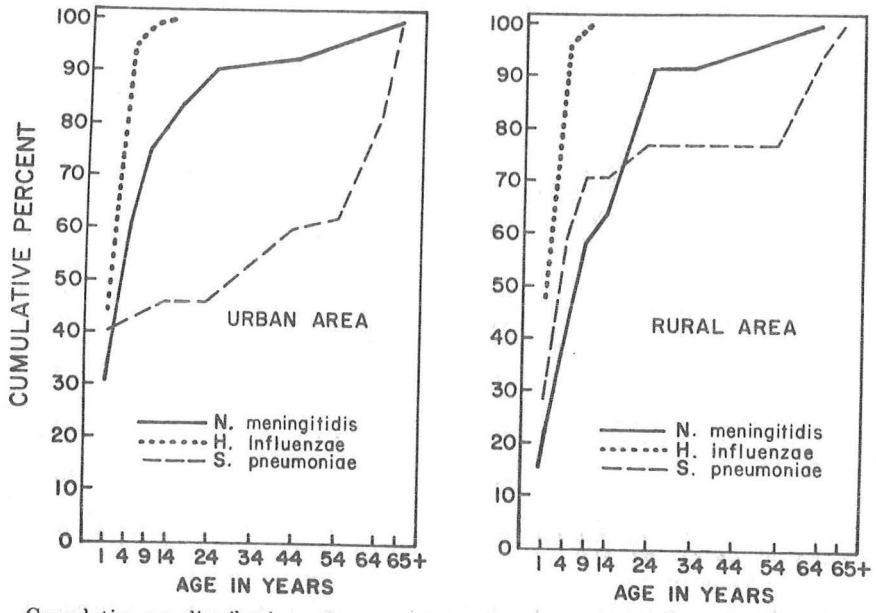
Age-adjusted Annual Incidence of Bacterial Meningitis by Income and Education Characteristics

	Income: < $10,000 Education: < 12 years		< $10,000 ≥ 12 years		> $10,000 ≥ 12 years
H. influenzae	5.2	($p < .01$)	2.8	(NS)	3.4
S. pneumoniae	2.9	($p < .05$)	1.1	(NS)	0.5

Bernalillo County, New Mexico. No difference in rates of meningococcal meningitis (Fraser, Geild & Feldman, 1974).

Figure 20 displays the relation of agent to age in a population-based study in Tennessee (Floyd, Federspiel & Schaffner, 1974); 90% of meningococcal meningitis occurs before age 24 and most before age 14. Ninety-five percent of *H. influenzae* meningitis occurs before age four and 99% before age 10; 40% of pneumococcal meningitis occurred in the first year of life with a sharp increase later after the fifth decade. These observations confirm impressions from earlier hospital-based studies (Carpenter & Petersdorf, 1962; Swartz & Dodge, 1965). In addition, it can be seen that pneumococcal meningitis in rural areas is also distributed through later childhood, but remains uncommon through young and middle adulthood.

Selected clinical features. Carpenter and Petersdorf observed that the duration of symptoms prior to admission was of some prognostic significance (1962). Their patients with fulminant disease of less than 24 hours were much more likely to have a fatal outcome (47%) than those with a more gradual development of symptoms (24%). However, a closer examination reveals (Table 16) that this difference was entirely among patients with meningococcal and *Hemophilus* meningitis and that case-fatality rates among patients with pneumococcal disease were uniformly high (50-66%) regardless of duration of symptoms. An exception to these observations is the patient with recurrent meningitis who comes to the emergency room early and has a low risk of dying of his meningitis (Levin et al., 1970).



Cumulative age distributions of cases of meningitis due to *N. meningitidis*, *H. influenzae*, and *S. pneumoniae* in the urban and rural study areas.

Figure 20. (Floyd, Federspiel & Schaffner, 1974).

Table 16

Duration of Symptoms at the Time of Hospitalization for Bacterial Meningitis

Duration of Presenting Illness	% of Cases Represented	% With Respiratory Illness	Case Fatality Rate (%)		
			All Cases	Pneumococcal Cases	Meningococcal Cases
< 24 hours	26	4	47	66	38
1 - 7 days	53	36	23	50	7
> 7 days	21	93	33	60	0

From data of Carpenter & Petersdorf, 1962.

A fifth of the Seattle cases presented with a prolonged (> 7 day) illness, 36% of which was respiratory and two cases of pneumococcal meningitis in the Seattle series had an obscure febrile illness without evident source for several weeks prior to diagnosis. A quarter of cases presented with more than a week of respiratory illness. There was no difference in distribution of illness duration

among the three major etiologies, except that *Hemophilus* rarely presented later than a week. Patients with rapid onset had almost no associated respiratory symptoms (4%).

The classic manifestations of bacterial meningitis require no review; however, as Osler (1892) observed:

> *The diagnosis is often difficult... In the case of a patient with a high fever, marked stiffness of the back and neck muscles, or opisthotonus with rigidity and tremor..., it is not unnatural to make a positive diagnosis of spinal meningitis, but every symptom of the condition may be present without any inflammatory exudate... On the other hand, there are instances of well marked leptomeningitis, ...in which spinal symptoms are trifling or absent.*

Osler's discomfiture with the diagnosis persists in the antibiotic era. Carpenter and Petersdorf comment that 41% of their cases of pneumococcal meningitis were not correctly diagnosed in the emergency room (Table 17).

Table 17

Failure to Diagnose Bacterial Meningitis on Initial Examination

Etiology (Cases)	% Incorrect Diagnoses
Streptococcus pneumoniae (53)	41%
Neisseria meningitidis (53)	15
Hemophilus influenzae (35)	9
Other (58)	21

From Carpenter & Petersdorf, 1962.

In cases of pneumococcal meningitis, pneumonia often overshadowed meningitis and minor alterations in mental status were overlooked or attributed to hypoxia or sepsis. Confusion tended to be attributed to associated illness, e.g.,

cerebrovascular accident, volume depletion, hepotic coma, ketoacidosis, alcoholic intoxication. Meningeal symptoms or signs were sometimes delayed in appearance until many hours after admission. Oddly the case-fatality rate was no higher in those whose therapy was delayed beyond four hours of admission than in those treated promptly, regardless of agent. This merely means that patients with florid meningeal symptoms, who are at higher risk of a fatal outcome, are more likely to have a prompt lumbar puncture. The case fatality rate might be reduced further in lower risk patients, if lumbar puncture is promptly performed and treatment promptly administered. Adult patients who are particularly likely to have absent meningeal signs, thos who are alcoholic, elderly or comatose, although when adults have been considered separately, only 5% have had absent meningeal signs (Swartz & Dodge, 1965). Some revision of this rule may be appropriate however. Hospital-acquired aerobic Gram-negative bacillary meningitis has become substantially more common than in the years 1956-1962 surveyed by Swartz & Dodge. Finland and Barnes (1977) reviewed bacterial meningitis in interval years between 1935-72 at Boston City Hospital; calculating from their voluminous data, only 6% of acute bacterial meningitis was due to aerobic Gram-negative bacilli (AGNB) in 1951-57, whereas 35% of cases were due to the organisms in 1961-72. This was associated with an increase in the role of hospital-acquired meningitis to 36% of the total. Among hospital-acquired cases, AGNB were the agents in 53%. The lack of nuchal rigidity or other distinctive signs of meningitis in these patients has been remarkable in series of cases due to *Acinetobacter* (absent in 80%; Caplan & Hoyt, 1979), *Klebsiella* (55%; Price & Sleigh, 1972) and *Pseudomonas* (Case Records MGH, 1972). In addition a number of confusing initial clinical configurations of meningitis due to classical agents have recently be reported (Table 18). Both pneumococcal and meningococcal meningitis have presented as an acute abdomen without meningeal signs; in each case, the absence of meningeal signs caused a delay in lumbar puncture. In one case however, the patient did have

pneumococcal appendicitis in addition to meningitis (Dimond & Proctor, 1976).

Table 18. Confusing Presentations of Adult Bacterial Meningitis

	Unexpected	Expected
Pneumococcal	Acute abdomen	Pneumonia
	Acute toxic psychosis without fever	
	Acute cerebellar ataxia	
Meningococcal	Acute abdomen	Pericarditis
	Epididymitis	Endophthalmitis
	Episcleritis	Morbilliform rash
	Acute cerebellar ataxia	Arthritis
		Hemorrhagic pustule

Salinger, Rose & Raff, 1973; Davis & Scardino, 1972; Dimond & Proctor, 1976; Maron et al., 1971; Whittle et al., 1973; Schwarz, 1972; Yabek, 1973.

Skin lesions, usually petechiae or purpura, accompany 50-75% of sporadic cases of meningococcal meningitis. An occasional patient will have purpura fulminans, with frank acral necrosis, or a more subtle indication of microvascular injury elicited by drawing a fingernail across the skin; the patient who develops erythema and congestion along the track is said to have *tache méningéale* or *tache cérébrale*. Bacterial meningitis due to *S. pneumoniae* or *Hemophilus* may also rarely cause such lesions, (Haggerty & Ziai, 1964) as may septicemia or endocarditis of any etiology. Several case reports of *Acinetobacter calcoaceticers* meningitis appeared prior to 1960 (Olafson, Lee & Abernethy, 1958) describing a petachial rash suggestive of meningococcal disease; since *Acinetobacter* is a small pleomorphic Gram-negative rod, it could be confused on Gram stain with the meningococcus as well. During the late spring and summer, febrile patients who have travelled in endemic areas, are candidates for Rocky Mountain spotted fever (American tick typhus), Colorado tick fever and leptospirosis, all of which may produce a petechial rash, fever and meningismus.

Neurologic deficits associated with bacterial meningitis in two major series (416 cases) are displayed in Table 19. Particularly striking is the proportion of cases with focal findings (20.4%) which usually would lead to concern about an intracranial mass lesion. Several qualifications are pertinent, based on the comments of

Table 19. Proportion of Cases of Bacterial Meningitis With Indicated Neurologic Signs

	All Agents (Carpenter & Petersdorf, 1962)	Pneumococcal (Dodge & Swartz, 1965)	Meningococcal (Dodge & Swartz, 1965)
Hemiparesis	15.3	17.9	5.1
III	--	10.7	12.8
IV	1.4	--	--
VI	5.3	3.6	12.8
VII	2.3	3.6	2.6
VIII	2.8	5.4*	10.3
Head/Eyes deviated	4.8	7.1	2.5
Seizure	19.1	25*	10

Dodge & Swartz (1965). Seizures were usually brief and generalized but often focal; they were particularly severe among cases of pneumococcal meningitis, four of whom died in status epilepticus. A particularly common focal seizure was a rhythmic conjugate jerking of the eyes to one side. Focal deficits were usually post-ictal and transient, lasting several days. Patients with ocular seizures suffered sustained conjugate deviation to the opposite side post-ictally. Two patients developed dysphasia and hemiparesis after they had begun to recover, healded by a flurry of focal seizures. This was attributed to cortical vein thombosis, a well described lesion in autopsy series (Adams, Kubih & Bonner, 1948). (See case #257135).

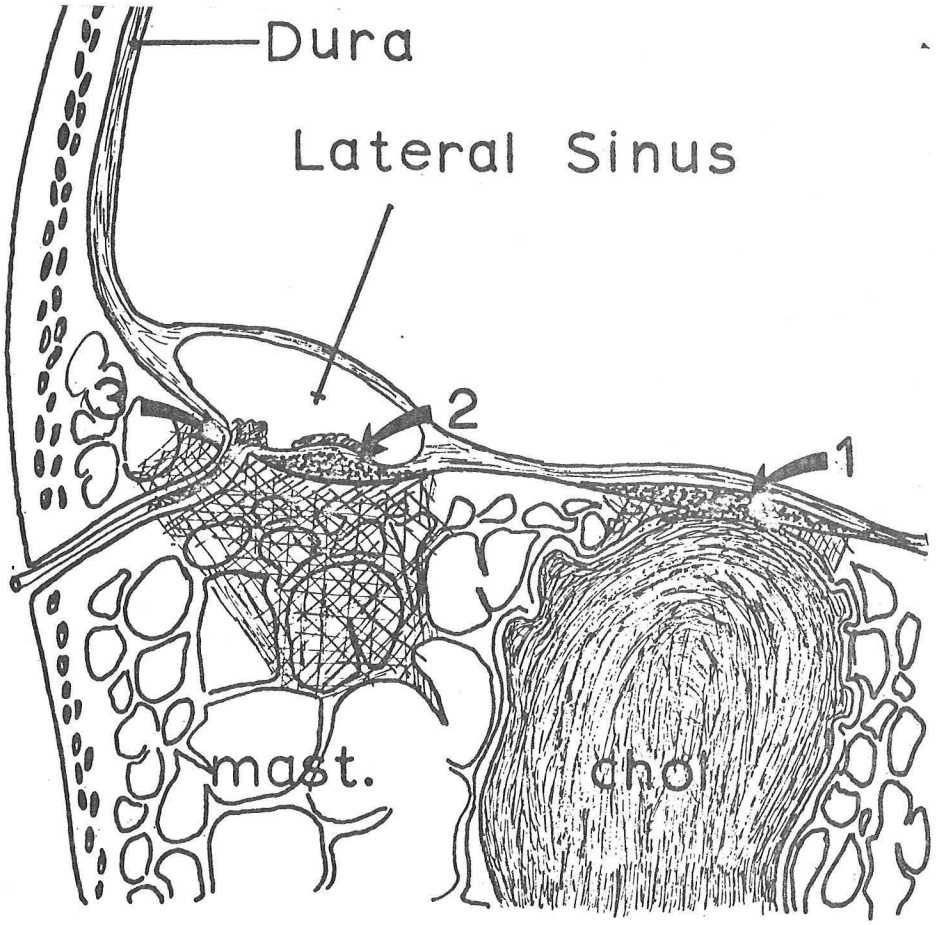
Papilledema did not occur in adults in either series, despite high CSF pressures. An equivocal disc margin was noted in one case of pneumococcal pneumonia. CSF pressure is not reported in detail, but in an early series (Merritt & Fremont-Smith, 1937), 15% of patients were said to have a pressure >500 mm H_2O.

Deafness differs from other cranial nerve deficits in not being so consistently reversible. In the Dodge & Swartz series, two of seven patients resolved their deficit during recovery, but an eighth developed deafness during convalescence. The lesion

is more than cranial nerve injury in its transit through subarachnoid pus; frank labyrinthitis is found usually without dural communication, suggesting to some workers; (Igarishi et al., 1974) that meningitic deafness results from secondary hematogenous spread from meninges to the labyrinths. Thirty-four per cent of pneumococcal meningitis is associated with otic pathology, yet surprisingly the clinical configuration of the ear disease associated with meningitis has not been well studied. In the major series of meningitis cases, the means and certainty of diagnosis is not presented nor are ear findings described in any detail. Based on pathologic material and surgical experience, meningeal involvement is thought to occur in three ways as a result of severe chronic ear infection (Fig. 21):

1) Cholesteatoma. Metaplasia or hyperplasia of the middle ear epithelium in response to chronic infection creates an expanding tumor, secreting osteolytic enzymes, and eroding into mastoid bone; erosion superiorly puts it in opposition to the dura, and pachymeningitis followed by leptomeningitis may result. How prevalent this disorder is among patients with meningitis is entirely unknown.

Figure 21.



Pathogenesis of complications; methods of spread to the meninges: *1*, a cholesteatoma has caused erosion of the mastoid with the matrix lying against the dura; infection has resulted in an extradural abscess; *2*, osteitis of the mastoid has caused thrombophlebitis of the haversian system with resultant perisinus abscess; a mural thrombus is forming in the lateral sinus adjacent to the abscess; *3*, osteitis has involved a mastoid emissary vein; the infected thrombus is propagating into the lumen of the lateral sinus.

Perforation or granualtion tissue at the posterior-superior margin of the tympanic membrane should sought on physical examination.

2) Mastoid osteitis due to chronic mastoiditis leads to extradural abscess formation adjacent to the lateral sinus; the resulting septic sinus thrombophlebitis is sollowed by bacteremic of tributary meningeal veins.

3) Mastoid emissary vein bacteremia leads to tributary meningeal vein bactermia.

Aside from the questions of anatomic pathology, many otolaryngologists believe that undrained pus in mastoid bone may contribute to the morbidity and mortality of otogenic meningitis (Bastrup-Madsen & Norby, 1955; Juseluis & Kaltiokallio, 1972). Keim (1977) designed a prospective study of ear and sinus disease in bacterial meningitis, including careful history, examination by an ear, nose and throat (ENT) surgeon, tympanocentesis, sinus and mastoid x-rays. The examination of medical house officers bore little relationship to the findings of the ENT surgeon except for normal ears. In 46% of 193 cases of bacterial meningitis, the ENT surgeon disagreed with the physician's examination; 75% of the ears judged abnormal by the surgeon had abnormal aspirates and/or mastoiditis on x-ray, regardless of what the internist found. Internists missed 80% of the disease and found pathology in 21% of the ears with normal aspirates and x-rays. Contrary to previous assumptions, the case distribution of abnormal sinus and mastoid x-rays was equivalent in children and adults (Fig. 22), although children accounted for more cases of meningitis. To what extent correct diagnosis led to improved patient outcome is not clear, but seven patients required ENT surgery (4%) whose hospital stay would have been shortened by earlier intervention. In any case in an academic institution, we could certainly benefit from early consultation with our ENT colleagues.

Table 20. Discrepancy between Medical & ENT Evaluation of Ears in Cases of Bacterial Meningitis

	M S 0 0	M S 0 +	M S + 0	M S + +
# cases	95	61	29	8
% abnormal	5.3%	75%	6%	75%

Keim, 1977. m=medical physician; s=surgeon; o=judged normal exam; +=judged abnormal.

KEIM: MENINGITIS: 290 CASES.

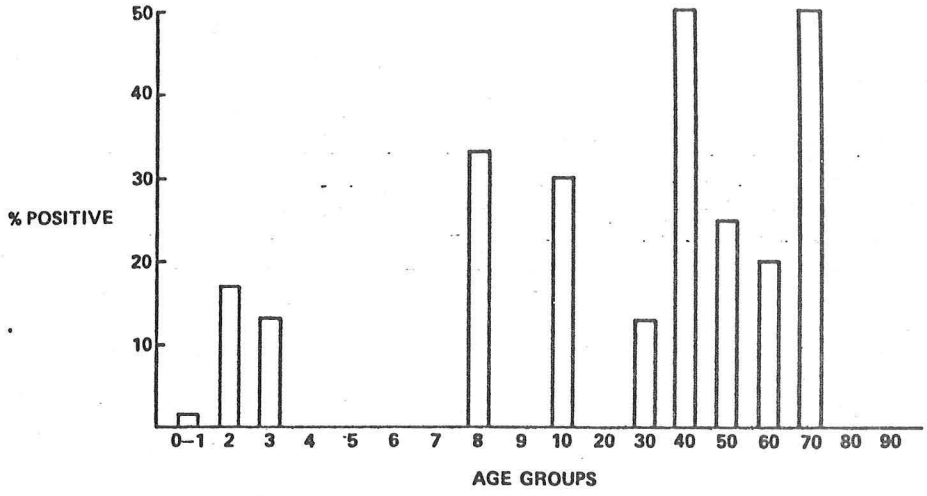


Figure 22. Abnormal sinus xrays in cases of bacterial meningitis by age group. Keim, 1978.

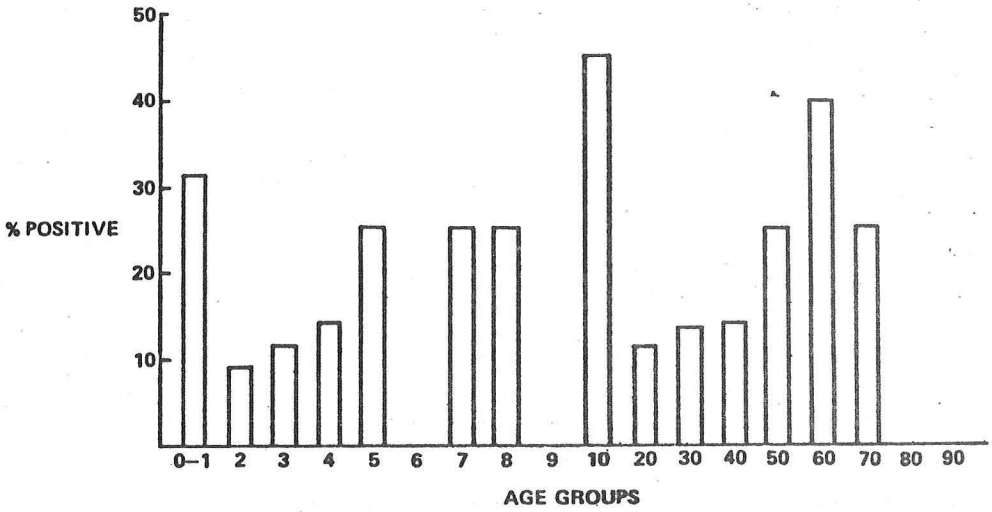


Figure 23. Abnormal mastoid xrays in cases of bacterial meningitis by age group. Keim, 1978

Streptococcus pneumoniae

The pneumococcal capsule consists of polysaccharide which is usually typeable as one of 84 serotypes. Since serotypes were numbered in order of definition from clinical material, the lower serotypes tend to be more commonly associated with serious infection, especially 1, 2, 3, 4, 7, 8 and 14, which account for 50% of pneumococcal infection (Austrian et al., 1976). Serotypes affecting children differ somewhat; type 6 is the predominant serotype causing otitis media. When higher serotypes cause meningitis, they tend not be associated with an extrameningeal source. The capsule confers a smooth mucoid appearance to colonies; it can be shed in response to anticapsular antibody, both in vivo and in vitro. Unencapsulated forms produce rough colonies. Dead organisms, which lose their capsule, become Gram-negative. The capsule is capable of activating the alternate complement pathway, and patients with serious pneumococcal disease tend to have deficient alternate pathway activity. Capsular antigens cross-react with several other antigens, e.g. type 14 cross-reacts with human A, B, H and Le^a blood groups. Acute hemolysis reported in patients with type 14 pneumococcal infections has been attributed to this property

The pneumococcus is relatively fastidious and will not tolerate drying, so specimens must be inoculated, streaked and incubated promptly, preferably with some source of moisture. Because they are catalase-negative, pneumococci may poison themselves with their own H_2O_2, if not provided catalase; red cells are provided for this purpose in blood agar. Five to 10% of pneumococci require CO_2 for growth.

The incidence of pneumococcal meningitis in large population-based studies in the U.S. is 1.4-2.2 per 100,000 annually (Broome et al., 1980; Fraser et al., 1974; Fraser et al., 1973). In large hospital based studies in the northeast, 6-8% of cases of pneumococcal bacteremia are associated with meningitis (Austrian & Gold, 1964; Burke et al., 1971). About 12% of healthy persons carry the pneumococcus in the throat, with higher rates in the spring (Foy et al., 1975). Carriage rates in adults are related to the presence of children in the household, who have higher carriage rates, 35% in pre-school, 29% in grammar school; intrafamilial spread of the pnemococcus is enhanced by rhinovirus infection (Gwaltney et al., 1975). Individual serotypes persist for shorter periods in adults, who usually have homotypic antibody

A capsular polysaccharide vaccine (Pneumovax, MSD) containing 14 serotype antigens has been approved for immunization of individuals special at risk of bactermia and meningitis, such as those listed in Table 21. In addition the vaccine is recommended for others at risk for serious pulmonary disease. Serotypes for the vaccine were chosen, based on data from a ten hospital nationwide monitoring study, to immunize against serotypes that cause 87% of pneumococcal disease (Austrian et al.) 1976). Vaccine efficacy in healthy volunteers against homologous serotypes is 75-90%, so overall expected efficacy is 56-68%, if the distribution of agents producing disease does not change. The critical question is: will the vaccine protect those at special risk? The answer seems to be for patients with sickle cell disease, yes; for patients with Hodgkin's disease who receive chemotherapy, antibody responses are very low, (Amman et al., 1977; Siber, 1978). Further disadvantage are that cancer patients have a somewhat different distribution of infecting serotpye than the general population, and only 58% of their infections may be covered by the vaccine.

Table 21. Patients at Special Risk*

Pneumococcal Meningitis		Meningococcal Meningitis	*H. influenzae* Meningitis
Splenectomy	Cranial trauma	Recruits	Children <5 y.o.
Hypo γ-globulinemia	Congenital dural defects	Household contacts of a case	Splenectomy
Nephrotic syndrome	Sickle cell anemia	Complement deficiencies of terminal sequence	Hypo γ-globulinemia
Multiple myceloma	Alcoholism		Dural defects
Pregnancy	Elderly		

*Cf. Table 7 re: Complement deficiency syndromes: associated with increased risk from all three agents.

Neisseria meningitidis

The meningococcus is somewhat more fastidious than the pneumococcus, and always requires 5-10% CO_2 and moisture for growth. Blood, chocolate and Mueller-Hinton agar are satisfactory media. The meningococcal capsular polysaccharide serogroups are: A, B, C, X, Y, W-135 and 29E. Vaccines are available for groups A and C for use in military recruits. Group B isolates frequently lack a capsule.

Table 22

	1978 Proportion of U.S. Isolates*	Vaccine	Detected by CIEP	Disease Pattern
A	4%	Yes	+	Epidemic
B	49	Poor immunogen	+	Sporadic
C	20	Yes	+	Epidemic
Y	9	Planned	0	Epidemic
X, W135, 29E	8	No	0	Sporadic
Ungroupable	10	--	0	Sporadic

*CDC MMWR, June 22, 1979.

Groups A and C are the predominant epidemic agents. During epidemics secondary cases occur in 1.4-4.8% of household contacts; for sporadic cases the secondary case rate is 0.4%. Risk to school and hospital contacts resemble risk in the community at large; although respiratory isolation of a case of meningococcal meningitis is standard, there is no data on its value. Meningococci are eradicated from the throat within hours of the initiation of penicillin (WHO, 1976).

Management of household contacts at the present time consists of rifampin 600 mg q 12h for two days (4 doses) for adults (child: 10 mg/kg q 12h x 2 days), unless the strain is sensitive to sulfadiazine (<0.1 mg/dl). The disadvantage of rifampin is that it induces rifampin-resistant meningococci in 10-27% of carriers treated (Weidner et al., 1971).

Meningococcemia should be differentiated from meningococcal meningitis. The former is characterized by sepsis, shock, petechial or purpuric rash, other manifestations of disseminated vascular coagulation (DIC) and a case-fatality rate of 25% (in the U.S.). Meningococcal meningitis is associated with a petechial rash in 50% of cases, but generally not DIC or shock, and the case-fatality rate is 14%. Either pattern can be associated with hypersensitivity phenomena including pericarditis, arthritis and episcleritis, but meningococcemia is almost uniformly complicated by these events (Whittle et al., 1973).

Haemophilus influenzae

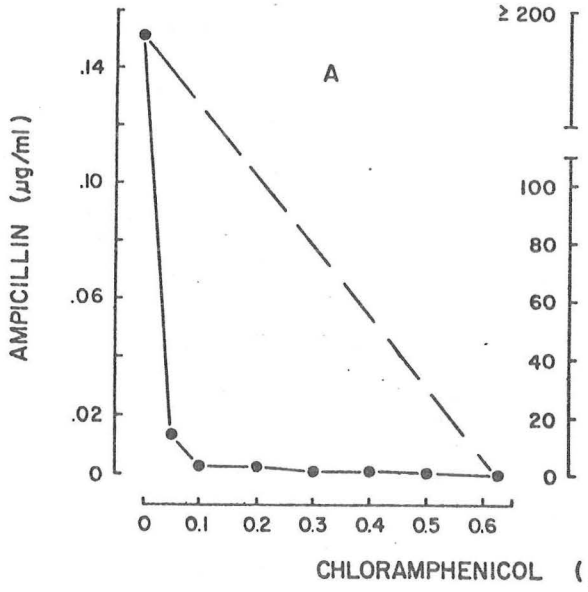
H. influenzae type b is primarily an agent of disease in children <4 years old and older than six months. In classic studies Fothergill & Wright (1933) demonstrated that this pattern corresponded to the age-distribution of bactericidal antibody. At that time 100% of healthy adults had antibody. Recently however 30% of newborns and 20% of mothers have been shown to be seronegative. Increasing numbers of cases of adult infection are being reported (Weinstein, 1970; Quintilliani & Hymens, 1971), although nearly all of these are cellulitis or respiratory tract disease. Four of Swartz & Dodge's (1965) adult patients had *H. influenzae* meningitis, of which two were non-typeable. We have seen three cases at PMH in the past five years in adults age 18-38, all post-traumatic, all non-typeable strains and all ampicillin-sensitive. It remains true that when type b *H. influenzae* is recovered from an adult that hypo-γ-globulinemia or a CSF fistula should be ruled out. Although the epidemiology of the organism may be changing, at the present time it should not be considered seriously in diagnosis of an adult with meningitis, unless there is associated epiglottitis or cellulitis. The cellulitis of *H. influenzae* is of a characteristic violaceous hue usually buccal, occasionally involving the neck and upper chest.

The high attack rate of serious disease among household contracts of cases has recently been appreciated (Filice et al., 1978). For children <4 years: 2%; <2 years:

4.9%. The overall attack rate of 0.4% is comparable to meningococcal disease. A satisfactory prophylactic agent has not yet been defined. A tentative approach is to use 20 mg/kg q 12h for four days of rifampin, which was effective in Nelson's and McCracken's hands in Dallas in a small series. Prophylaxis, if given, is appropriate only for households with unaffected children <4 years old, and then the entire household must take prophylaxis.

Since the classic study of Jawetz & Gunnison (1953), drugs have been classified as either bactericidal or bacteristatic and combinations of the two were considered antagonistic. However the distinction between bactericidal and bacteristatic drugs is relative to inoculum and to the organism. Chloramphenicol is bactericidal rather than bacteristatic for *H. influenzae*, and the combination of chloramphenicol and ampicillin in a recent study was either synergistic or additive in all 21 strains tested, including ten ampicillin-resistant (Feldman, 1977). The well established pediatric practice of treating *H. influenzae* meningitis with ampillicin and chloramphenicol seems vindicated, provided the diagnosis is correct.

Figure 24. Synergistic and additive effects on a sample strain A and 21 strains of *H. influenzae* type b (Feldman, 1978).



Isobolograms showing synergistic effects of ampicillin and chloramphenicol against a strain of *H. influenzae* type b. A, Large inoculum (10^7 CFU/ml).

EFFECT OF INOCULUM ON COMBINATIONS OF AMPICILLIN AND CHLORAMPHENICOL AGAINST 21 STRAINS OF *HAEMOPHILUS INFLUENZAE* TYPE B

Inoculum	*Effect (No. of Strains)*		
	Synergy	*Addition*	*Antagonism*
Ampicillin-susceptible			
10^4 CFU/ml	6	7	0
10^7 CFU/ml	9	4	0
Ampicillin-resistant			
10^4 CFU/ml	5	3	0
10^7 CFU/ml	2	6	0

Table 23. Agents of Intracranial Infection in Neoplastic Disease

	Head & Neck Ca	Lymphoma	Leukemia	Other Ca
Listeria monocytogenes	0	9	2	5
Pseudomonas aeraginosa	7	2	5	1
Other AGNB*	19	2	2	5
S. aureus	12	0	0	0
S. pneumoniae	0	6	1	3
Misc. streptococci	14	1	1	5

*Including *E. coli*, *Klebsiella* spp, *Proteus nirabilis*, *enterobacter* spp., *Acinetobacter* spp. Chernik, Armstrong & Posner, 1973.

Acute Meningitis in the Immunosuppressed Patient

The major agents of bacterial meningitis in the compromised host are *Listeria monocytogenes*, *Pseudomonas*, enteric aerobic Gram-negative bacilli (AGNB), *Strep. pneumoniae*, miscellaneous streptococci and *staphylococcus aureus*.

Some distinctions can be made between immunologically impaired patients in terms of likely infecting organisms (Chernick et al., 1973; Chernick et al., 1977). Patients with leukemia are vulnerable, when neutropenic, to *Pseudomonas aeruginosa* fermentative AGNB meningitis. They do not often develop meningitis when white blood cell (WBC) counts are normal, and then the most likely organism is *Listeria*. Patients with lymphoma usually have normal WBC counts and are most at risk of *Listeria* and pneumococcal meningitis. Patients with disorders of humoral immunity, e.g. myeloma, hypo γ-globulinemia and complement deficient are at greatly increased risk of infection due to encapsulated meningotropic organisms, and if made leukopenic have the same added risks as leukemic patients. Patients with head and neck cancer are at hazard for infection related to spread from contiguous sites as a result of surgery or local tumor invasion. Accordingly meningitis in these patients is due to the flora of sinuses, nasopharynx and ears: streptococci, *S. aureus* and, because their pharyngeal

Table 24. Patterns of Meningeal Infection

Leukemia	Lymphoma	Multiple Myeloma Hypo γ-globulinemia
*Pseudomonas**	*Listeria*	*S. pneumoniae*
Enteric AGNB*		
Listeria	*S. pneumoniae*	*H. influenzae*
Transplantation	Head & Neck Ca	Complement deficiency
Listeria	Enteric AGNB	*S. pneumoniae*
	Streptococci	*H. influenzae*
	S. aureus	*N. meningitidis*

*Related to neutropenia; these organisms also cause meningitis in other compromised patients, when neutropenic.

mucosae become colonized in the hospital, enteric AGNB. Patients with Wegener's granulomatosis have a similar pattern of infection. Rational empiric treatment regimens for meningitis associated with these disorders can be designed accordingly (Chernik, et al., 1977).

Nonbacterial meningitides may confound the evaluation of the compromised patient. *Candida albicans* causes a purulent meningitis that may easily be confused with bacterial meningitis, especially in leukemia, lymphoma and transplantation patients, and especially in the setting of hyperalimentation and other kinds of catheters (Bayer et al., 1976). CSF cell counts are usually modest, averaging 600, predominantly neutrophils in 52% of cases, with minor alterations in protein and glucose. However in neutropenic patients, the CSF pattern in bacterial meningitis may be similarly unimpressive. In cancer patients, malignant involvement of the meninges must be ruled out. Other infectious CNS syndromes associated with impaired host defenses are shown in Table 25. The importance of aggressive evaluation in the compromised patient with undiagnosed nervous system infection should be apparent.

Table 26.

Murphy, Mackowiak & Luby, 1979.

Agents of Central Nervous System Infection in the Compromised Host

Acute Purulent Meningitis	**Chronic Lymphocytic Meningitis or Meningoencephalitis**
Enteric gram-negative bacilli	*Cryptococcus*
Pseudomonas	*Toxoplasma*
Listeria	Acanthamoeba
Candida	*M. tuberculosis*
Mucorales	**Mass Lesion**
	Nocardia
Cerebrovascular Thrombosis	*Aspergillus*
Aspergillus	Mucorales
Mucorales	*Cryptococcus*
Penicillium	*Penicillium*

The single most common agent of acute meningitis in the immunosuppressed patient is *Listeria monocytogenes*. It accounts for 33% of bacterial meningitis at the Memorial Sloan-Kettering Cancer Center (Chernik, Armstrong & Posner, 1977), and nearly all of the cases of bacterial meningitis in renal transplant centers (Schröter & Weil, 1977). At PMH it has accounted for ten consecutive cases over the past five years. The clinical configuration of the disease is usually similar to that of acute bacterial meningitis in otherwise healthy individuals; occasional patients (Schröter & Weil, 1977) have an initially normal or unimpressive CSF formula but positive CSF culture. Others have an unusual indolent evolution of the infection likely to be confused with cryptococcal meningitis.

Listeria monocytogenes is a motile, hemolytic Gram-positive rod easily confused with diphtheroids. Listeria also causes occasional disease in pregnant, elderly, alcoholic or even apparently healthy individuals (Lavetter et al., 1971), therefore report of a Gram-positive rod from the laboratory should always prompt the questions: Is it hemolytic? Is it motile? In one proficiency testing survey 29 of 46 laboratories misidentified this organism. Three cases of cerebritis were recently reported in patients with *Listeria* meningitis, two of whom relapsed following 10-14 days of penicillin (Watson et al., 1978). In reviewing the therapeutic details of reported experience with *Listeria* meningitis, these authors noted a 35% relapse rate in patients treated for <3 weeks. They recommended a therapeutic course of 4-6 weeks.

Craniospinal Trauma and Surgery

Following nonpenetrating head injury requiring hospitalization, meningitis is generally due to endogenous nasopharyngeal, otic or sinus organisms during the first

three days (*S. pneumoniae, S. aureus* or *H. influenzae*); meningitis occuring later than three days in the hospital is usually due to a hospital-acquired organism, *S. aureus*, enteric AGNB or Pseudomonas (Table 26). Caplan & Hoyt (1979) have recently observed nine cases of *Acinetobacter* meningitis following craniospinal trauma; this is of some importance because of the frequency (30% at PMH) with which *Acinetobacter* is resistant to gentamicin. It is usually sensitive to tobramycin, tetracyclin and kanamycin, and the seven appropriately treated patients in Caplan & Hoyt's series survived. Following penetrating craniospinal trauma, meningitis may be due to a variety of skin and soil organisms, including streptococci, staphylococci and AGNB with unusual antibiotic susceptibility patterns. Late post-traumatic meningitis following discharge from the hospital is nearly always pneumococcal (Hand & Sanford, 1970).

Table 26. *Etiologic Agent According to Time Interval from Trauma to Onset of Meningitis*

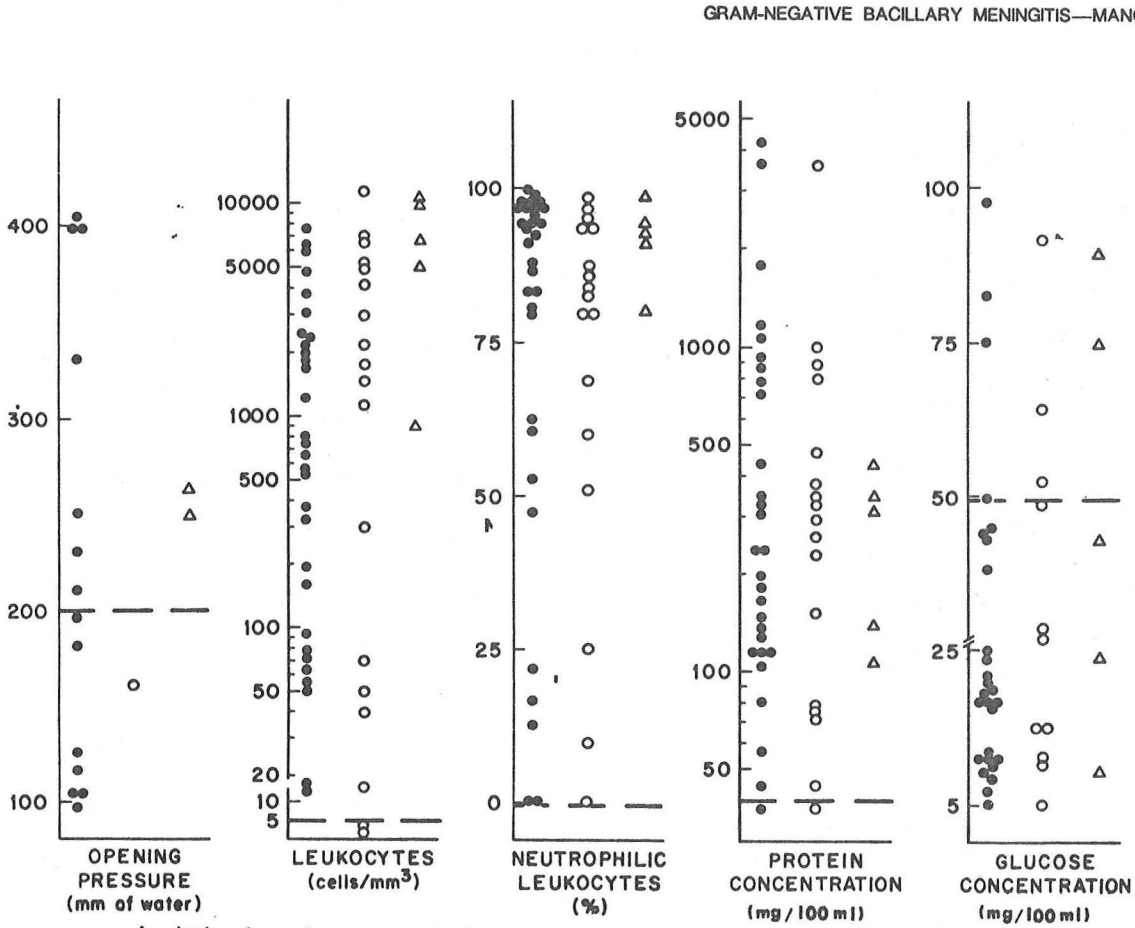
Interval (days)	Pneumococcus	Streptococcus	Staphylococcus	Gram-negative enteric	Pseudomonas	No organism isolated
0-3	5	1	1			3
4-6				1		3
7-9			1			
10-14				4	1	
>14			1		1	
	5	1	3	5	2	6

Jones, Luby & Sanford, 1973.

Similarly, bacterial meningitis following spinal and intracranial surgery is most often due to AGNB (80%), *S. epidermidis* and *S. aureus* (Buckwold et al., 1977). *Pseudomonas* meningitis following ear and sinus surgery has been the subject of several recent case reports. Likewise a high proportion of nosocomial meningitis follow lumbar puncture or spinal anesthesia is due to *Pseudomonas* (Beaty, 1979); epidemic nosocomial meningitis related to spinal anesthesia has occurred as a result of contamination of equipment or solutions with both *Pseudomonas* and *Klebsiella*.

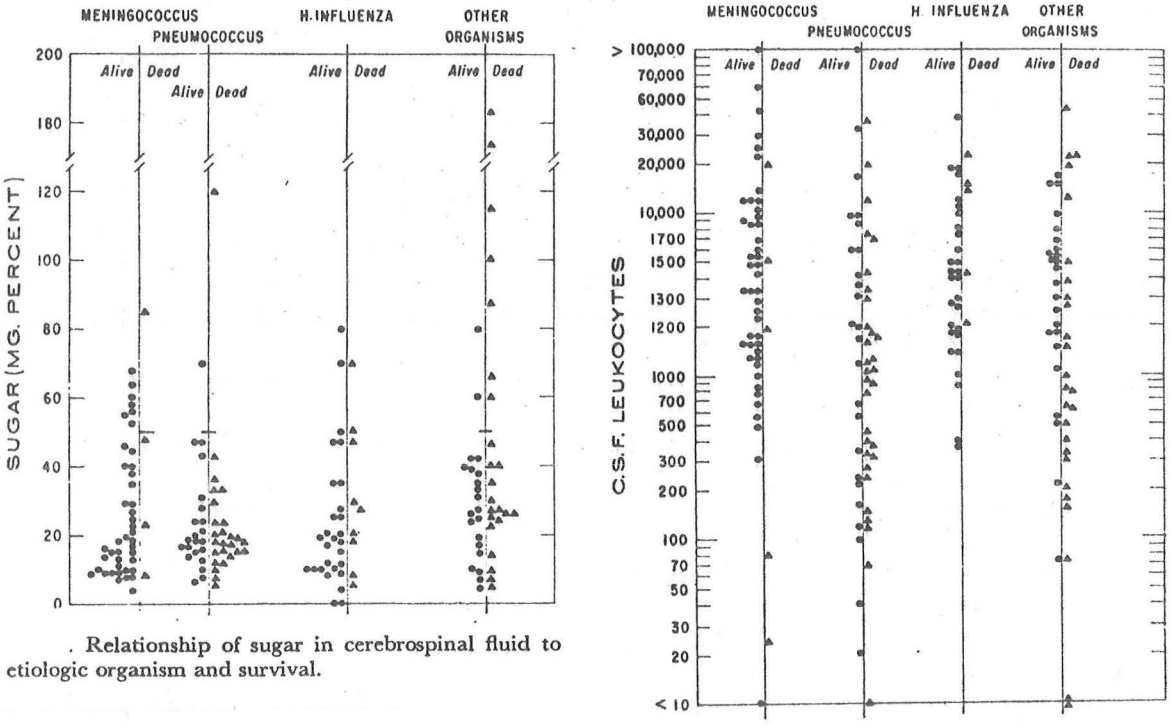
There is some difficulty in recognizing meningitis in the post-operative neurosurgical patient, since peak frequency of meningitis is in the first four days after surgery, when neurosurgical patients frequently have meningismus, headache, altered

mentation or low grade fever (Mangi et al., 1975). In the 48% of patients whose onset is >1 week post-operation, the infection is commonly indolent, without striking meningitic features. Late fever >38°C is often the only clue on examination. Similarly when lumbar puncture is performed, post-operative cellular pleocytosis and increased protein are easily confused with CSF changes due to bacterial meningitis, since the latter is not striking in many of the cases (Fig. 25). Hypolycorrhachia, which is a very uncommon post-operative change, was the most helpful clue to the diagnosis in the series of Mangi et al. (1975). The critical importance of a Gram stain of CSF sediment in this setting cannot be over-emphasized.



Analysis of cerebrospinal fluid that contained the first isolation of a gram-negative bacillus. The broken line indicates upper limits of normal for each determination. Values for each item were not available for every patient. ● = neurosurgical, ○ = neonatal, △ = miscellaneous.

Figure 25. CSF findings in post-operative neurosurgical patients. Mangi, Quintilliani & Andriole, 1975.



. Relationship of sugar in cerebrospinal fluid to etiologic organism and survival.

Relationship of leukocyte count in cerebrospinal fluid to causative pathogen and survival.

Figure 26. CSF findings in community acquired bacterial meningitis. Carpenter & Petersdorf, 1962.

In contrast to infections occurring within days or weeks after neurosurgery, infections of ventricular shunts occur from the first month to more than a year after placement (Schoenbaum, Gardner & Shillitoe, 1975). Ventriculo-peritoneal (VP) and ventricuarlo atrial (VA) shunts have a similar infection rate of about 22%. The usual organism is *S. epidermidis*, *S. aureus* or *Propionobacterium acnes*. The most commonly isolated *S. epidermidis* strain is Baird-Parker S.II, which produces a mucoid substance that promotes adherence to smooth prosthetic surfaces (Holt, 1970). However patients with intracranial shunts also appear to be at enhanced risk of meningitis due to classical agents (Shurtleff et al., 1971; Schoenbaum, Gardner & Shillitoe, 1975), with an incidence of approximately 200/100,000 annually. Infections due to *S. epidermidis* and *P. acnes* are remarkably indolent; when *S. aureus* is the agent there is usually tenderness and erythema over the shunt. Most patientswith VA shunts have

bacteremia, which can be enhanced by pumping the shunt prior to drawing blood. VP shunts infections rarely cause bacteremia. If CSF and blood cultures are negative and the diagnosis is in question, CSF should be cultured directly from the shunt reservoir or valve. The highest rate of cure with antimicrobial therapy alone is 36% with a 10% mortality. Removal of the shunt combined with antibiotics, e.g. vancomycin, gives a 93% cure rate and a 3% case-fatality rate (Schoenbaum et al., 1975).

Infective Endocarditis

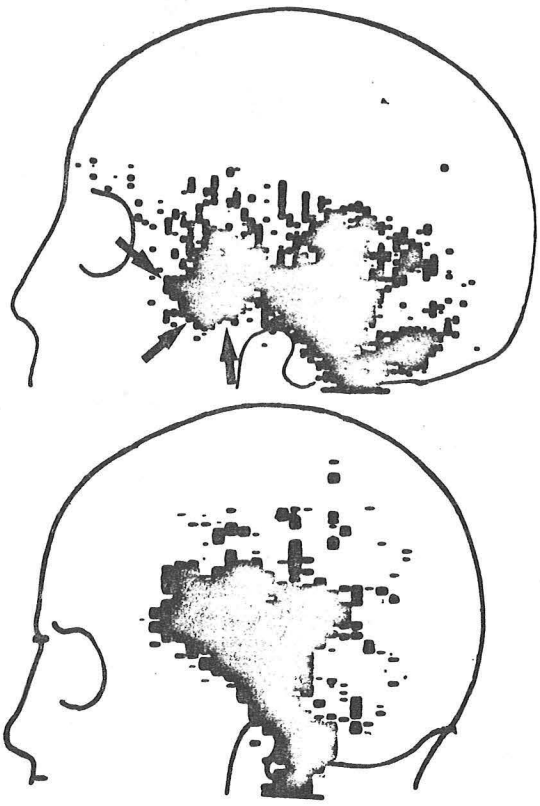
Meningoencephalitis is the most common neurologic complication of infective endocarditis (Ziment, 1969). The patient may present with the appearance of bacterial meningitis with a purulent spinal fluid (Bergen & Dermksian, 1957), but other neurologic involvement is also invariably present, including cerebritis, brain abscess or mycotic aneurysm. In any patient with unexplained culture-negative meningitis, or isolation of an enterococcus or viridans streptococcus from CSF, the diagnosis of endocarditis should be considered and evaluated. In addition any patient with pneumococcal meningitis may have associated endocarditis, especially if pneumonia is present (Colomiati's triad) and careful examination for features of endocarditis is essential.

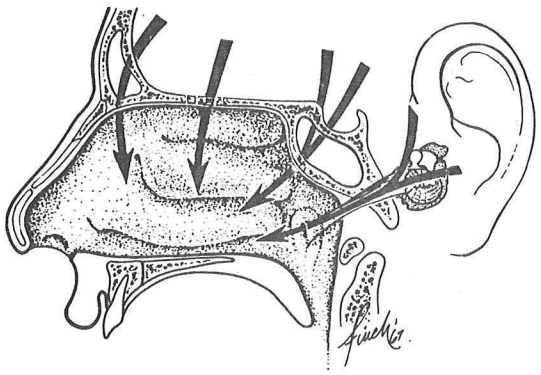
Recurrent Bacterial Meningitis

Eleven per cent of patients with pneumococcal meningitis have had more than one episode of bacterial meningitis, whereas only 0.2% of cases due to other agents have had a previous episode (Levin et al., 1970). Patients with recurrent disease differ significantly in several respects from initial cases: a) they are more likely to give a history of significant head trauma (35%), b) they are predominantly male, c) they seek care earlier (53% within 24 hours vs. 25% in initial cases), d) they are virtually all alert on admission and have a low mortality (<6%) but e) more neurologic complications (30%), and f) uniformly have a pneumococcal etiology (89%). In addition recurrent cases are somewhat more likely to have a positive blood culture, probably illustrating secondary bacteria, since they are less likely than initial cases to have a respiratory prodrome or associated extrameningeal infection.

The majority of these patients have congenital, iatrogenic or traumatic dural defects. However hemoglobinopathy should be ruled out, especially in Black children, together with hypogammaglobulinemia, C3 deficiency and multiple myeloma (Table 27). Three kindreds have now been described in which deficiency of C3b-inactivator has been associated with recurrent pneumococcal meningitis (Thompson & Lachman, 1977; Seligman, 1980). Therefore when a low C3 is found, both C3 and C3b-INA deficiencies should be considered.

Dural defects occur in each of the cranial fossae and along the spine. Dermal sinus communications with the subarachnoid space are found at the occiput and the sacrum, since midline fusion of the epithelial ectoderm along the dorsum of the embryo begins centrally and proceeds both cranially and caudally. Acquired defects as a result of decubitus pressure ulcers occur in paraplegic patients. Communicating dural defects in the floor of the anterior fossa occur (1) most often in relation to the cribriform plate, either as a result of fracture with a dural tear, as a result of an eroding subarachnoid cyst, encephalocoele or tumor, or a congenital fistula. Alternate communications can occur (2) anteriorly through the frontal sinus, or (3) posteriorly through the sella into the sphenoid sinus (Fig. 27); the latter occurs as a complication of empty sella syndrome, an expanding subarachnoid cyst of the sella. These defects give rise to CSF rhinorrhea, which should be distinguished from "nasal hydrorrhea" by (1) demonstration of glucose and (2) demonstration of the absence of a stringy mucin clot on adding acetic acid. The glucose oxidase strip is not a satisfactory tool for this purpose, as it is too sensitive. CSF rhinorrhea may also occur as a result of a leak through the eustachian tube from the ear, a so-called "closed" temporal bone CSF fistula, which drains past an intact tympanic membrane.





Some pathways for CSF rhinorrhea.

Figure 27. Above. From DiChiro et al., 1968.

Figure 28. Left above, an isotope cisternogram in a case of CSF rhinorrhea with communication from a sellar cyst through the sphenoid sinus. Left, a normal cisternogram. DiChiro, et al., 1968.

Table 27

Communication	Route of CSF Leak	Associated Defects
Middle fossa	Extralabyrinthine	Tegmen tympani fistula Longtudinal temporal bone fracture Congenital persistence of the petrosquamous suture
Posterior fossa	Labyrinthine	Stapedial foot plate defect Klippel-Feil Syhdrome Congenital absence Congenital, post-operative or traumatic fistula Cochlear aqueduct cyst Mondini's malformation (labyrinthine agenesis) Acoustic neuroma & posterior fossa tumors
		Transverse temporal (petrous) bone fracture

Biggers & Howell, 1973; Schulz & Stool, 1970; Stool et al., 1967; Morus-Jones, 1974; Pariser & Birken, 1976.

Patients with persistent CSF rhinorrhea incur an ultimate risk of meningitis of 14-25% (Lewin, 1954; MacGee et al., 1970).

Route of CSF otorrhea may be either extralabyrinthine from the middle fossa, or through the labyrinth from the posterior fossa. The anatomic routes of these lesion are shown in figures 29 and 30; the associated defects are displayed in Table 27.

Table 28. Features of Recurrent Bacterial Meningitis

Pneumococcal	Early care sought
Male predominance	Alert on admission
Head trauma (>6 mo prior)	Low mortality
Age < 29	Neurological complications
Positive blood culture	

Levin et al., 1972.

The labyrinthine route is taken through the tegmen tympani, the boney roof of the mastoid antrum and typmpanic cavity (Fig. 30). The intralabyrinthine route occurs most commonly

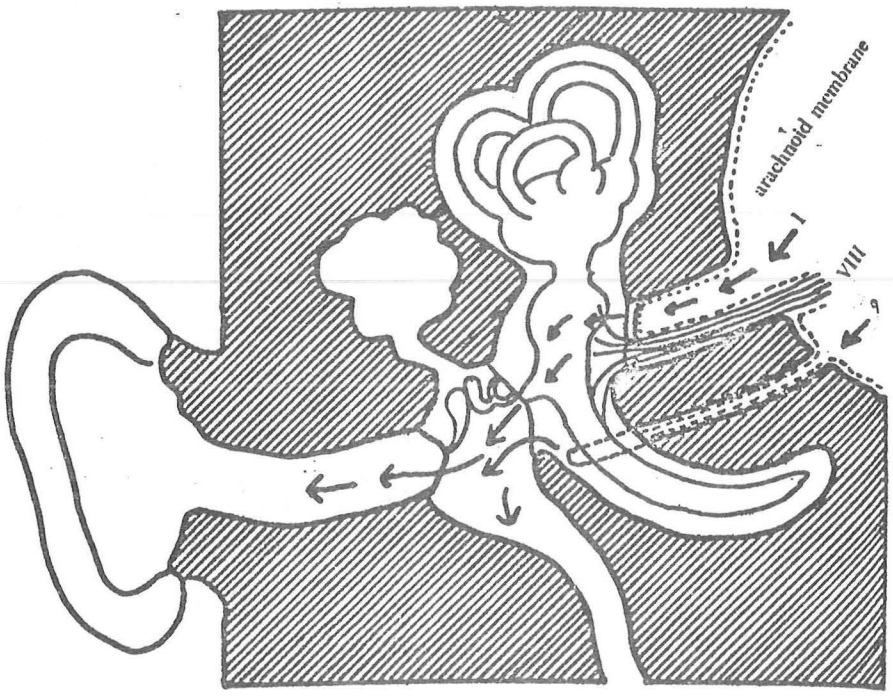


Figure 29. Two routes by which CSF leaks occur in congenital and acquired CSF otorrhea (Manaka, Hashimoto & Nawata, 1976).

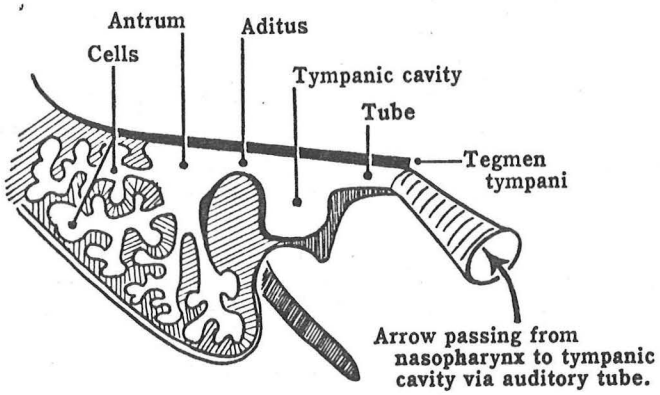


Diagram of Tegmen Tympani

The mastoid air cells are in communication with the outside air via the mastoid antrum, aditus ad antrum, tympanic cavity, and bony and cartilaginous parts of the auditory tube.

A thin plate of bone, called the tegmen tympani, forms a roof for these.

Figure 30. From *An Atlas of Anatomy*, J.C.B. Grant. Williams & Wilkins, 1972.

through the stapedial footplate perforated as a result of congenital malformation, surgical injury or trauma. It should be apparent from the figure that a further communication through either the internal auditory meatus or the cochlear aqueduct is required to give CSF otorrhea. This may be part of a congenital malformation, e.g. labyrinthine agenesis (Mondini's malformation), a result of a cochlear ductal cyst, acoustic neuroma, an abnormally shallow internal meatus, or a result of a transverse petrous fracture.

Evaluation of the patient should begin with assessment of humoral immunity: serum protein electrophoresis, quantitative immunoglobulins, CH_{50}, and if appropriate, sickle cell test and hemoglobin electrophoresis. A careful cranial nerve examination, including tests of anosmia should be performed together with sinus and mastoid films. An isotope cisternogram (Fig. 31; D. Chiro et al., 1968) should be performed to identify a site of leak. A suitable isotope, e.g. ^{111}Indium, is introduced by lumbar puncture. Early (1/2-1 hours post-injection) scans identify posterior fossa leaks, 1-2 hour scans identify middle fossa leaks, including those through the sella turcica. Far anterior leaks are seen at 3-6 hours. Occasionally subarachnoid cysts communicating with a nasal cavity are seen only on a 24-48 hour scan. Polytomograms should be obtained of any leak site found. Repair can then be carried out, usually using a fascia lata graft.

Unusual Bacterial Meningitides

Salmonellosis. The central nervous system may be affected in two ways in the course of *Salmonella* infection, by direct invasion or indirectly by toxicity or hypersensitivity. Gulati et al. (1968) have noted that encephalopathy and peripheral vascular collapse have replaced intestinal hemorrhage and perforation as the most common complication of typhoid fever.

Non-typhoidal salmonellosis, when associated with bacteremia, may produce metastatic infection with predilection for meninges, bone, arterial endothelium and endocardium; salmonella serotypes *cholerasuis* and *typhimurium* are particularly prone to produce septicemia and ensuing focal infections. Impaired function of the mononuclear phagocyte system, as in lymphoproliferative disease, and chronic hemolytic anemia, schistosomiasis, malaria and bartonellosis, favor sustained high-grade salmonella bacteremia and therefore meningitis; in additional antecedent meningeal injury, as after meningococcal and luetic meningitis, predisposes to salmonella meningitis. Since typhoid fever is characterized by sustained bacteremia, *S. typhi* and the paratyphoid group (Athoout et al., 1970) may also cause purulent meningitis. Salmonella meningitis is six times more common in children than adults and most cases occurring in the neonate. The reported neonatal cases have generally occurred in nursery epidemics; basilar localization with resulting obstructive hydrocephalus is particularly prone to complicate the neonatal form (Rabinowitz & MacLeod, 1972). The presence of salmonella meningitis is an indication for ^{67}gallium-citrate and bone scan to identify other sites of infection.

Chloramphenicol, 750 mg every six hours for two weeks, is the drug of choice for adult typhoidal or septicemic syndromes of salmonella infection, with or without meningitis. For chloramphenicol-resistant strains, ampicillin or amoxicillin and the combination of trimthoprim-sulfamethoxasole are acceptable alternatives, provided the organism is sensitive in vitro to the drug chosen. Intravenous ampicillin is the drug of choice in the infant with complicated salmonellosis, 100 mg/kg in the first week of life and 200 mg/kg thereafter. Salmonellae are commonly sensitive in vitro to tetracycline, cephalosporins and aminoglycosides, but these drugs are clinically ineffective and have no place in the treatment of salmonella infections.

In response to treatment, the frank delirium of typhoid subsides with the fever in 3-5 days, but psychotic symptoms and cranial neuropathies, such as deafness, respond more slowly. Meningitis due to serotypes *paratyphi, schottmuelleri* and *panama* has been generally associated with recovery; that due to other serotypes, especially *enteritidis, typhimurium* and *havana* carries a poor prognosis (Black et al., 1960). In the neonate, the 10% case fatality rate of salmonellosis rises to 80-90% when complicated by meningeal involvement.

Anaerobic bacterial meningitis. In contrast to their important in brain abscess, anaerobes are not often implicated in meningitis. The mean proportion of meningitis due to anaerobes in commonly cited series totalling 1,027 cases is 0.2% (Carpenter & Petersdorf, 1962; Swartz & Dodge, 1965; Karandanis & Shulman, 1976; Finland & Barnes, 1977). However in five smaller series, anaerobes have accounted for 5-10% of cases, and because they are fastidious, they may also account for some of the 5-10% of purulent meningitdes that are culture-negative. Several features of the 198 cases reviewed by Finegold (1977) and additional cases reviewed by Reich & Maki (1979) are worthy of comment. As in staphylococcal infection of the CNS, there was frequently associated surgery, trauma or contiguous infection, and there were five cases of localized meningitis. When underlying otitis media or mastoiditis were the predisposing factors,

Fusobacterium species are the most likely isolates. Post-operative and post-traumatic anaerobic meningitis was most commonly related to *Clostridium perfringens*. These two species were rarely isolated under other circumstances. In contrast *Bacteroides* spp. were found in all chemical settings of purulent meningitis including hematogenous spread from a distant focus. Anaerobic meningitis is associated a greater likelihood of focal neurologic deficit (60%), sometimes due to associated brain abscess, than is aerobic bacterial meningitis. Mean duration of illness prior to admission is long (10 days). Anaerobic meningitis is not especially a disease of immunosuppressed patients. Gram stain of CSF demonstrate the organism in 70% of cases. The mortality rate is 44% higher (70%) if associated with coma, abscess or venous sinus thrombosis.

About 35% of cases were associated with brain abscesses, but anaerobic meningitis contrasted with brain abscesses in two respects: meningitis was associated with bacteremia in 17%, while brain abscesses alone rarely (4%) is; meningitis was most after (92%) a monomicrobial infection, whereas brain is usually polymicrobial. Clues to the diagnosis of anaerobic meningitis are 1) associated hemolytic anemia (when clostridial), 2) foul odor of drainage from a concomitant site of infection or of the spinal fluid itself, 3) radiographic evidence of tissue emphysema, 4) characteristic Gram stain morphology and 5) failure to culture an organism from obviously purulent spinal fluid. Because of penicillin resistance of *Bacteroides fragilis* and some strains of *Fusobacterium*, as well as the relative resistance of *C. ramosum*, chloramphenicol is the drug of choice for suspected anaerobic meningitis. In the infant, carbenicillin is an acceptable alternative to chloramphenicol; metronidazole also has a suitable spectrum of activity against anaerobic bacteria, and reaches therapeutic concentrations in CSF, but has not been adequately studied in infants.

IV Diagnosis in Acute Purulent Meningitis

Routine Evaluation

The essential first step in the diagnosis of meningitis is the decision to to perform a lumbar puncture. As Carpenter & Petersdorf emphasize, no single sign or symptom of meningitis is consistently present. Certainly the possibility of meningitis should be considered in *any* febrile patient to the extent of seeking meningeal and neurologic signs. The diagnosis should be seriously considered when fever is accompanied by lethargy, prostration, severe headache, vomiting, photophobia

Table 29. Suspicion of Bacterial Meningitis

Fever associated with any of the following:	Confusion or Lethargy
	Unusually severe headache
	Acute neurologic deficit
Vomiting	
Photophobia	
Suggestive rash	
Headache	
"Toxicity" or prostration	
Previous head trauma or bacterial meningitis (or other predisposing conditions, Tables 7, 21, 24)	

a rash that is petechial, purpuric or maculopapular, or a predisposing condition (Tables 7, 21, 24), such as history of head trauma or previous bacterial meningitis. Even in the absence of fever, the diagnosis should be considered in (a) acute confusional states, even if apparently explained by ketoacidosis, hypoxia, alcoholic intoxication, heat stroke, etc., (b) severe headache, (c) headache associated with vomiting.

In cases in which a severe headache or neurologic deficit has been sudden in onset (<30 minutes), the possibility of intracranial hemorrhage should of course be evaluated by emergency brain scan or computerized tomogram (CAT) before a lumbar puncture. Suspicion of a brain abscess is also grounds for obtaining an emergency scan before performing an LP, but potentially disastrous delay in diagnosis and appropriate therapy should be weighed very carefully in such a decision (cf. below).

Standard laboratory evaluation of patients with suspected acute meningitis should include blood culture (cf. Table 30) and culture of other involved sites, as well as of CSF. If turbid CSF is noted upon LP, the first dose of an appropriate antibiotic should be given immediately I.V.

Cultures and Gram stain of CSF should be taken from the centrifuged sediment, after 15 mintues at the highest setting of a standard clinical centrifuge. A full 10 ml should be centrifuged, if CSF pressure has not precluded removal of this much volume. Centrifugation does not sediment bacteria very effectively at forces generated by a clinical centrifuge (up to 1000g), but neutrophils containing bacteria are sedimented. Sixty to 90 minutes of centrifugation would be required to sediment most of the pneumococci in a specimen at a maximum (1000g) setting and 90 minutes for *H. influenzae*. Thus the chances of finding bacteria may be enhanced somewhat by prolonging centrifugation for an hour, if an initial Gram stain is negative. If a centrifuge is available that runs at >5000 rpm, that may be helpful. Approximately 10^5 organisms/ml are required before they are likely to be found microscopically. The sensitivity of the Gram stain is founded on the fact that most patients with meningitis have CSF colony counts in excess of 10^5/ml (Feldman, 1976).

Table 30. Usefulness of CSF Sediment Gram Stain And Blood Culture

	Positive Blood Culture (%)	Correct Positive* CSF Gram Stain	Positive CSF Gram Stain & Negative Culture
S. pneumoniae	24-85%	84%	9%
N. meningitidis	33-76	62	13
H. influenzae	32-86	70	4
All agents	31-65%	65-80%	3-7%

Carpenter & Petersdorf, 1962; Haggerty & Ziai, 1964; Swartz & Dodge, 1965; Tugwell et al., 1976; Overturf et al., 1977; Finland & Barnes, 1977; Romer, 1977; Underman et al., 1978.

*Incorrect positive Gram stains were reported in 6-14% of cases.

The spinal fluid sediment should be inoculated on warm blood agar and chocolate (or Mueller-Hinton) agar plates and in thioglycollate broth. Selective media should not be used. The plates should be incubated at 35-37°C in a candle jar to provide CO_2. Moisture should be provided by placing a wet filter paper or gauze pad at the bottom of the jar; the plates should be shielded from the pad to prevent contamination.

Microsopic examination of CSF should be performed immediately and not merely "sent" to the laboratory.

To enhance the sensitivity of culture, Isenberg et al. (1974) recommend filtration of CSF through 0.45 μ filter and direct culture of the filter on agar. Bailey & Scott (1974) suggest culturing the residual sediment directly in the collection tube by adding 5 ml of cooled destrose ascitic fluid semisold agar, after routine culture and Gram stain. There is no published data bearing on these techniques however.

Table 30 displays the sensitivity of the CSF Gram in several series. Its value is that it permits immediate and etiologically specific confirmation of a diagnosis of bacterial meningitis. In pneumococcal meningitis, i.e. most adult cases appearing in an emergency room, the sensitivity was 84% in Swartz & Dodge's series. In 3-7% of cases in three series, the Gram stain was the sole basis of diagnosis because of negative cultures. However when Gram stains were reported by physicians, incorrect identification of the organism occured in 6-14% of positive Gram stains. The most common errors involve *H. influenzae*, because it is small and difficult to distinguish from a pink background. False positive Gram stains have been reported due to contamination of reagents, glass slides or CSF tubes. However, relatively heavy contamination is required; 10^8 bacteria/ml of stain do not affect the result if slides are washed well. Bacteria adherent to epithelial cells suggests skin contamination.

For these reasons saving both the CSF and the Gram stain(s) for later review should be standard practice. Swartz & Dodge noted that a nocturnal Gram stain interpretation was commonly reversed in the light of morning. At least 20 minutes should be spent studying the Gram stain before calling it negative. If the Gram stain is negative, then a wet mount for amebae should be done.

done. A VDRL should always be done.

At times the interpretation of CSF findings in suspected meningitis is uncertain, since in early aseptic meningitis a predominance of neutrophils may be found and among these patients, 10% have a CSF glucose <50% of the plasma glucose values (Feigin & Shackelford, 1973). Although the mean number of cells is relatively low, usually <500/cmm, the cell count is also low in early bacterial meningitis. Several reports covering 25 cases have appeared in recent literature of "normocellular" bacterial meningitis (Moore & Ross, 1973; Rapkin, 1974; Fischer et al., 1975; Smales & Rutter, 1979; Milne & Hamilton, 1976). These cases seem to be of two sorts, the patient who has trivial or no CSF abnormalities but a positive CSF culture, and the patient with a normal CSF who 18-48 hours later worsens and has bacterial meningitis demonstrated on lumbar puncture (LP). Some but not all of the latter group were bacteremic at the time of the original LP. Feigin and Shackleford (1973) reviewed 31 cases of aseptic meningitis in which a second LP was performed because of an initial predominance of neutrophils. In 87% of thos tapped at 6-8 hours and 94% at $\geq$12 hours, a reversal to lymphocyte predominance occurred. Repeat lumbar puncture in stable patients with equivocal findings should be routinely performed at 6-8 hours. Blood cultures should be routinely obtained and patients with positive blood cultures should be re-examined and the LP repeated, if any suspicious symptoms or findings are still present.

A 15 year old girl was seen in the PMH ER with complaints of headache, fever and one episode of vomiting over the preceding three days. There was no nuchal rigidity and no papilledema. The CSF was normal but the patient was instructed to return the following day. She was unaccompanied by her mother on return and was turned away by the clerk. The following day she returned lethargic, with worse headache and a stiff neck. This time she had CSF leukocytosis and hypoglycorrhachia. Both the original blood culture and second CSF culture grew *S. pneumoniae*.

This case illustrates the pattern of meningitis following an initially normal LP. Whether the first LP is merely too early or may cause meningeal seeding during bacteremia is moot. However it is clear that patients with a positive blood culture and normal CSF, at the time of initial evaluation should have the lumbar puncture repeated unless substantially improved.

The Problem of Possible Brain Abscess

In three series of cases of brain abscess 13-22% of patients undergoing lumbar puncture exhibited signs of brain stem compression in the ensuing two hours (Morgan et al., 1974; Samson & Clark, 1973; Jefferson & Keogh, 1977). In comparison three (1.4%) of the Dodge and Swartz (1965) patients with meningitis exhibited herniation within two hours of LP and one patient herniated before LP. For this reason there is considerable concern about distinguishing between these two intracranial infections (Table 31). The most useful features that distinguish the two syndromes are: 1) papillederma, 2) fever >101°; 3) meningismus and 4) duration of symptoms prior to admission. A fifth feature, focal neurologic deficit, seems somewhat less useful taken alone. Only about 40% of patients with brain abscess have fever and nearly all of these are low-grade (<101°F), mean 99.5°. Meningismus in brain abscess is uncommon, but when seen with ataxia should suggest a cerebellar abscess; nevertheless in 17 cases of cerebellar abscess reported by Morgan & Wood (1975), none had meningismus. Most patients with brain abscess report symptoms of more than one week duration, while 75% patients with meningitis report symptoms of <1 week. As previously noted (p. 41-42), seizures in meningitis are usually brief and generalized though frequently focal.

Ocular seizures should suggest meningitis rather than brain abscess, even though "focal". Hemianopsia was unusual (2%) among the Dodge & Swartz patients but very common (17%) in some series of brain abscess. Hemiparesis is common in both diseases, but fixed hemiparesis that is not post-ictal should generally be attributed to parenchymal disease, e.g. brain abscess, until a scan is obtained.

Thus any patient with acute papilledema should have a CAT or brain scan and neurosurgical consultation immediately without performing an LP; if brain abscess is suspected, antibiotics usually penicillin and chloramphenicol should be started.

A patient with fever >101.5° and meningismus should generally be considered to have meningitis until the LP is done. If (s)he has had a sustained focal seizure, other than an ocular seizure, or a fixed hemiparesis that is not post-ictal, then an

attempt should be made to obtain a scan before the LP. If the scan cannot be obtained within the hour, then a decision must be made to either proceed with an LP or begin antibiotics. If the latter course is taken and the patient has meningitis, the possibility of making a diagnosis of purulent meningitis is probably not impaired, but the chance of establishing a specific etiology is reduced. The possibility that the patient has special risk of infection other than *S. pneumoniae* or *N. meningitidis* (Tables 23-26) should be weighed, as well as how stable the patient is. If the patient is stable, antibiotics should generally be delayed until after the LP. If the patient is unstable but likely to have an unusual bacterial meningitis, then LP should generally be done without further delay.

The patient with low grade or no fever and no meningismus, who has developed hemiparesis or hemianopsia, with or without obtundation, should have a scan before an LP, and antibiotics may be started depending on the urgency of the case.

Table 31. Distinguishing Between Brain Abscess and Meningitis

Papilledema	45%	<0.5%
Fever >101.5	6%	95%
Meningismus	9-12%	80-95%
Usual duration of symptoms	>1 week	<1 week
Seizure	26-33%	19%
Focal Sign	40%	15-20%*
Hemiparesis	26%	15%
Herniation post-LP	13-22%	1%

*Fixed and unrelated to seizure, not including cranial deficit or fixed eye duration.

Samson & Clark, 1973; Carey et al., 1972; Jefferson & Keogh, 1977; Morgan et al., 1973. Dodge & Swartz, 1965.

Partially Treated Meningitis

When a lumbar puncture is done for a suspected diagnosis of bacterial meningitis the chances are about one-fourth that the patient has already received an antibiotic (Converse et al., 1973; Dalton & Allison, 1968). Gram stains and cultures are often altered by this misguided therapy but cell counts, protein and glucose are not greatly altered (Jarvis & Sarena, 1972) unless the patient has been taking frequent doses for >48 hours. Therefore if a CSF pattern suggesting viral meningitis is found, that should be accepted; no antibiotics should be given, provided the patient is stable, and the LP should be repeated in 8-12 hours.

Ancillary Tests of CSF

These are of two kinds, those intended to distinguish between viral and bacterial meningitis and those intended to identify specific organisms. In the former category are LDH, pH, lactate, CSF anion gap, muramidase and lysozyme. The difficulty with all of these tests is that, although some discriminate well between viral and bacterial meningitis, they are no better than the combination of WBC, differential, protein and glucose.

Rapid tests for identification of bacteria in CSF suffer from a similar problem. Those best studied, counter-immunoelectrophoresis (CIEP) and latex agglutination, are only slightly more sensitive than the Gram stain.

In patients with negative CSF Gram stains, CIEP may yield a diagnosis within the hour, provided serum and urine are tested in addition to CSF (Feigin et al., 1976). The test is 90% sensitive in pneumococcal meningitis; if the culture is negative, so will be the CIEP. Limulus lysate assay is very useful in rapid diagnosis of neonatal Gram-negative meningitis (McCracken, 1976), but it has had limited study in adults (Jorgenson & Lee, 1978) and is not generally available.

ELISA methods of antigen detection may greatly improve the sensitivity of these systems. Harding et al. (1979) found it 25 times more sensitive than CIEP in detecting pneumococcal antigen. An equalling promising technique recently applied to detection of bacterial products in CSF is gas liquid chromatography (LaForce et al., 1979).

Culture-negative Meningitis

CSF cultures are negative in 9-15% of cases of acute purulent meningitis thought to be bacterial (Carpenter & Petersdorf, 1962; Haggerty & Ziai, 1964; Swartz & Dodge, 1965). Potential reasons for negative cultures are listed in Table 32. The cases that follow illustrate the need to critically re-evaluate the diagnosis of bacterial meningitis, when CSF culture are negative.

Table 33. Factors Accounting for Culture-Negative Bacterial Meningitis

1. Improper culture
2. Anatomic distribution of organisms; low concentration of organisms in lumbar CSF.
3. Wrong diagnosis or parameningeal suppuration.
4. Fastidious organisms, e.g. anaerobes.
5. Prior antibiotic therapy

Diagnostic Problems: Case Reports

#702149: A 41 y.o. engineer was admitted to his local west Texas hospital 4/29/79 with severe headache, fever, malaise, stiff neck. A lumbar puncture drained cloudy CSF under pressure (210 mm) and containing 2083 WBC (92% PMN), protein 170 mg/dl, and glucose 18 mg/dl (plasma 88). Gram stain demonstrated no organisms, and subsequent culture was negative. He was treated with intravenous "high dose" penicillin for 10 days with symptomatic resolution. On day 11 his CSF formula was: 249 WBC (100% lymphocytes), protein 135, glucose 40 mg/dl (plasma 95). During the ensuing week, he had intermittent headaches, which became severe three days before readmission 5/22/79. During this period he became progressively lethargic, disoriented and confused. On examination he had marked nuchal rigidity with a positive Kernig's sign. A brain scan was normal, so LP was performed: 5000 wbc (predominantlyPMN), glucose 16, protein 545 mg/dl. The Gram stain revealed no organisms; CSF culture was negative. He was treated with I.V. penicillin and chloramphenicol. Computed tomogram two days later showed a left thalamic mass lesion. He was transferred to PMH for surgical drainage. At operation adhesions were found in the interhemispheric fissure. The left lateral ventricle was entered through the corpus callosum where a grossly purulent choroid plexus was encountered obstructing a communication into a left thalamic abscess cavity. Gram stain of cavitary pus performed by a senior infectious disease consultant revealed two morphologic types of Gram-positive coccus, neither of which was recovered in culture. He subsequently completed a month of antibiotic therapy and returned to work as a design engineer for an oil and gas company.

Comments:

This case illustrates that a brain abscess lying close to the ventricular space can produce ventriculitis and meningeal inflammation without positive cultures. Indeed it may "leak" into the ventricle without producing the proverbial catastrophe of intraventricular rupture (Reed, Williams & Cooper, 1974). Had anaerobic cultures been done on spinal fluid they might well have yielded an organism. This illustrates the importance of the Gram stain; had an organism been demonstrated that did not subsequently grow or had more than one organism been seen on Gram stain that would have been strong presumptive evidence of anaerobic meningitis and possible brain abscess.

#690809: A 36 y.o. unemployed Black male alcoholic was well until February, 1979, when he developed frontal headaches, culminating after four weeks in an acute confusional state, nausea and vomiting. On admission he was obtunded, with a temperature of 103°F and a stiff neck. A 2-3 cm nodule on his forehead had been noted by the family for two weeks and was noted by the admitting resident; 20,000 wbc in his CSF were all PMNs and glucose was 3 mg/dl. No organisms were seen by an infectious disease consultant on the CSF Gram stain. Radiographs initially showed left frontal, maxillary and ethmoid sinusitis with opacification, and frontal osteomyelitis was apparent on a later film. When the patient's mentation cleared after a few hours of I.V. penicillin, CAT was delayed. His fever persisted and on the third day, he underwent trephination of the left frontal sinus and maxillary sinus irrigation on the left. Two aerobic streptococcal species were recovered from the maxillary sinus, including a viridans streptococcus.

Case #690809 continued

The following day an abscess was noted in the left frontal lobe with an extensive surrounding edema and cerebritis on CAT. He underwent bifrontal craniectomy; an epidural abscess was found overlying the left frontal lobe, subdural empyema was found bifrontally, and an intracerebral abscess communicated with the left subdural space. A viridans streptococcus and an anaerobic Gram negative-rod were recovered from the brain. CSF and blood cultures remained negative.

Comments:

This case illustrates the usually longer duration and indolence of symptoms with a brain abscess, but also shows that when direct communication beyond the abscess and subarachnoid space occurs, meningitis indistinguishable from primary bacterial meningitis results. Negative CSF cultures here as in the previous case were a clue that this was a more complicated disease than "simple" meningitis. The value of early ENT consultation is seen. All patients with bacterial meningitis should have an early CAT. A PMH Death Conference case discussed eight months ago by Dr. Robert Munford was a man who relapsed with his brain abscess after two weeks of therapy for "culture-negative meningitis".

#704463: This 55 y.o. alcoholic woman was admitted in June, 1979 as Ms. X after she was found by the Fire Department in a makeshift shelter under a bridge on Lamar Street in Dallas. She was somnolent between obscenities, hypotensive and febrile (101.8° F). She had pronounced nuchal rigidity, with Kernig's and Brudzinski's signs, jaundice, ascites and a generalized petechial rash with acral ecchymosis and hemorrhagic pustules. Her leukocyte count of 5600 included 29% bands; platelets were 70,000, Na 125 meq/L, K 3.7, CO_2 25, Cl 86; pH 7.56, pCO_2 30, pO_2 68; Bilirubin 10.5, alkaline phosphotase 38, SGOT 147, CPK 35, prothrombin time 18 sec (control 11.5), albumin/globulin ratio 1.9/4.2. After infusion of fresh frozen plasma, a lumbar puncture revealed 500 wbc (93% PMN), glucose 13 mg/dl (plasma 110), protein 43 mg/dl, non-reactive VDRL and opening pressure 250 mmH_2O. No organisms were seen on Gram stain. CIEP of CSF and urine for *S. pneumoniae*, *H. influenzae* and *N. meningitidis* antigens was negative, a CAT was normal. She was treated with volume replacement, phytonadione, thiamine.

Over the next three days on penicillin and gentamicin, she remained jaundiced, febrile and obtunded, developing leukocytosis, while blood and CSF cultures remained negative. There were still 510 wbc (88% PMN) in CSF. A proteus OX19 titer of 1:1280 then returned, and chloramphenicol was substituted for penicillin. Over the ensuing four days, her bilirubin fell, her WBC, platelets returned to normal, her fever subsided, and she became alert and oriented, though intermittently confused. A week later she suddenly evolved a severe lactic acidosis, followed by hypothermia, azotemia, and shock. Following unexplained death, a complement fixing titer of $\geq$1:256 to Rocky Mountain spotted fever returned.

Case #704463 continued

Comments:

Penicillin is not effective against Rickettsia rickettsii. A negative CSF culture was a clue that further investigation was needed. The case also illustrates one of numerous mimics of meningococcal meningitis.

#257135: A 15 y.o. Black girl was well until two weeks prior to her admission in February, 1979, when she experienced transient dysuria and blurred vision; three days pta she developed severe headache and sore throat, followed by abdominal pain and nausea. The night prior to admission, she vomited twice; the following day she was found stuporous in her car. She had a previous admission for gonococcal arthritis. On admission she required intubation because of depressed Cheyne-Stokes respiration. Her temperature was 103.6, BP 100/50, pulse 125. She was decoricate with leftward ocular deviation, sluggish pupillary responses and flaccid areflexive lower extemities. Her neck was supple, and she had red papular rash of the trunk and legs, with some pustules.

Laboratory findings included: WBC 16,200 (69% PMN, 18% bands), pyuria (5-10 wbc/hpf). CSF: opening pressure >400 mm H_2O, 498 wbc (92% PMN), glucose 3 mg/dl (Plasma 295), protein 604 mg/dl, Gram stain and CIEP for *S. pneumoniae*, *H. influenzae* and *N. meningitidis* negative. CAT was normal and remained so. Blood and spinal fluid cultures remained negative.

On penicillin (3 mu q 4h) over the next three days, she gradually regained consciousness, discontinued her endotracheal tube without incident and revealed a right hemiparesis, ataxic gait and slurred speech. Resolution of these was slow and fever lingered. LP was repeated twice without a VDRL. A blood VDRL was reported as 1:16 with + FTA-abs, but another LP was unsuccessful. She completed two weeks of intravenous penicillin. A month after discharge she exhibited drift of her outstretched extremity as the only residual of her right hemiparesis, but found calculation and concentration difficult. She has refused subsequent lumbar puncture.

Comments:

Although meningovascular syphilis could not be proved in this case without a CSF VDRL, it illustrates both the importance of critically reviewing cases whose CSF culture is negative and the importance of routine CSF VDRL in patients with meningitis. Her late appearing hemiparesis and dysphasia may have been due to cortical vein thrombosis.

V. Therapy of Bacterial Meningitis

Basic Principles: The "Blood-Brain Barrier"

Conventional criteria for susceptibility and resistance of microorganisms are generally based on expected *serum* concentrations of drugs tested. In CNS infections minimum inhibitory concentrations (MIC) of antibiotics must be gauged against achievable concentrations in brain, or in the case of bacterial meningitis, in CSF. CSF drug concentrations are determined at two sites: the brain capillary and the choroid plexus. The capillary is an anatomic barrier, the secretory selectivity of the choroid plexus, a physiologic barrier, and their combined operation creates a functional "blood-brain barrier"

The brain capillary. Outside the CNS, drugs and other plasma solutes pass out of the blood by an extracellular route through intercellular clefts between endothelial cells, and then through fenestrations in the capillary basement membrane (Fig.31), which are freely permeable to solutes < 20,000 daltons. In the brain, this route of emigration is blocked by tight junctions between endothelial cells of CNS capillaries (Katzman & Pappius, 1973; Davson, 1976). Therefore, to reach the extracellular fluid of brain and spinal cord, plasma solutes must run a transcellular gauntlet across an inner bimolecular lipid membrane, through the endothelial cytoplasm, across an outer bimolecular lipid membrane and a CNS capillary basement membrane that lacks fenestrations, and finally through an investment of glial cell foot processes (Oldendorf, 1974).

The selectivity of the CNS capillary governed in the first instance by a drug's relative affinity for *plasma* water and protein on one hand and endothelial *membrane* lipid and carrier protein on the other (Oldendorf, 1976). A drug may also be subject to degradative membrane and cyotoplasmic enzymes on its obstacle course into brain.

The most predictable element in this pharmacologic steeplechase is solubility of a drug in the endothelial membrane (Oldendorf, 1976); membrane solubility is favored by a low degree of ionization at physiologic pH and a high degree of lipid solubility of the unionized drug. The charge site of an ionized drug, like a sulfonamide, firmly anchors it in plasma water. The degree that an unionized species will be drawn into the inner lipid membrane can be predicted from the lipid-water partition coefficient of the drug (Fig.31), which expresses the *relative* affinity of drug for an oil, such as octanol, as compared to water. The ideal partition coefficient lies in the range of 0.03-0.04. Higher concentrations are not associated with greater penetration of brain, but may be associated with rapid clearance by lung or redistribution to adipose tissue, thereby limiting a drug's CNS activity. Certain highly lipid-soluble drugs, on the other hand, bind avidly to tissue sites in brain permitting concentration of the drug in brain, e.g. chloramphenicol is concentrated in brain 9-fold with respect to plasma (Kramer et al., 1969). Measurements of drug levels in CSF may not fully reflect this property, e.g. CSF chloramphenicol concentration is only 50% of simultaneous plasma levels.

A second mode of transit in some instances may be membrane carrier proteins, such as transport glucose, however this mechanism of antibiotic transport has received little attention. Aldomet may be actively transported into brain, but no examples of antibiotic active transport at the brain capillary are known.

The choroid plexus and weak organic acid pump. As in urinary, respiratory and biliary epithelia, highly selective secretory cell stands between pericapillary extracellular fluid and the secretory surface of the choroid plexus (Lorenzo & Spector, 1976).

Regulation of CSF constituents occurs at the choroid plexus in both directions. Plasma is filtered through fenestrated capillaries, and this plasma dialysate is selectively secreted by choroidal epithelial cells. In addition, certain CSF constituents are actively reabsorbed by the choroidal epithelial cell, contributing to their new efflux from the CNS. Physiologically, this function serves to clear the CSF of brain amines, prostaglandins and other metabolically active substances. Pharmacologically, the choroid plexus functions to remove tertiary and quarternary amines, e.g. narcotics and anesthetics, as well as weak organic acids, e.g. salicylate and penicillin (Lorenzo & Spector, 1976).

The active transport system for weak organic acids in the choroid plexus removes penicillin and *p*-aminosalicylic acid (PAS) and is inhibited, like its renal counterpart, by probenecid (Fishman, 1966; Dacey & Sande, 1974). The clearance of penicillin from CSF to blood by the weak organic acid pump is several-fold greater than that from blood to CSF. Therefore when probenecid is administered, both the renal and choroid plexus pumps are inhibited, and the concentration of penicillin in CSF increases out of proportion to its increase in plasma. For uncertain reasons the increase in brain concentrations of penicillin is less than that in plasma, possibly because of saturation of tissue binding sites at lower concentrations or competition between probenecid and penicillin for entry into brain (Braude, 1976).

The higher concentration of penicillin achieved in meningitic CSF is conventionally attributed to increased penetration of a barrier rendered more permeable by inflammation. However, in rabbits with *Hemophilus influenzae* or staphylococcal meningitis, penicillin clearance form CSF by the weak organic acid transport system is also impaired (Spector & Lorenzo, 1974). In children peak CSF levels of penicillin one hour after intravenous injection are similar on the first day and tenth day of therapy for pneumococcal meningitis, suggesting that penicillin *entry* into CSF is not enhanced in early meningitis. However, *disappearance* of CSF penicillin is much more

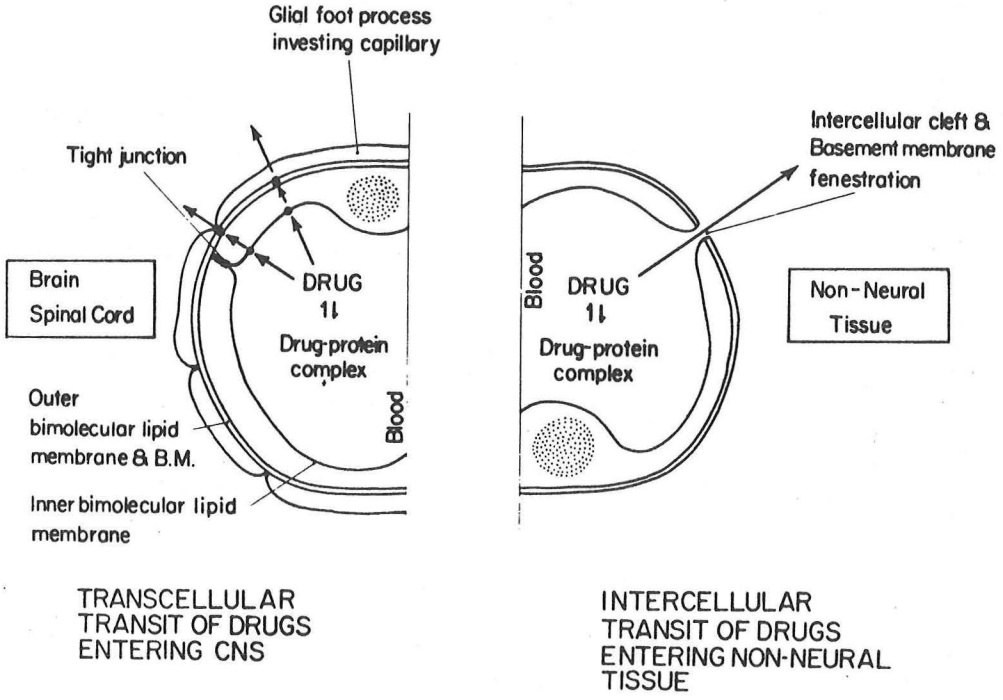
rapid late in the course than initially (Hieber & Nelson, 1977). This suggests that repair of the weak organic acid pump may be more important than diminished capillary permeability in determining CSF penicillin levels late in resolving bacterial meningitis.

In contrast the β-lactamase-resistant semi-synthetic penicillin, nafcillin, as well as certain cephalosporins, do not seem to be transported out of CSF by a probenecid-sensitive pump, although renal secretion of nafcillin, cefazolin and cefacetrile is inhibited by probenecid (Dacey & Sande, 1974). Only modest increases in CSF concentrations of these drugs are seen when probenecid is administered, i.e. in proportion to increased plasma concentration. This may reflect important carrier affinity differences between the renal and the choroid plexus weak organic acid pumps. Cephalothin is however metabolized by the choroid plexus to its less active product, desacetylcephalothin (Nolan et al., 1980). This choroidal plexus function is also inhibited by inflammation, which may account for the high levels of cephalosporins achieved during bacterial meningitis. The clinical patients with bacterial meningitis who are treated cephalothink initially improve but relapse (Southern & Sanford, 1969). Relapse on cephalosporins may coincide with repair of choroid plexus metabolism rather than reconstriction of a permeability barrier.

The aminoglycoside, gentamicin, is actively transported out of CSF. So little aminoglycoside penetrates the CNS capillary or the choroid plexus at usual plasma concentrations that efflux is ordinarily of little practical consequence (Lorenzo & Spector, 1975). Active transport may be important when aminoglycosides are administered intrathecally however.

Our ability to enhance CSF levels of selected antibiotics by pharmacologic ablation of their transport system has potential utility in the management of meningitis due to relativley resistant new strains of penumococci and group B

streptococci; this strategy may also prove useful in carbenicillin therapy of meningitis due to susceptible gram-negative bacilli. On the other hand interference with a major clearance mechanism for removal from CSF of prostaglandins, neurotransmitters and possibly toxic metabolites (Davson, 1976) should be approached with caution, especially in CNS inflammation; furthermore, probenecid is believed to compete with penicillin for entry into brain parenchyma (Braude, 1976), and should be avoided in parenchymal bacterial infections, such as brain abscess or cerebritis.



The structural component of the "blood/brain barrier": anatomic differences between neural parenchymal and systemic (extraneural) capillaries. Unlike other neural capillaries, those of the hypophysis, tuber cinereum, area postrema, pineal gland, and preoptic recess resemble systemic capillaries. B.M. = basement membrane.

Figure 31. From Murphy, Mackowiak & Luby, 1979.

Consideration of New Antibiotics

The greatest therapeutic problem in bacterial meningitis has been the management of aerobic Gram-negative bacillary meningitis. The most effective antibiotics available for these organisms do not achieve adequate levels in cerebrospinal fluid. Although some strains of enteric AGNB are susceptible to chloramphenicol or trimethoprim-sulfamethoxasole, which achieve excellent levels in CSF, many are not. Therefore it has been encouraging to learn within the past year that several of the "third generation" cephalosporins achieve satisfactory levels in rabbit CSF and are effective in treating experimental AGNB meningitis in the rabbit. The most promising are tabulated below. In the mean time therapy of Gram-negative meningitis requires administration of chloramphenicol and/or trimethoprim-sulfamethoxasole in combination with IV and intrathecal aminoglycoside until sensitivities are known. If Pseudomonas is identified or suspected, carbenicillin or ticarcillin should be added. If the patient fails to improve, then an intraventricular (Ommaya) reservoir must be placed for intraventricular administration. Unfortunately neurosurgeons are sometimes reluctant. Although Kaiser & McGee (1975) showed that gentamicin admininstered at the lumbar sac does not achieve ventricular levels above 1

Investigational Agents for Gram-negative Meningitis

Moxalactam (Ly 127935)

RO 13-9904

Cefaperazone (T1551)

Cefotaxime (HR 756)

microgram/ml, this study was not accompanied by cisternographic studies. Cisternography may have the potential of identifying those patients in whom drug may reach the ventricle from the lumbar sac by virtue of relative obstruction to bulk flow at the arachnoid villi.

VI. Evaluation of Therapy and Prognosis

Persistent or recurrent fever. When currently recommended antibiotics are used, treatment failure in bacterial meningitis is a distinctly unusual, though commonly considered, cause of prolonged or recrudescent fever (Balagtas et al., 1970). More common reasons for new or persistent fever are catheter-induced phlebitis (48%), drug hypersensitivity (16%), nosocomial infection and extracranial foci of infection. In the adult with culture-proven bacterial meningitis such fevers are uncommonly due to subdural effusions or to suppurative complications of meningitis, e.g. brain abscess, venous sinus thrombophlebitis or other parameningeal infection, mastoiditis, otitis.

The emergence of multiply resistant strains of pneumococci in South African patients with meningitis and other life-threatening infections poses a new clinical hazard of unknown proportions (Applebaum et al., 1977). So far only one case of resistant pneumococcal infection has been reported in the U.S., however 2.4% of 6000 isolates in Alberta recently exhibited intermediate resistance to penicillin (0.1-0.9 g/ml) (Dixon, Lipinski & Graham, 1977). Accordingly attention must now be paid to susceptibility tests of pneumococcal isolates. If an isolate in pneumococcal meningitis is resistant to chloramphenicol as well as penicillin, then rifampin and trimethoprim-sulfamethoxasole should be initiated empirically, until sensitivity to these drugs can be tested.

Repeated lumbar puncture. Some authors recommend repeating the CSF examination at 24-48 hours and again at the end of therapy to evaluate response (Underman et al., 1978). However in *Hemophilus*, pneumococcal and meningococcal meningitis the persistence of positive cultures after 48 hours of therapy is related to the initial concentration of bacteria in CSF and not to subsequent success of therapy (Feldman, 1977). Furthermore nearly 50% of patients have persistent pleocytosis, hypoglycorrhachia and elevated CSF protein after 14 days of therapy and yet do not relapse

(Jacob & Kaplan, 1977). The use of repeated CSF examination may be helpful in patients with Gram-negative meningitis, in determining the need for intraventricular therapy, particularly when quantitative culture is performed. In general, however, physical examination and interview yield more useful information than repeated lumbar puncture. Two cases of paraspinous staphylococcal infection in patients subjected to repeated lumbar puncture to demonstrate improving CSF formulas have been seen at PMH in the past two years. *Res ipsa loquitur.*

Prognosis of Bacterial Meningitis

Of the common bacterial agents of meningitis beyond the neonatal period, the pneumococcus is the most lethal. The overall mortality in treated penumococcal meningitis is 30% or more as compared to 5-8% in *Hemophilus* meningitis and 6-15% in meningococcal meningitis. Prognostic factors associated with poor outcome of any bacterial meningitis are age above 50 or below one year, bacteremia, associated sites of infection, associated illness, e.g. diabetes, delayed therapy and altered state of consciousness on admission. The mortality rate in pneumococcal meningitis in the patient who is alert on admission is 4% or less, but more than 40% in comatose or semicomatose patients. Most deaths due to *Hemophilus* meningitis occur in the first year of life, usually with an associated site of infection, e.g. osteomyelitis, arthritis or pneumonia. Regardless of age, *Hemophilus* meningitis mortality is usually in the uncommon fulminant presentation of the disease, death occurring in the first 24 hours of hospitalization.

Specific adverse prognostic factors in meningococcal disease are the elements of the meningococcemic syndrome: 1) less than 100 leukocytes in the CSF associated with positive blood cultures, 2) hypotension, 3) petechiae appearing 12 hours or less prior to admission, 4) a rectal temperature above 40° C, 5) a blood leukocyte count less than 15,000, 6) thrombopenia. Nearly all patients with less than two of these features survive, whereas 70-90% of patients with the first four factors die (Niklasson et al.,

1971). The severity of CSF glucose depression, protein elevation and pleocytosis does not correlate with outcome (Carpenter & Petersdorf, 1962).

The overall rate of observed sequelae of bacterial meningitis is 20% but is only 4% after meningococcal meningitis. The most common sequelae of bacterial meningitis are deafness (5-10%), hydrocephalus (5%), and seizures (4%). The proportion of patients show intellectual function is affected is difficult to assess but significant (Underman et al., 1978). Hemiparesis or quadriparesis occurs in 0.2 to 10% of surviviors, but most of these resolve in the first year of observation (Feigin & Dodge, 1976). Less common late sequelae are ataxia, amaurosis and cranial nerve palsies. Post-meningitic children should be evaluated with audiometry, so that learning disability related to deafness may be avoided, and with serial head measurement for early detection of hydrocephalus. Neurologic psychomotor and developmental testing are indicated at intervals during the first year of convalescence.