Cerebrospinal Fluid Outflow Resistance in Rabbits with Experimental Meningitis

ALTERATIONS WITH PENICILLIN AND METHYLPREDNISOLONE

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ABSTRACT Acute bacterial meningitis may be associated with increased intracranial pressure, neurological sequelae such as communicating hydrocephalus, and a slow response to antibiotic therapy. Alterations in cerebrospinal hydrodynamics are at least partially responsible for these complications. Constant, low-flow short-duration manometric infusion studies through a hollow-bore pressure monitoring device in direct continuity with the supracortical subarachnoid space were performed in rabbits with experimental meningitis. Maximal resistance to cerebrospinal fluid (CSF) outflow from the subarachnoid to vascular space was markedly increased in acute pneumococcal meningitis when compared to control, uninfected animals (6.77±3.52 vs. 0.26±0.04 mm Hg/μl per min, $P < 0.001$). Similar elevations (8.93±4.15 mm Hg/μl per min) were found in experimental *Escherichia coli* meningitis. Despite eradication of viable bacteria from the CSF by penicillin therapy during the acute stage of pneumococcal meningitis, resistance remained elevated (6.07±4.68 mm Hg/μl per min) and had not returned to norml up to 15 d later. Administration of methylprednisolone during the early stages of acute pneumococcal meningitis reduced mean peak outflow resistance towards control values (0.59 mm Hg/μl per min) and no "rebound" effect was apparent 24 h later. These hydrodynamic alterations in experimental meningitis prevent normal CSF absorption and decrease the ability of the brain to compensate for changes in intracranial volume and pressure.

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INTRODUCTION

The mortality rate in pneumococcal meningitis has remained constant since the introduction of high-dose penicillin therapy in the early 1950's. Hodges and Perkins (1), when reviewing 439 patients with this disease treated between 1948 and 1973 from six series, found the fatality rates ranged from 17 to 59%, with a mean of 28%. An identical figure was reported by the Center for Disease Control, Atlanta, Ga. for cases treated in 1978 (2). Of the three major etiologic agents in bacterial meningitis, the pneumococcus consistently produces the highest mortality rates in all series (3).

Some of these deaths are due to overwhelming infection with bacteremia early in the disease course, but a significant proportion remain poorly explained. The contribution of raised intracranial pressure (ICP)[1] may be substantial in these cases. Moderate to marked elevations of ICP are common in pneumococcal meningitis and there is an association between the highest levels and an unfavorable outcome (3). In 30 patients who died during the acute stage of bacterial meningitis, diffuse cerebral swelling with or without cerebral/cerebellar herniation was found at autopsy in 10 (3). Raised ICP was found in over 50% of patients with acute pneumococcal meningitis in other studies (4, 5).

In addition to a high mortality rate, neurological sequelae are found in 15–25% of the survivors of pneumococcal meningitis (6). Sequelae are particularly common in children with this disease and may develop in over 80% of cases (7). Hydrocephalus is one of the most common complications and is usually ascribed to obstruction by purulent material (or later glioticfibrotic reaction) in the aqueduct, foramina of the fourth ventricle, in the subarachnoid space, or at the arach-

[1] *Abbreviations used in this paper*: CSF, cerebrospinal fluid; ICP, intracranial pressure; SAS, subarachnoid space.

noid villi. The latter would cause alterations in cerebrospinal fluid (CSF) absorption with an increase in the resistance of CSF outflow from the subarachnoid space (SAS) back into the venous system. Since postmeningitic hydrocephalus is of the communicating type in over two-thirds of the cases (8), alterations in CSF absorption may explain a major proportion of these sequelae.

The exact mechanisms responsible for increased ICP and hydrocephalus in meningitis remain obscure. Cerebral edema, of both vasogenic and cytotoxic types, may contribute to the raised ICP in some cases (9). Cerebral edema may be secondary to pial vessel invasion by microorganisms with resultant vessel thrombosis and cerebral infarction (10) or the direct cytotoxicity of leukocyte products within the SAS (11). Cortical venous thrombosis may develop during meningitis (3, 10), which may raise cerebral venous pressure and contribute to an increase in ICP. Since purulent material accumulates within the SAS in bacterial meningitis, alterations in the circulation of the CSF may also contribute to the pathogenesis of the increased ICP since the CSF constitutes a major compensatory volumetric buffer system. Although CSF production was unchanged when measured by the ventriculocisternal perfusion technique in rabbits inoculated intracisternally with *Hemophilus influenzae* (12), the rate of penicillin clearance from the CSF was decreased, suggesting a block of specific transport mechanisms in the choroid plexus. However, the effect of infection on CSF circulation and absorption have not been systematically or quantitatively studied.

Manometric infusion of fluid into the SAS has been used since 1933 to investigate the normal and abnormal physiology of the CSF system. Earlier techniques employed infusions of artificial CSF through catheters implanted in the lumbar sac or lateral ventricle (13), or direct bolus installation by an intracisternal needle (14). However, access to the supracortical SAS by means of a hollow bolt threaded through the calvarium allowed continuous monitoring of ICP (15) and this technique is now widely used in neurosurgical practice (16). Coupling of this method to infusion manometics has permitted detailed analysis of CSF hydrodynamics in a wide variety of mammalian species including rat, rabbit, dog, and man (17). In experimental subarachnoid hemorrhage in dogs, resistance to CSF outflow into the venous system is raised significantly (18) due to the accumulation of plasma products in the SAS or at the arachnoid villi. In addition, CSF production rates were reduced over sixfold.

The purposes of the present study were: (*a*) to assess the influence of experimental bacterial meningitis on resistance to CSF outflow and CSF production rate by a manometric infusion technique; (*b*) to compare the changes induced by different organisms (*Streptococcus pneumoniae* and *Escherichia coli*) that produce quantitatively different CSF inflammatory responses; and (*c*) to determine the influence of antibiotics and corticosteroids (agents known to reduce cerebral edema and the inflammatory mass within the SAS in experimental meningitis) (19–21) on these alterations of CSF hydrodynamics.

METHODS

Insertion of intracranial pressure monitoring device

New Zealand White rabbits (2–3 kg) were mildly anesthetized with 30 mg of sodium pentobarbital i.v. (Barber Veterinary Supply Co., Richmond, Va.). Before surgery, 4 g of sodium mannitol injection, U. S. Pharmacopia, 25% (Invenex Laboratories, Orlando, Fla.; No. 14-60) was injected intravenously. A midline scalp incision was made, and the scalp and periosteum retracted. A ¼-in. hole was made in the calvarium with a twist drill 2 mm caudal and lateral to the left coronal and saggital sutures, respectively. Under ×4.5 magnification the dura mater was opened and the SAS entered. The appearance of CSF indicated entrance into the SAS. A hollow bolt (16) was then threaded into position in the hole in the calvarium until the tip lay 0.05 mm below the open dura and in direct continuity with the supracortical subarachnoid space. The lumen of the bolt was then filled with sterile 0.9% NaCl. Fluctuations of the fluid level within the lumen were observed with pulse and respiration, and the bolt was capped. Cyanoacrylate ester (Eastman 910 adhesive, Eastman Kodak Co., Rochester, N. Y.) was then applied liberally around the bolt-skull margin to assure a water tight seal. Dental acrylic was then attached around the bolt to facilitate immobilization of the animal's head in a stereotaxic frame, as described (22), and the animals were returned to their cages.

All initial manometric infusion experiments (see below) were performed 48–72 h after bolt insertion. To eliminate the possibility of leakage of CSF at the site of insertion, which would invalidate manometric studies, infusions of Evans blue were performed in five rabbits at 125 μl/min until ICP reached 40 mm Hg (see below). No dye was seen around the bony margins despite backflow from the bolt lumen when the infusion was discontinued and disconnected. In addition, 0.8 ml of meglumine iothalmate (Conray, Mallinkrodt Inc., St. Louis, Mo.) was infused over 60 s and serial roentgenograms performed in two other rabbits. Conray was detected streaming over the convexities in the SAS without leakage along the bolt insertion track. Convexity-cisternal perfusions with radioactive tracers and subsequent sampling of brain and dura, have indicated that the perfusate enters the SAS but not the subdural space (23).

No apparent wound or central nervous system infections resulted from these experimental procedures. Animals did not become febrile before intracisternal inoculation of bacteria with the bolt in place, gained weight normally, and appeared healthy. Repeated CSF aspirations under sterile conditions from the bolt lumen failed to grow any organisms in trypticase soy agar pour plates (BBL Microbiology Systems, Becton, Dickinson & Co., Cockeysville, Md.) in over 30 animals so handled.

Challenge organisms

The strain of *S. pneumoniae* type III used in these studies was originally isolated from an adult with meningitis and has

been characterized (24). Overnight (16 h) growth in trypticase soy broth (Difco Laboratories, Detroit, Mich.) supplemented with 5% defibrinated sheep's blood at 37°C was centrifuged (1,000 rpm for 5 min to remove erythrocytes), recentrifuged (3,000 rpm for 15 min), washed in physiological saline twice, and resuspended in 2.0 ml of 0.9% NaCl. The *E. coli* clinical isolate (k_1+) has also been characterized in this laboratory (25). A 10^{-4} dilution of an overnight growth in tripticase soy broth was centrifuged, washed, and resuspended as described above. The inoculum introduced into the animals (see below) was 10^7 and 10^5 colony forming units for the *S. pneumoniae* and *E. coli*, respectively. Intracisternal inoculations of 0.25 ml 0.9% NaCl did not alter the CSF parameters analyzed during manometric infusion studies 20 h later.

Production of meningitis

After insertion of the pressure screw and preparation of the inoculum, meningitis was induced in the rabbits as described (22–25). The animal was again mildly anesthetized with 30 mg of sodium pentobarbital and positioned in the stereotaxic frame. A Quincke spinal needle (Becton, Dickinson & Co., Parsippany, N. J.) 24 gauge by 3.5 in. (~9 cm) was introduced atraumatically into the cisterna magna with a geared electrode introducer. After withdrawal of CSF (0.3 ml), the inoculum (0.25 ml) was introduced, the needle withdrawn, and the animal returned to its cage. All animals developed meningitis as manifested by fever (>39°C), lethargy, and a CSF pleocytosis with positive cultures, as shown (22–25). These models result in a uniformly fatal infection within 2–5 d if untreated.

Manometric infusion method

Animals with meningitis or uninfected controls (see below) were anesthetized with 30 mg of sodium pentobarbital i.v. polyethylene catheters (Intramedic 7420, Becton, Dickinson & Co.) were inserted into the femoral artery and vein. The animal was then repositioned in the stereotaxic frame. Artificial CSF (17) was used to fill lines connecting the bolt lumen with an infusion pump and a pressure transducer via a three-way stopcock. ICP and femoral artery blood pressure transducers were calibrated with a mercury manometer and connected for continuous display on a Gould brush recorder (Gould Inc., Cleveland, Ohio). Base-line ICP recordings always revealed cyclical respiratory changes in the tracings. All animals were intubated, placed on a small animal ventilator (Harvard Apparatus Co., S. Natick, Mass.) and end-tidal CO_2 constantly monitored (Beckman Instruments Inc., Fullerton, Calif.). Arterial blood gases were performed frequently (Instrument Laboratories Corp., Chicago, Ill., model 113) and P_{CO_2} maintained in the normal range (30–38 mm Hg). The femoral venous catheter was used for the administration of supplemental pentobarbital, as required.

The manometric infusion tests were performed according to an adaptation of the method described by Mann et al. (17). This method consists of a graded series of low-flow rate infusions of artificial CSF directly into the supracortical SAS. During the course of each constant rate infusion, CSF pressure was simultaneously measured and noted to rise until an equilibrium pressure elevation level was achieved. Thus, by determining equilibrium pressure at a series of known CSF system flow rates, resistance to CSF outflow can be calculated as described in Data analysis. Flow rates varying between 1.2 and 195 μl/min were achieved using a syringe pump (model 975; Harvard Apparatus Co.), which was calibrated before and after each series of experimental infusions. After each infusion, CSF pressure was allowed to return to base-line, preinfusion level before the next infusion was begun.

Data analysis

The nonlinear mathematical model originally described with the constant, low-volume manometric infusion technique used in a wide variety of mammalian species (17) was used for analysis of the data obtained in these experiments. According to this model, the nonlinear relationship between equilibrium pressure and flow is described by:

$$Q = \frac{1}{M} e^{P/P_r}, \quad (1)$$

where Q is the infusion rate (microliter per minute), P is the equilibrium ICP attained (millimeter Hg), and M (microliter per minute × −1) and P_r (millimeter Hg) are species-specific parameters described in detail by Mann et al. (17). The steady-state pressure elevations were plotted against the logarithm of corresponding Q for each animal. Application of least-squares curve fitting techniques to the log Q-equilibrium ICP data determined the parameter values for M and P_r. After derivation of these parameters for each animal, CSF outflow resistance can be calculated by:

$$R = MPe^{-P/P_r} \quad (2)$$

where R is the CSF outflow resistance (millimeter Hg per microliter per minute). R was then plotted against steady-state ICP over a wide range to obtain the peak CSF outflow resistance for each group of animals. Maximal R values were compared by using Student's *t* test analysis for unpaired data.

Experimental design

Infusion manometric studies were performed on 49 rabbits in six groups:

Group 1. Animals were the uninfected controls (n = 6).

Group 2. Animals with acute pneumococcal meningitis were studied 20 h after inoculation (n = 11).

Group 3. Animals with acute *E. coli* meningitis were studied 16 h after inoculation (n = 5).

Group 4. Animals were studied immediately after curative penicillin therapy of acute pneumococcal meningitis (n = 6). Rabbits were prepared as in group 2 and treated with 1.2×10^6 U of aqueous penicillin G (Squibb, & Sons, Inc., Princeton, N. J.) over 8 h by constant intravenous infusion. Antibiotic therapy was begun 12 h after inoculation. In 16 other animals treated under identical conditions, this dose of penicillin uniformly sterilized the CSF within 8 h in this model of pneumococcal meningitis and no relapses were seen.

Group 5. All animals were treated as in group 4 and subjected to infusion manometric studies 2, 5, and 10 d after penicillin therapy to define the duration of the CSF hydrodynamic abnormalities after cure of the infection (n = 12). Two animals were also studied 15 d after injection.

Group 6. Animals were inoculated with *S. pneumoniae*, as described above. At 16 and 20 h after inoculation, 30 mg/kg of methylprednisolone sodium succinate (Solumedrol, Upjohn Co., Kalamazoo, Mich.) was administered intramuscularly (n = 9). Except for the steroid treatment, these animals were identical to those in group 2 when infusion manometrics were performed. Three animals were restudied 20 h after the last dose of methylprednisolone to determine if a "rebound" effect occurs after cessation of steroid therapy.

RESULTS

Effect of meningitis on CSF outflow resistance

Pressure vs. time analysis. Each animal was infused with artificial CSF at flow rates that varied over a wide range (1.2–195 μl/min; <0.1–>20 times normal CSF bulk flow in the rabbit [26]). Infusions were continued for 4–9 flow rates until a family of steady-state pressure curves was generated for each animal (Fig. 1). A marked increase in the steady-state ICP was observed for any given flow rate in the presence of meningitis. Animals without meningitis required flow rates 10–20 times those required in animals with meningitis to produce equivalent steady-state ICP (Fig. 1). For example, the mean flow rates (microliters per minute) required to raise resting ICP to a steady-state elevation of 30 mm Hg were 99.8±32.2 (SD), 6.5±3.4, and 5.8±2.3 for uninfected controls, acute pneumococcal meningitis, and acute *E. coli* meningitis, respectively ($P < 0.001$ for each type vs. controls). When animals were subjected to infusion rates that exceeded the CSF reabsorptive capacity of the system, the ICP rose continuously to 45 mm Hg without achieving a steady-state plateau area in the curve. The flow rates necessary to exceed this absorptive capacity were much higher (15–20 times) in uninfected controls then in the animals with meningitis.

Infusion-pressure analysis. A linear relationship was found to exist between steady-state ICP and the log of the test flow rate (Fig. 2). By a least-squares regression analysis the species-dependent parameters, M and P_r, were determined. For control animals, mean±SD M was 0.22±0.003 $\mu l/min^{-1}$ and P_r was 29.8 ±3.1 mm Hg. Marked changes in these parameters occurred with meningitis. Mean M ($\mu l/min^{-1}$) increased with meningitis from 0.22±0.003 in controls to 1.1±0.7 and 1.9±1.2 in pneumococcal and *E. coli* meningitis, respectively. Conversely, mean P_r (millimeters Hg) decreased with infection from 29.8±3.1 in controls to 19.2±7.3 and 13.6±3.2 for the two meningitis groups, respectively. These changes are reflected by a shift in the log Q vs. P curve to the left when compared to uninfected controls (Fig. 2).

Peak outflow resistance analysis. After determination of M and P_r parameter values, resistance was calculated (Eq. 2) and plotted against pressure for all groups of animals. Maximal outflow resistance was markedly elevated in untreated animals with acute pneumococcal meningitis when compared to controls (Fig. 3). This was true over the entire range of CSF pressures evaluated. The peak resistance for the uninfected control animals was 0.26±0.04 mm Hg/μl per min; in close agreement with values found in other small mammalian species (17). In contrast, the mean

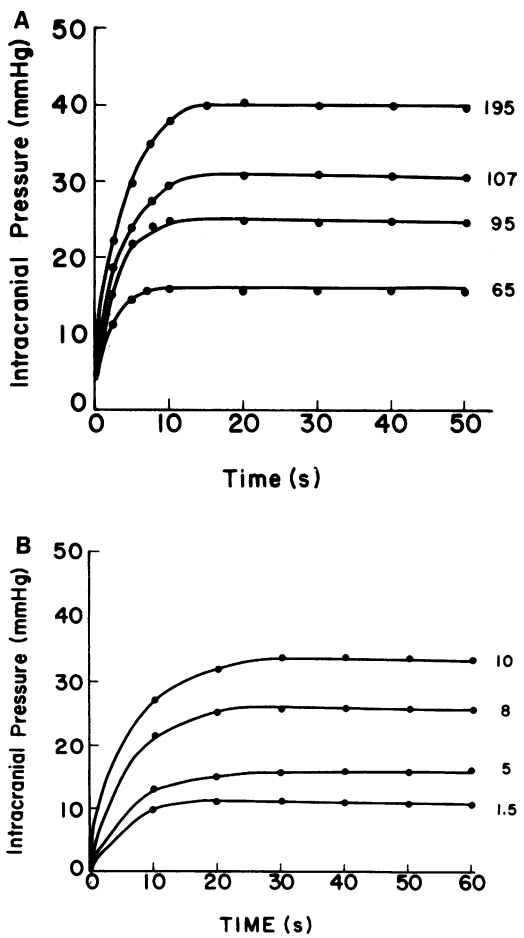

FIGURE 1 Intracranial pressure vs. time after start of manometric infusion. Experimental flow rates (microliters per minute) are indicated to the right of each curve. A, controls; B, acute pneumococcal meningitis.

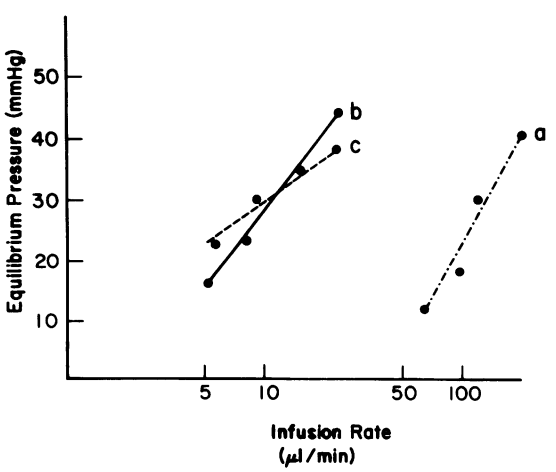

FIGURE 2 Semilog plot of equilibrium intracranial pressure vs. infusion rate. a, control (---); b, acute *S. pneumoniae* meningitis (——); c, acute *E. coli* meningitis (– – –).

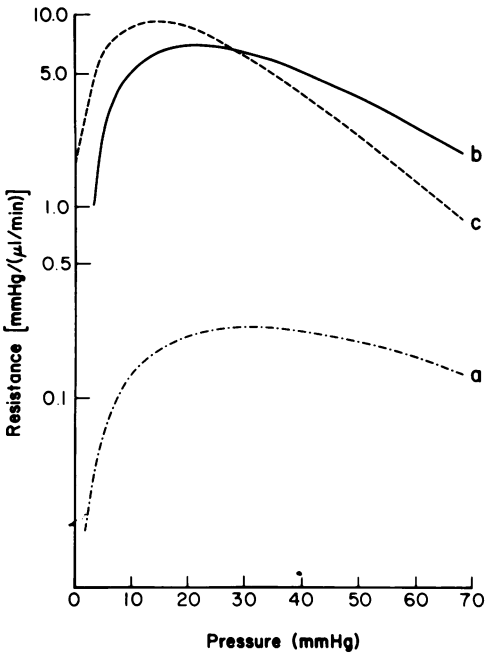

FIGURE 3 Semilog plot of CSF outflow resistance vs. intracranial pressure. a, control (---); b, acute *S. pneumoniae* (——); c, acute *E. coli* meningitis (– – –).

peak CSF outflow resistance was 6.77±3.52 mm Hg/μl per min in animals with acute pneumococcal meningitis ($P < 0.001$ vs. controls). Thus, in the presence of acute meningeal inflammation, the resistance to translocation of CSF from the intracranial compartment is markedly elevated.

Effect of meningitis on CSF production rate

Extrapolation of the log Q vs. ICP curves (Fig. 2) to base-line resting pressure (5–10 mm Hg) allows an indirect estimation of CSF production rate. These curves are consistently shifted to the left by meningitis (Fig. 2), indicating a reduction of CSF production rate of 5- to 10-fold in the presence of infection when compared to controls.

Influence of bacterial species

Both experimental pneumococcal and *E. coli* meningitis produced a uniformly fatal infection in all untreated animals, but they differ in several important respects. While all animals became febrile (>39°C) and were lethargic, the time from intracisternal inoculation until death was shorter in the animals infected with pneumococci (mean±SD = 28±17 vs. 110 ±31 h for *E. coli* $P < 0.01$). In addition, the mean leukocyte response 18 h after intracisternal inoculation was higher in *E. coli* meningitis (5,084±860 cells/mm³) than in the pneumococcal disease (2,816±412 cells/mm³ $P < 0.001$). More than 95% of these cells were polymorphonuclear leukocytes in both groups. Despite the differences in host response to the bacterial challenge, the peak resistance to CSF outflow was similar in both groups. Mean determinations for this value were 6.77±3.52 and 8.93±4.15 mm Hg/μl per min ($P > 0.05$) for acute untreated pneumococcal and *E. coli* meningitis, respectively (Figs. 2 and 3). The curve of log Q vs. P is shifted to the left in *E. coli* meningitis (Fig. 2) and the slope differs from that obtained in the acute pneumococcal group. The resistance was also increased over the entire range of CSF pressures in *E. coli* meningitis (Fig. 3) and although the values are higher than those found with pneumococcal meningitis, the mean peak resistance did not statistically differ between the two infected groups. Thus, under the conditions of these experiments, the alterations in CSF hydrodynamics induced by bacterial meningitis were similar despite differences in host response in the rabbit to gram-positive cocci and gram-negative bacilli.

Effect of antibiotic therapy

Animals with acute pneumococcal meningitis were treated with 1.2 million U of aqueous penicillin G continuously infused over 8 h. This dose of penicillin sterilized the CSF in 16 of 16 identically treated animals within this period when subjected to follow-up cisternal puncture. Serum and CSF concentrations of penicillin in 12 animals were 11.8±1.6 (SD) and 0.5 ±0.2 μg/ml, respectively, with a 4.24% penetration into the CSF ([CSF]/[Serum] × 100%). The minimum bactericidal concentration for penicillin G against the test strain was <0.06 μg/ml. Since no relapses were seen and CSF was again sterile on days 5 and 10, these animals were considered to be cured under the conditions of these experiments. Despite the eradication of viable bacteria from the CSF, the response to manometric infusion of artificial CSF was essentially unchanged in those animals examined at the end of the 8-h treatment interval when compared to untreated animals with acute pneumococcal meningitis of the same duration (Figs. 4 and 5). The plot of log Q vs. P curve (Fig. 4) was not altered significantly by antibiotic treatment ($P > 0.05$ by analysis of variance) and the peak resistance was similar (Fig. 5). There was a wide variation, but the peak did not differ from acutely infected untreated animals with pneumococcal meningitis (6.07 ±4.68 vs. 6.77±3.52 mm Hg/μl per min for penicillin treated and untreated pneumococcal meningitis, respectively, $P > 0.05$). Two uninfected animals treated with identical doses of penicillin revealed peak resistances unchanged from controls.

Manometric infusion studies were repeated in all treated animals 5 and 10 d after the administration of penicillin. All were afebrile, had gained weight, and

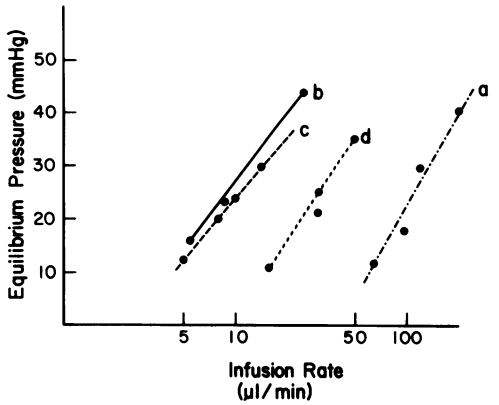

FIGURE 4 Semilog plot of equilibrium intracranial pressure vs. infusion rate. a, control (- - -); b, acute *S. pneumoniae* meningitis (——); c, acute *S. pneumoniae* meningitis after 8 h intravenous penicillin therapy (- - -); d, acute *S. Pneumoniae* meningitis after two injections methylprednisolone 30 mg/kg i.m. (· · · · ·).

appeared normal. The peak resistance to CSF outflow remained elevated and slowly returned towards normal; mean values were 3.63 and 0.76 mm Hg/µl per min ($P < 0.05$ vs. control value of 0.26) at 5 and 10 d, respectively. When sacrificed on day 11, all animals had sterile CSF. Two additional animals were studied at 15 d after innoculation and antibiotic therapy. Peak

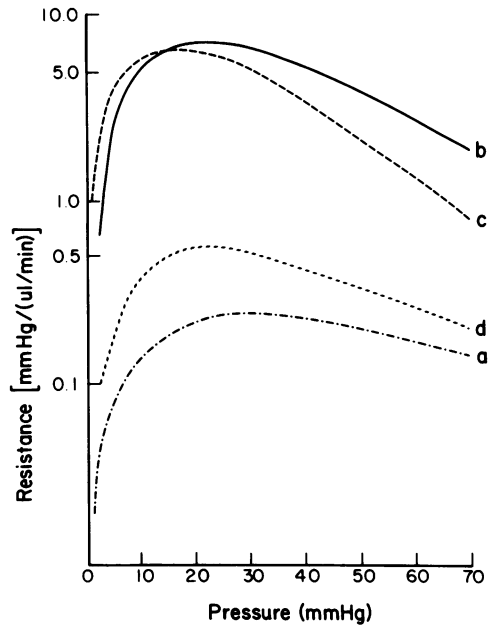

FIGURE 5 Semilog plot of CSF outflow resistance vs. intracranial pressure. a, control (- - -); b, acute *S. pneumoniae* meningitis (——); c, acute *S. pneumoniae* meningitis after 8 h intravenous penicillin therapy (- - -); d, acute *S. pneumoniae* meningitis after two injections of methylprednisolone 30 mg/kg i.m. (· · · · ·).

resistance values were still abnormal (0.46 and 0.71 mm Hg/µl per min). Thus, despite rapidly bactericidal "curative" antibiotic therapy early in the disease process, the alterations in CSF hydrodynamics persisted at least 2 wk. Uninfected animals ($n = 6$) studied with infusion manometrics up to 15 d after pressure screw placement did not differ significantly from the control group.

Effect of methylprednisolone

Animals with *S. pneumoniae* meningitis were given 30 mg/kg methylprednisolone i.m. at 16 and 20 h after intracisternal inoculation and then studied with the infusion manometric technique. The duration of infection was identical to that of the untreated pneumococcal meningitis group and to those treated with penicillin. Marked changes were observed after steroid therapy (Figs. 4 and 5). The log Q vs. P curve (Fig. 4) is shifted back towards values from uninfected animals and the resistance is lower over the entire range of CSF pressures when compared to untreated or penicillin treated pneumococcal meningitis (Fig. 5). The peak resistance (0.59±0.38 mm Hg/µl per min) was reduced markedly in the steroid-treated group ($P < 0.001$ vs. untreated and penicillin treated pneumococcal meningitis). This value is, however, still higher than that found with uninfected controls (0.26±0.04, $P < 0.05$) and is more variable (range: 0.23–1.31 mm Hg/µl/min). Peak resistance remained <1.3 mm Hg/µl per min for up to 4 h after the last dose of methylprednisolone. Three of these animals were restudied 20 h after cessation of steroid therapy. The rabbits were hypothermic with temperatures < 39°C, cyanotic, and semi-comatose due to pneumococcal meningitis. The peak resistance had increased to values of 3.87, 4.31, and 5.06 mm Hg/µl per min, respectively, similar to values obtained in animals with untreated acute pneumococcal meningitis. Two additional animals were infected with *S. pneumoniae* and treated with both methylprednisolone and penicillin by protocols identical to those used above; the peak outflow resistance was 0.63 and 1.01 mm Hg/µl per min, respectively, unchanged from the animals that received steroids alone.

DISCUSSION

This study demonstrates that experimental bacterial meningitis in the rabbit induces marked alterations in the hydrodynamics of the CSF, as exemplified by an increase in the resistance to CSF outflow. This change was apparent in both pneumococcal and *E. coli* meningitis and resolved slowly after successful antibiotic therapy in the former. In contrast, steroid therapy in the acute stage of pneumococcal disease reduced CSF outflow resistance towards control levels. Alterations of this magnitude would be expected to

have profound effects on the ability of the brain to compensate for changes in intracranial volume and pressure during acute meningitis.

The mechanism of the increase in resistance is not precisely understood. In all mammalian species examined to date, including the rabbit, the majority of the CSF (≥70%) is formed by the choroid plexi with the minority thought to arise from extrachoroidal sites, presumably brain and spinal cord extracellular space at the level of the microcirculation (27, 28). The CSF flows through the ventricular system and exits through the foramina of the fourth ventricle to circulate through the SAS until its absorption into the venous blood occurs through arachnoid villi in the major dural sinuses (29). Even though the spinal compartment acts as an expansion vessel for raised ICP and contributes to the shape of the CSF pressure-volume curve (30), and small volumes of CSF can escape from arachnoid villi along spinal nerve roots (31), the bulk of CSF is removed via intracranial arachnoid villi (29, 32). Absorption from spinal arachnoid villi may be proportionately greater in smaller mammals (e.g., rat, and rabbit) since intraventricular injection of Evan's blue stains the central canal of the spinal cord in these species in direct continuity with the lumbosacral SAS via the filum terminale (31). Similar connections were not observed in other species (e.g., cat and rhesus monkey), thus, in man, the contribution of intracranial outflow obstruction may be proportionally more important in CSF outflow resistance than in the experiments reported here in the rabbit. CSF outflow resistance is largely dependent on the rate of CSF bulk flow. The actual physiological mechanism by which CSF is absorbed through arachnoid villi and its alteration by pathological states is not completely understood and the influence of meningitis previously unknown.

The studies of Weed (33) suggested that the arachnoid villi functioned primarily as a semipermeable membrane by filtration of CSF into the venous sinuses and were supported by morphological studies demonstrating intercellular tight junctions in the dural endothelium (34, 35). This view prevailed until 1960 when a valvelike function was demonstrated in isolated arachnoid villi in vitro that permitted transport of particles as large as 7 μm (erythrocytes) in size (36). Later morphological studies demonstrated that when the arachnoid villus was fixed under physiological distending pressures (37, 38) transient transcellular pores were evident and the valvelike function of this structure is now generally accepted (29). This explains the transport of large molecules (e.g., albumin) and erythrocytes from the CSF to blood under experimental conditions (39, 40). When pneumococcal meningitis is induced by intracisternal inoculation in dogs, bacteremia occurs early in the disease course, presumably by bulk transport out of the CSF into venous blood (41). This occurs before the peak CSF pleocytosis, but later alterations in arachnoid villus transport function were not examined.

The development of the manometric infusion technique allows the direct quantitative measurement of CSF outflow resistance. Rapid volume increments have been used to measure intracranial compliance (14). No direct measurements of brain elastance or intracranial compliance were attempted in our study since the low flow continuous infusion technique permits better estimation of outflow resistance (17, 42). This method of low flow constant infusion of short duration (17) through a pressure monitoring device in direct continuity with the supracortical subarachnoid space (15) was used in this study to document that the resistance to CSF outflow was markedly elevated in bacterial meningitis. This is in agreement with analogous studies in other pathological states. When particulate matter (kaolin, whole blood, or colloidal graphite) was introduced intraventricularly into rabbits, steady-state ICP was reached at lower infusion rates with a shift of the log Q vs. P curve to the left (26). Cisternographic analysis with ^{131}I or ^{99}Tc human albumin after the introduction of a kaolin-charcoal mixture into the SAS of dogs (43) demonstrate a delay in transport of the radiopharmaceutical from the SAS to blood. Similar results were observed for albumin transport from the SAS to blood in experimental meningitis (44). Analogous results were found in a small series of eight patients with acute and chronic meningitis of variable etiology (45). An identical effect was demonstrated after the intracisternal inoculation of bacteria in the current experiments (Figs. 2 and 4). A 3- to 10-fold increase in CSF outflow resistance was also demonstrated after the intracisternal inoculation of whole blood into rats and dogs associated with accumulation of fibrinlike debris in the subendothelial space and a reduction in arachnoid vesicular transport (18) confirming earlier studies (46, 47). Accumulation of leucocytes and eosinophilic debris has been identified in supracortical SAS in experimental meningitis (48) and has been confirmed in the rabbit model used in this study by light microscopy (personal observations). The increase in fibrin degradation products in the CSF of patients with pneumococcal meningitis (49) may reflect breakdown of plasma constituents in the SAS and levels of these products were higher in the fatal cases. This suggests that as inflammation increases, CSF absorption is curtailed by obstruction either in the supracortical SAS or at the arachnoid villus with subsequent elevations in ICP, neurological sequelae (e.g., hydrocephalus), raised fibrin-degradation product within the CSF and perhaps an increase in mortality rates. Although the most likely site(s) of CSF outflow obstruction is in the SAS and/or arachnoid villi, other factors (e.g., altered brain compliance,

increased intracranial blood volume, and dural sinus thrombosis) may contribute to the alterations in CSF outflow resistance reported here. Although cerebral venous pressure was not measured in these experiments, dural sinus thrombosis was not found in autopsied animals with experimental pneumococcal meningitis after intracranial perfusion with saline under physiologic conditions.

The rate of CSF formation has never been measured in patients with bacterial meningitis but was found unchanged in six rabbits with experimental *H. influenzae* meningitis (9). The influence of increased ICP on CSF formation is controversial but in the 15 studies cited by Pollay (32), 12 demonstrated a decrease in CSF production as ICP increased. This is a controversial area, however, since CSF production as measured by ventriculo-cisternal perfusion did not decrease when ICP was raised (to 20 mm Hg) experimentally in cats. Only when the cerebral perfusion pressure (CPP = mean systemic aortic pressure − ICP) was reduced substantially (from normal of 113 to 50 mmHg) in these animals did CSF production rate decline (50). In addition, CSF production rate increased by ~11% for every degree elevation in temperature over a wide range (31°–41°C) in cats (51).

A sixfold decrease in CSF production rate was estimated in experimental subarachnoid hemorrhage where outflow resistance increased (18). Although CSF formation was not measured directly, similar results were seen in the present study. When the logarithm of the infusion rate is plotted against the experimentally derived steady-state pressure (e.g., Fig. 2), extrapolation of this line to resting ICP (5–10 mm Hg) yields an indirect estimate of basal CSF production rate because at resting ICP outflow must equal production. Since this relationship is shifted to the left in the presence of meningitis (Figs. 2 and 4), it suggests that at basal ICP the CSF formation rate is reduced 5- to 10-fold in the presence of meningitis. Since this extrapolation is made at the lower end of the log Q vs. P curve, where ICP is relatively normal, and the mean aortic pressure was not significantly reduced in the animals with meningitis (mean±SD femoral artery pressure of 106±11 vs. 118±15 for controls, $P > 0.05$), alterations of cerebral perfusion pressure (50) cannot fully explain the reduction in CSF production rate suggested in these experiments. When rabbits with experimental pneumococcal meningitis are studied somewhat later, in a moribund state less than 1 h before death, aortic pressure and CPP decline precipitously which would potentially decrease CSF production rate further. The animals with experimental meningitis in this study were febrile, with a mean temperature of 41°C (39°C is the upper limit of normal in the New Zealand White rabbit), which is known to increase CSF production rate (51); however the results were in the opposite direction when extrapolated from the manometric infusion data. These results require confirmation by other more direct and quantitative techniques such as ventriculocisternal perfusion but, if confirmed, have important implications. In meningitis, decreased CSF absorption (increased outflow resistance) and formation would hinder the removal of metabolic end-products by CSF and conceivably lead to the buildup of toxic bacterial, brain, or leucocytic substances. In addition, decreased CSF formation may alter vital transport processes (e.g., glucose) in the choroid plexus and the delivery of antibiotics into the SAS.

The rabbit model of experimental bacterial meningitis used in these studies varies with the infecting organism. Previous well-characterized models employed in this laboratory have included *S. pneumoniae*, *H. influenzae*, *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Listeria monocytogenes* (52). Despite differences in host response to infection (duration of survival, CSF pleocytosis), CSF outflow resistance was similarly increased in both pneumococcal and *E. coli* meningitis in this study. Resistance was higher in the *E. coli* group (as were CSF leukocyte counts) but this did not achieve statistical significance. This likely reflects the poor correlation between the CSF leukocyte concentration and the actual inflammatory mass present in the SAS (21, 53). In addition, in contrast to other types of meningitis, pneumococcal infection is associated with a more extensive accumulation of leucocytes over the convexities than the basal region (54). The reasons for this are unknown but more direct continuity with arachnoid villi is thus present with the possibility of augmenting the increase in CSF outflow resistance.

In this study, rapidly bactericidal penicillin therapy sterilized the CSF within 8 h but the increased CSF outflow resistance in treated animals remained unchanged from untreated infected rabbits and did not return to normal even in some animals 15 d later. Unlike the other common types of meningitis, at least 20% of the deaths due to pneumococcal meningitis occur 7–19 d after the institution of antibiotics (55). In another study of 61 cases of pneumococcal meningitis treated between 1960 and 1970, 25% of the deaths occurred after meningitis had "cleared" with a sterile, nearly normal CSF (56). The aggregate affects of vascular involvement with secondary infarction or necrosis (7), cerebral edema, direct invasion of the brain parenchyma by bacteria (48), or hydrocephalus-induced changes in periventricular brain tissue (57) may be potentiated by an alteration in CSF hydrodynamics and blockage of CSF absorption and thus may be involved in these cases. This possibility deserves further consideration. Despite a slow return to the resistance to

normal in this study, none of the rabbits initially treated with penicillin died. The slow restoration of normal CSF hydrodynamics may explain the prolonged duration of neurological signs and the typically long clinical course of patients with pneumococcal meningitis.

The possible adjunctive role of corticosteroids in bacterial meningitis remains controversial (20). Some uncontrolled studies suggest a definite beneficial effect with steroids in pneumococcal meningitis (58–60), whereas other suggest an equivocal or detrimental effect (61–64). Unfortunately, the results are difficult to interpret due to inconsistent study design (where more comatose patients received steroids), and the comparatively low dosages administered in all these earlier studies. When large dosages (30 mg/kg) of methylprednisolone were given to rabbits, resulting in serum levels approximating those found in man after 1 g i.v., the inflammatory response within the SAS after intracisternal inoculation of pneumococci was diminished (21). This data suggested that corticosteroids might ameliorate the increased CSF outflow resistance demonstrated in our model. When identical dosages of methylprednisolone were used, two injections significantly decreased the resistance to CSF outflow to levels similar to control, uninfected animals. This reduction in outflow resistance was apparent up to 4 h after the second injection of methylprednisolone. No rebound effect was seen after cessation of steroid therapy. When rabbits were restudied 20 h later, the peak resistance was similar to values found in rabbits with untreated acute pneumococcal meningitis and there was no increase in peak resistance above this level. In addition to a suggested reduction of cerebral edema by unknown mechanisms (19), this effect of methylprednisolone may explain the reduction in ICP seen after their administration. Steroids also lyse adhesions in the SAS (65) and may prevent the occurrence of postmeningitic hydrocephalus; this phenomenon has been demonstrated for late hydrocephalus occurring after experimental subarachnoid hemorrhage in rabbits (66). In addition to decreasing resistance to CSF outflow, corticosteroids may also decrease CSF production (67), although this finding has been disputed by other investigators. The "decreased CSF formation" with steroid therapy (67) may in fact be due to enhanced absorption as suggested by the present study. This point remains controversial, since Vela et al. (68) found no change in either CSF formation or absorption with steroid therapy. Although methylprednisolone dramatically alters the response of the CSF system to meningitis, their possible detrimental effects, including leukocyte entrance into the CSF with possible decreased host resistance, and secondary decreases in antibiotic penetration across the blood brain barrier must be considered.

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