Chloramphenicol is formed by a soil actinomycete, Streptomyces venezuelae, and has been isolated in pure state and synthesized in the laboratory. It is a yellowish-white crystalline powder which is relatively insoluble in water and extremely stable. Concentration of 2.5 mg./cc. can be obtained at room temperature. Solutions withstand boiling for five hours or autoclaving for thirty minutes without change in structure or loss of antibacterial action (1).

This drug is a potent bacteriostatic agent against most of the gram-negative organisms, as well as many of the gram-positive cocci. Of all the antibiotics, chloramphenicol diffuses most readily into blood and cerebrospinal fluid after oral administration (2). In adults, most clinicians have advised an initial dose of 1 to 2 grams followed by 750 mg. every 6 hours, and, in children, 750 mg. initially followed by 250 mg. every 4 to 6 hours. On such a regime, serum concentration of 5 to 50 μg/cc can be maintained (2). Cerebrospinal fluid levels are rapidly established over a period of a few hours and remain about one half the serum concentration. The drug can be given intravenously or intramuscularly in an organic solvent base in doses of 100 mg./kg. daily, but such injections sometimes cause local irritation at the injection site together with headache, dizziness, nausea, and vomiting.

Chloramphenicol was first given intrathecally by Anderson and Ellis (1) in cases of staphylococcal meningitis, resistant to penicillin and streptomycin, with excellent results. Using daily intrathecal injections of 750 μg in 1 cc. of distilled water, together with large oral doses, they were able to maintain a cerebrospinal fluid level of 40 μg/cc. They briefly report their later use of daily intrathecal injections of 3 mg. of chloramphenicol with no evidence of meningeal irritation.

Since little was known of the local action of chloramphenicol on the central nervous system, it seemed worthwhile to study the effects of this drug injected intrathecally and applied to the cortex in experimental animals. We have also evaluated the epileptogenic properties of the other antibiotics and have attempted to summarize the experimental and clinical data pertaining to their direct action on the central nervous system.
A total of 23 experiments were carried out on cats weighing from 1.5 to 3.5 kgs. Light ether anaesthesia was used for 6 cats, which were subjected to daily cisternal puncture for 8 days. One cc. of a sterile solution of chloramphenicol containing 100 ug., 250 ug., 500 ug., 750 ug. and 1000 ug. (1 mg.) was injected daily into each of 5 cats. One cc. of sterile distilled water was injected daily into the sixth cat as a control. Short bevelled no. 23 hypodermic needles were used for the injections, which were performed under sterile conditions. Pure crystalline synthetic chloramphenicol* was used in making the solutions which were sterilized by autoclaving for 20 minutes. Bacteriological assay showed no loss in potency of the drug following this method of sterilization. One to 4 days following the final cisternal injection the animals were anaesthetized by intraperitoneal nembutal, and bilateral electrocorticograms were obtained. Surface recordings were carried out with small silver wire bipolar electrodes with a tip separation of 2 mm. Electrical activity was recorded after amplification through the usual condenser coupled amplifiers with a six channel ink-writing apparatus. The animals were sacrificed with an overdose of nembutal, and the brain, spinal cord, and cauda equina were removed and fixed in 10 per cent formalin. After fixation, representative blocks were embedded in paraffin, sectioned and stained with cresyl violet and hematoxylin, and Van Gieson's method. In one cat a sterile craniotomy was performed under nembutal anaesthesia, and pure chloramphenicol powder was applied to the sensori-motor cortex. One month later electrocorticography was carried out under curare and local anaesthesia. The area of cortex to which the drug had been applied was excised, fixed in formalin-ammonium-bromide solution and 10 per cent formalin, and stained by metallic and aniline dye methods. The remainder were all acute experiments. All animals were lightly anaesthetized by intravenous sodium pentothal. A tracheotomy was performed and the animals maintained on artificial respiration. Nupercaine 1:1500 was injected into the scalp. Small doses of curare were given intravenously to reduce spontaneous movement; no changes were ever observed in the electrical activity which could be attributed to this drug. Both cerebral hemispheres were exposed, and electrocorticograms were obtained. Solutions of chloramphenicol in varying strengths were applied to the cortex with small pieces of filter paper approximately 3 mm. square. Recordings were continued for at least 30 minutes following the application of each solution. The cortex was washed with warm Ringer's solution following each application.

In addition to chloramphenicol, all of the other commonly used antibiotics were applied topically to the cerebral cortex under similar conditions, and the local effects and epileptogenic properties were observed.

RESULTS

The Local Action of Chloramphenicol on the Central Nervous System

1. Repeated Cisternal Injection: Daily cisternal injections of 1 cc. of sterile chloramphenicol solution produced no untoward effects. The animals recovered rapidly from the light ether anaesthesia, were usually beginning to move spontaneously at the completion of the cisternal injection, and were able to sit and walk in from one to three minutes. No seizures were observed at any time. No evidence of meningeal irritation occurred if the chloramphenicol solution was slightly warmed and if the injection was done slowly over a period of at least one minute. The use of chilled solutions or rapid injection usually produced opisthotonos which was transient. Vomiting, shivering or paralysis were not observed. At the time of each injection the cerebrospinal fluid was clear, but cell counts and protein

* This was not the chloramphenicol powder dispensed commercially in capsular form, but was the pure crystalline drug supplied for experimental purposes by Parke, Davis and Company.
FIG. 1. Cerebral cortex at base of hemisphere. A. Control animal. B. Animal which had received 1 mg chloramphenicol intracisternally daily. Cresyl violet stain; X125.
determinations were not carried out. Twenty-four hours following the last of the cisternal injections, all of the animals appeared normal.

At the time of autopsy one to four days following the final injection, no gross abnormalities were observed in the brain, spinal cord, or cauda equina. Microscopic sections showed slight thickening of the leptomeninges over the base of the cerebral hemispheres, but there were otherwise no inflammatory changes in the meninges, ependymal lining of the ventricular system, choroid plexus, or cauda equina (figs. 1, 2 and 3). No degenerative changes were found in the cerebral cortex, brain stem, spinal cord or cauda equina, in Nissl stained sections. Myelin stains were not carried out.

2. Acute Experiments—Application to Cortex: Solutions of chloramphenicol ranging in concentrations from 100 μg./cc. to a supersaturated solution containing 5 mg./cc. were

Fig. 2. Choroid plexus, ependymal lining of fourth ventricle and adjacent portions of cerebellum. A. Control animal. B. Animal which had received 1 mg chloramphenicol intracisternally daily. Cresyl violet stain; ×60.
applied directly to the motor cortex. Neither seizures nor high voltage spike potentials were observed. Powdered chloramphenicol, placed over the motor cortex, failed to produce epileptiform activity over a period of nine hours of observation.

Chloramphenicol in concentration up to 5 mg./ce. had no effect on the spontaneous electrical cortical activity. The direct application of the powdered drug caused a transient depression of activity which occurred within 2 minutes. Complete recovery of the spontaneous activity was observed within 30 minutes even though the powdered chloramphenicol remained on the cortex. Slow wave forms were not seen. The characteristics of the spon-
FIG. 4. A. Spontaneous activity from sensory and parietal areas before application of drug. B. Thirty minutes after a supersaturated solution (5 mg per cc.) of chloramphenicol had been applied to sensory area. C. Four minutes after application of chloramphenicol powder to sensory area, showing transient depression of cortical activity. D. Thirty-three minutes after application of chloramphenicol powder to sensory area, showing recovery of electrocortical activity. E. Three hours after application of chloramphenicol powder to sensory area, showing absence of epileptiform activity.
taneous activity before the drug was applied, and following recovery from the transient depression appeared the same (fig. 4).

An interesting observation was made concerning the effect of chloramphenicol on evoked potentials recorded from the somato-sensory and primary auditory cortex. Solutions of the drug containing 750 μg./cc. applied to these cortical areas produced a noticeable increase in the amplitude of potentials evoked by striking the opposite limbs or by a noise. Higher concentrations of chloramphenicol, and especially the crystalline powder, produced an even greater increase in the evoked responses. During the period of transient depression of spontaneous cortical activity produced by powdered chloramphenicol, the evoked po-

Fig. 5. A. Evoked potentials obtained from somato-sensory area on tapping opposite forepaw, before application of drug. B. Increased amplitude of same evoked responses observed thirty minutes after application of chloramphenicol solution, 5 mg per cc. C, D, E. Application of chloramphenicol powder to sensory cortex: C, after 2 minutes; note depression of both spontaneous activity and evoked potentials; D, after 20 minutes, note recovery of spontaneous activity and increased amplitude of evoked responses; E, after 1 hour; note marked increase in evoked potentials.
Fig. 6. A. Area of cortex which had been exposed for six hours, but to which no drug had been applied. B. Area of cortex which had been covered with chloramphenicol powder for 6 hours. Cresyl violet stain; X125.
tentials recorded from that particular area were also of extremely low amplitude. However, as the spontaneous activity returned to normal, the evoked potentials increased in amplitude, and one to two hours after the application of the drug to the cortex, the evoked responses had increased 3 to 4 times in amplitude over that normally observed (fig. 5).

Chloramphenicol in either solution or powder form caused no gross damage to the cerebral cortex even after it had been applied for periods as long as 9 hours. Histological examination of the cortex which had been covered by powdered chloramphenicol for 6 hours showed only a slight number of inflammatory cells in the subarachnoid and perivascular spaces (fig. 6). These minor changes were even less than those seen in other cortical areas which had been exposed for the same period of time, but to which no drug had been applied, suggesting that the chloramphenicol powder had actually protected the cortex from the effects of drying. No changes were observed in the neurons throughout the cortex covered by chloramphenicol.

3. Chronic Experiment: Powdered chloramphenicol was applied over one sensori-motor cortex, and the animal was allowed to survive for one month. Seizures were never observed, nor at any time was there evidence of motor weakness or paresthesiae in the contralateral extremities. Just before the animal was sacrificed, the cortex was exposed bilaterally and an electrocorticogram was obtained. A few thin adhesions were present between the dura and cortex in the region of the previous craniotomy, but there was no other gross cortical abnormality. The spontaneous electrical cortical activity showed only minor irregularities, but there was no evidence of epileptiform activity.

Histological examination with both aniline dye and metallic staining techniques showed thickening of the pia-arachnoid membrane containing increased numbers of inflammatory cells in the perivascular spaces (fig. 7). No definite neuronal changes could be seen. The

![Fig. 7. Area of cortex 1 month following application of chloramphenicol powder. Slight thickening of leptomeninges was the only abnormality noted. Cresyl violet stain; X125.](http://jnen.oxfordjournals.org/)

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The Local Action of Other Antibiotics on the Central Nervous System

Experiments with Penicillin: Soon after penicillin became available for clinical use, several reports (3, 4, 5, 6) appeared, showing that the usual intravenous and intramuscular doses of 20,000 to 200,000 units every 3 to 4 hours failed to produce significant levels of penicillin in the cerebrospinal fluid both in cases with normal and inflamed meninges. This led to the injection of penicillin intrathecally and intraventricularly in cases of purulent meningitis. The report of untoward reactions in several patients prompted Walker, Johnson, and co-workers (7, 8) to study the problem experimentally. Seizures were produced by the intracortical injection of no more than 0.1 cc. of penicillin in concentrations of 250 to 500 units/cc. The injection of 20,000 units of penicillin into the lumbar subarachnoid space of the monkey sometimes led to convulsions, coma and death within 12 hours. In other monkeys, surviving such an injection, there was evidence of paresthesiae, and later anatomical studies showed arachnoiditis in the cauda equina of some of the animals. Swift and Bushby (9) studied the effect of penicillin injected into the cisterna magna of dogs. Doses of 20,000 units produced convulsions within 10 minutes and death within 2 to 4 hours. In one animal the seizures were controlled by repeated injections of barbiturates, and the dog regained consciousness 24 hours later, but had weakness of the hind legs and a spinal fluid pleocytosis of 1100 cells/cc. Doses of 10,000 units were toxic but not lethal, and 24 hours later the cerebrospinal fluid contained 900 polymorphonuclear leucocytes and 600 lymphocytes per cubic millimeter.

In our experiments, a detailed study of the epileptogenic properties of penicillin was not carried out. With local cortical application neither spikes nor seizures were observed using concentrations of crystalline penicillin* up to 1000 units/cc. With 5000 units/cc, however, numerous high voltage spike potentials were quickly produced with widespread cortical diffusion and marked clonic jerking of the contralateral limbs (fig. 8). These epileptic phenomena gradually disappeared after the cortex had been washed with Ringer’s solution. No gross cortical damage was noted.

Clinical Observations: Numerous examples of complications in man have been reported following the intrathecal injection of penicillin. Walker and Johnson (10) reported a case in which the injection of 100,000 units in 5 cc. of saline caused urinary retention, paresthesia, and unsteady gait. Walker (8) reported 2 additional cases: One patient developed root pain for 5 months and permanent difficulty in voiding after several intrathecal injections of 40,000 units, and the second case had permanent flaccid paralysis of the legs and loss of sphincter control following the intrathecal injection of 50,000 units. This patient was operated upon several months later and was found to have adhesive arachnoiditis in the thoracic region.

Erickson, Masten and Suckle (11) reported 4 cases of infection of the central nervous system whose course they had been complicated by the injection of penicillin into the subarachnoid space. In only one of them, however, did the evidence clearly suggest that the drug was the direct cause of the untoward effect. In this case of staphylococceic-cerebral abscess and meningitis, a delayed transverse myelopathy, associated with adhesive arachnoiditis and intramedullary cavitation, was found in the thoracic region 10 days after intrathecal therapy had been discontinued. One injection of 40,000 units in 6 cc. of saline and 3 injections of 50,000 units in 10 cc. of saline had been given. Siegal (12) and Bailey (13) also reported the delayed onset of transverse myelopathy involving the lower thoracic cord about 2 weeks after intrathecal penicillin therapy had been started in cases of purulent meningitis. Neymann and co-workers (3) treated cases of dementia paralytica by injecting penicillin into the cisterna magna. Repeated injections of 30,000 units produced vomiting and signs of meningal irritation with an elevated spinal fluid protein content and pleocytosis. Higher doses of 40,000 to 50,000 were capable of producing severe convulsions, coma, and

* Crystalline penicillin 1600 units = 1 mg.
Fig. 8. Epileptogenic effects following topical application of antibiotics to cortex of cat. Penicillin: 1 minute after 5000 units per cc. Streptomycin: 15 minutes after 100 mg per cc. Bacitracin: 38 minutes after 2500 units per cc. Neomycin: 1 hour after 250 mg per cc. Erythromycin: 12 minutes after application of the powdered drug.
death. Johnson and Walker (14) injected 50,000 units of penicillin in 5 cc. of saline into the lateral ventricle of a 22 month old child with staphylococcal meningitis. Within one hour the patient was comatose and in vascular collapse, having frequent generalized seizures. Later injections of 15,000 units were better tolerated, and the child eventually recovered. Applebaum and co-workers (15) reported complications in 5 patients in a series of 125 cases of pneumococcal meningitis treated with large doses of intrathecal penicillin. Adhesive arachnoiditis with a block in the cerebrospinal fluid occurred in one patient. Irritative symptoms such as pyrexia, delirium, and convulsions occurred in 4 cases. In one case, those symptoms occurred following the inadvertent intrathecal injection of 500,000 units. In 3 patients, however, the complications arose after doses of 50,000 to 100,000 units. One 4 month old baby developed pyrexia and convulsions after 50,000 units were injected intrathecally and expired.

*Experiments with Streptomycin*:

Johnson and co-workers (16) noted marked cerebellar signs following the injection of 10 mg. of streptomycin into the cisterna magna of monkeys; 1.25 mg. injected into the cortex of monkeys produced slow awkward waving movements of the contralateral limb. Five to 10 mg. applied to the cortex of the monkey led to epileptiform abnormalities. Walker and co-workers (17) consistently produced convulsions with the application of 75 mg. of streptomycin to the monkey cortex. Suckle and co-workers (18) produced seizures in rabbits, dogs, and monkeys by injecting small amounts (0.25-0.5 cc.) of streptomycin between the dura and cortex. Threshold values of 30 mg., 75 mg., and 50 mg. were found for these 3 species. The same authors found thickening of the dura with inflammatory changes in the pia-arachnoid membrane following cortical application of the drug. The intracortical injection of streptomycin produced round cell infiltration, tissue vacuolization, and perivascular cuffing. Pilcher and Smith (19) injected 50 mg. of streptomycin into the cisterna magna of a normal dog and noted immediate stupor, profuse salivation, facial twitching and vomiting followed by nystagmus, ataxia, and hyperthermia. The animal recovered within 48 hours. Following intrathecal doses of 25 mg., 15 mg., 10 mg., and 7.5 mg., the same symptoms and signs appeared with progressively diminishing severity and duration. With 5 mg. moderate lethargy and ataxia were the only symptoms and lasted only for a few hours. A marked pleocytosis was found in the spinal fluid with all injections. Swift and Bushby (19) injected 50 mg. of dihydrostreptomycin into the cisterna magna of dogs and reported vomiting, coma, spasticity and pleocytosis.

In our experiments paroxysmal electrographic abnormalities in the form of spikes and sharp waves were produced by streptomycin in concentrations of 100 mg./cc. (fig. 8). Seizures were not observed until the concentration was increased to 500 mg./cc., but persisted for over 4 hours after the cortex had been thoroughly washed with Ringer's solution. Depression of spontaneous cortical activity was noted with concentrations as low as 50 mg./cc. No gross cortical damage was observed in these experiments.

Clinical Observations: The extensive use of streptomycin, given both intrathecally and intraventricularly in the treatment of tuberculous meningitis, has shown that the drug, as it is produced today, can be given safely in doses as high as 100 mg. daily in adults and 25 to 50 mg. daily in children. The early report of Cairns and co-workers (20) described serious complications following the intraventricular injection of 25 to 100 mg. of streptomycin. These cases consisted of 7 gravely ill patients with meningitis and 2 of inoperable brain tumors, who either rapidly became comatose following the injection or died several hours later of respiratory failure. These untoward effects could have been due to increased intracranial pressure secondary to the ventricular injection, or, as has been suggested by several later workers, to impurities contained in streptomycin used at that time. Both Valergakis and associates (21) and Molitor (22) felt that streptomycin in sufficiently high concentration has a direct neurotoxic effect on medullary centers. The former workers have reported 2 cases of tuberculous meningitis with serious reactions secondary to the injection of streptomycin into the cisterna magna. In one case seizures, circulatory collapse, respiratory failure

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*Streptomycin 1,000 units = 1 mg.*
and death followed the injection of 50 mg., and, in the second patient, the injection of 100
mg. rapidly produced coma which lasted over 48 hours and was followed by several days of
profound mental change. Other workers reported pleocytosis (23), radiculitis and paraplegia
(24) following intrathecal injection of streptomycin.

*Experiments with Bacitracin*: Teng, Meleney and co-workers (25, 28) studied the local
effect of bacitracin on the central nervous system of animals. The intracerebral or intra­
ventricular injection of 5,000 units in 0.5 cc. of isotonic saline proved to be epileptogenic in
cats, but the animals usually recovered completely. The injection of 5000 units into the
cisterna magna of monkeys caused no untoward effects. Following a single intracisternal
injection of 10,000 units in dogs, there were transient signs of irritation with neck rigidity,
hyperthermia, and spinal fluid pleocytosis, but all animals survived and had no disability.
Dogs sacrificed six hours after such an injection showed mild acute inflammatory changes
throughout the intracranial and intraspinal leptomeninges which were most severe near the
inoculation site. In one animal there was extension of the inflammatory reaction into the
superficial portions of the parenchyma of the cerebral hemispheres, cerebellum, brain stem,
and cervical spinal cord. Animals allowed to survive for 7 days had slight leptomeningeal
inflammatory changes over the base of the brain stem, cerebrum and cerebellum. Mild de­
generation and inflammatory changes were noted in the medulla and sacral spinal cord.
The dogs which were killed 4 weeks after the cisternal injection showed no lesions in the
leptomeninges, brain, or spinal cord.

In our experiments, a transient depression of spontaneous electrocortical activity was
noted after the local application of bacitracin in concentrations of 200 units/cc. When solu­
tions containing 2500 units/cc. were applied to the sensori-motor cortex, electrographic
spikes were observed within 8 minutes which continued to increase in frequency and am­
pitude for a period of one hour (fig. 8). At this time evoked potentials recorded from the
sensory cortex on tapping the opposite forepaw appeared augmented at least twice that
normally observed. The application of bacitracin to the motor area in concentrations of
5000 units per cc. rapidly produced high voltage spikes, and clonic focal seizures were ob­
served in the opposite extremities.

Clinical Observations: Teng and Meleney (26, 27) found that in adult patients repeated
intrathecal injections of 5,000 to 10,000 units of bacitracin in doses of 3 to 5 cc. of normal saline
could be given safely once or twice daily for 5 to 10 days. The injection of 3,000 to 10,000
units in 10 cc. of saline into the lateral ventricles at 12 hour intervals was well tolerated. The
direct application of 5,000 to 10,000 units in 10 cc. of saline to the freshly cut cortical surface
following frontal lobe topectomies caused no ill effect. These authors report that repeated
injections of bacitracin in doses of 5,000 to 30,000 units into the epidural, subdural, intra­
cerebral, intrathecal, and intraventricular routes in 67 consecutive cases of neurological
or neurosurgical infections have produced no untoward effects.

*Experiments with Aureomycin*: In our experiments the commercially prepared aureomycin
for intravenous administration was applied to the cerebral cortex. This preparation con­
tained sodium glycinate as a buffering agent because of the acid reaction of pure aureomycin
in solution, and it is possible that this added drug may have affected the results. In concen­
trations of 100 mg./cc. this solution of aureomycin caused marked depression of spontaneous
cortical activity which showed no tendency to recover after a period of several hours (fig.
9). No epileptiform activity was observed. The surface of the cortex was permanently
stained a bright yellow color which could not be washed away. Histological study revealed
a thickened and yellow stained pia-arachnoid membrane which contained numerous poly­
morphonuclear leucocytes, lymphocytes and plasma cells. This inflammatory reaction
extended into the cortex by way of the perivascular spaces (fig. 10). Increased numbers of
microglia were present in the superficial cortical layers. Marked neuronal degenera­
tive changes were observed, especially in the larger pyramidal cells, many of which were
shrunken and pyknotic.

* Bacitracin 30 units = 1 mg.
Fig. 9. Depression of spontaneous electrocortical activity with no epileptogenic effects following topical application of antibiotics to cortex. Polymyxin B sulfate: A, spontaneous activity before application of drug; B, 1 hour after 50 mg per cc. Aureomycin: A, before and B, 2 hours after 100 mg per cc. Terramycin: A, before and B, 35 minutes after 200 mg per cc.

Clinical Observations: Significant cerebrospinal fluid levels are usually obtained within 4 hours following intravenous administration and between 21 and 24 hours following oral ingestion (2, 29, 30, 31, 32). The cerebrospinal fluid levels usually do not exceed 1 μg./cc. and this small amount of antibiotic has not produced untoward effects on the central nervous system.

Neter and co-workers (33) reported the successful treatment of a case of meningitis due
FIG. 10. Cerebral cortex 6 hours after topical application of A: aureomycin 100 mg per cc. and B: terramycin 200 mg per cc. Cresyl violet stain; X125.

to Aerobacter aerogenes using intrathecal and intraventricular aureomycin after oral and intravenous therapy had failed. Repeated injections of 10 mg. of aureomycin in 10 cc. of sixth-molar lactate solution intraventricularly and 1 mg. in 1 cc. of the same solution intrathecally in a newborn child caused no untoward effects.

Experiments with Terramycin: Terramycin hydrochloride containing sodium glycinate
is readily soluble with a pH of approximately 9.0 and can be given intravenously. In our experiments a small amount of this yellow solution in a concentration of 200 mg./cc. was applied to the motor cortex of the cat, and a marked depression of spontaneous electrocortical activity was observed which persisted for several hours (fig. 9). No evidence of epileptiform activity was seen. Marked injection of the pial vessels occurred, and the cortex developed a dark red color which persisted despite repeated washing with warm Ringer's solution. After a survival period of about 6 hours, the animal was sacrificed. Histological study disclosed as severe an inflammatory reaction as was observed with aureomycin (fig. 10). In addition, there was marked dilatation of the pial vessels and engorgement of intracortical vessels with numerous perivascular hemorrhages. The neuronal degeneration was even more marked than that seen when aureomycin was used. As in the case of aureomycin, the possible effect of the sodium glycinate has not been evaluated.

Clinical Observations: Terramycin has not been injected intrathecally in man. After oral administration, terramycin is absorbed into the blood serum better than aureomycin but not as well as chloramphenicol (2). The cerebrospinal fluid levels obtained are, however, no better than with aureomycin (34) and in these small quantities it has produced no adverse effect on the central nervous system.

Experiments with Polymyxin*: Swift and Bushby (9) studied the effect of polymyxin E injected intrathecally. In rabbits the injection of 1 mg. into the cisterna magna produced temporary paralysis of the hind legs. The same dose in dogs, given under barbiturate anesthesia, produced no neurological toxic signs, but there was a pleocytosis of 4,000 to 6,000 per cc., most of which were polymorphonuclear leucocytes. Repeating the dose daily for 5 days did not increase the number of cells, and 24 hours after the last dose the number of cells had dropped to 100 to 200 per cc. Doses of 3 to 5 mg. given by this route in dogs were very toxic, producing coma, spasticity, convulsions, and death.

In our experiments the epileptogenic properties of polymyxin B sulfate were investigated. The local cortical application of the drug in concentrations of 50 mg./cc. produced only a moderate depression of the spontaneous electrocortical activity (fig. 9). When the dry powdered drug was placed on the motor cortex, there was marked depression of cortical activity which persisted for several hours. There was never any evidence of epileptogenic activity in the electrocorticogram, and seizures were not observed. There was no evidence of gross damage to the cerebral cortex even after the powdered drug had been applied for several hours.

Clinical Observations: Polymyxin B and E have been given intrathecally and intraventricularly in cases of purulent meningitis due to gram negative organisms (9, 35, 36), and most investigators now agree that this drug should be used in all cases of meningitis due to Pseudomonas aeruginosa (37, 38, 39). Two to 5 mg. in 5 cc. isotonic saline daily has proven a satisfactory intrathecal dose. Swift and Bushby (9), in treating cases of influenzal meningitis, gave 1 to 6 mg. in 2 cc. of distilled water intrathecally twice daily for 2 to 3 days, and then daily until the spinal fluid was sterile and clinical improvement was satisfactory. In 3 out of 7 cases treated with polymyxin E, they found signs of meningeal irritation after the spinal fluid was sterile. Two of these cases improved as soon as the intrathecal dosage was reduced. In the third case the signs of irritation were severe, and medication had to be discontinued.

Experiments with Neomycin: In our experiments neomycin sulphate was found to have epileptogenic properties when applied to the cortex of cats. Within 30 minutes after application of the drug to the parietal cortex in a concentration of 250 mg./cc. high voltage spikes appeared and spread into adjacent cortical areas (fig. 8). No seizures were observed. There did not appear to be any gross damage to the cortex using this concentration of the drug.

Clinical Observations: Neomycin has a broad antibacterial spectrum, but because of its ototoxic and nephrotoxic effects, it has been used only as a topical agent and should not be injected intrathecally or intraventricularly(40).

Experiments with Erythromycin: In our experiments the 100 mg. tablets used for oral

* Polymyxin B 10,000 units = 1 mg.
administration were pulverized and the powder was applied to the cat cortex. Moderate depression of spontaneous electrotrophic activity was observed with random spikes and sharp waves (fig. 8). The constant type of epileptiform activity seen with penicillin, streptomycin, bacitracin and neomycin was not present following application of erythromycin powder, and seizures were not observed. There was no gross cortical damage.

Clinical Observations: In patients with normal meninges, erythromycin does not diffuse into the cerebrospinal fluid in significant quantities following oral administration (41, 42). However, this drug, given orally, has been used successfully in the treatment of a case of staphylococcal meningitis (43). Erythromycin has not been injected intrathecally.

DISCUSSION

The present trend away from frequent intrathecal injections in the treatment of purulent meningitis can be explained by several factors: The experimental study of the inherent dangers in the topical application of many of the antibiotics to the central nervous system, the reports of clinical complications following intrathecal and intraventricular administration, the discovery (4, 44, 45) that significant cerebrospinal fluid penicillin levels can be maintained with large intravenous or intramuscular doses of 0.5 to 1 million units every 2 to 3 hours, and the production of newer antibiotics which diffuse into the cerebrospinal fluid following oral or intravenous administration. It is now apparent that most cases of meningococcal meningitis will respond to sulfonamides and intramuscular penicillin and will not require intrathecal medication. Similarly, meningitis due to Hemophilus Influenzae appears to be controlled by sulfonamides and oral chloramphenicol, making intrathecal streptomycin unnecessary. However, it would seem that many of the cases of streptococcal and pneumococcal meningitis, as well as most of the infections due to staphylococcal, coliform, proteus, and pyocyaneus organisms will continue to require intrathecal injections of antibiotics, if optimal results are to be obtained (39, 46).

Chloramphenicol has proven to be a potent antibiotic whose ease of administration and prompt diffusion into serum and spinal fluid makes it a particularly useful agent in the treatment of many forms of purulent meningitis (36, 39, 47, 48, 49, 50, 51). The recent demonstration of the safeness of intrathecal injection adds greatly to the effectiveness of the drug (1). The minimal inhibiting concentrations of the drug in the spinal fluid for susceptible organisms ranges between 1 to 25 µg/cc. It may be found advisable in the future to supplement the oral administration of chloramphenicol with a few daily intrathecal injections to rapidly obtain relatively high spinal fluid levels of this bacteriostatic agent and promptly eliminate the infecting organisms.

Scattered reports of neurotoxicity (52, 53), and bone marrow depression (54, 55) due to orally administered chloramphenicol have appeared during the past few years. These cases had usually received the drug for a period of from 2 to 3 weeks to as long as several months, and in each instance a definite cause and effect relationship could not be clearly established. With this circumstantial evidence, it is clear that chloramphenicol should not be used indiscriminately. However, its effectiveness as an antibiotic in the treatment of purulent meningitis is so great, that it merits continued clinical use in selected cases.

From our experimental data it seems clear that pure crystalline chloramphenicol is relatively innocuous when injected intrathecally or applied locally to the
cerebral cortex. While epileptiform activity was never observed, either electrographically or clinically, the effect on the evoked potentials suggests an increase in the local excitability of the cerebral cortex. Only a transient depression of spontaneous electrocortical activity was observed after application of the powdered drug. The only significant histological abnormality found was thickening of the leptomeninges at the base of the cerebral hemispheres following repeated intrathecal injections of 1 mg. of chloramphenicol, and overlying the cortex which had been covered by the powdered drug for one month.

The local effects on the central nervous system of the other antibiotics have not been completely evaluated in this study. However, we have learned that this particular technic of cortical application and recording is capable of demonstrating epileptogenic properties. We have confirmed the experience of others concerning the convulsant effects of penicillin, streptomycin, and bacitracin, and have also shown that pure neomycin sulfate and erythromycin, as it is given orally, possess epileptogenic properties. Aureomycin and terramycin were found capable of causing severe cortical damage. Polymyxin B had no epileptogenic or destructive properties, producing only depression of cortical activity.

SUMMARY

1. Repeated daily intracisternal injections of as much as 1 mg. of chloramphenicol into lightly anesthetized cats produced no seizure or signs of meningeal irritation, and histological studies showed no inflammatory or degenerative changes in the central nervous system or leptomeninges.

2. Electroctograms obtained on cats under local anesthesia and curare showed no epileptiform activity up to 9 hours following the local application of pure crystalline chloramphenicol to the motor cortex. A transient depression of the spontaneous electrocortical activity was observed, as well as an increased response of evoked potentials recorded from sensory and auditory cortex.

3. No significant cortical damage was observed following the application of crystalline chloramphenicol to the cortex in cats surviving for several hours or in an animal who was allowed to survive for one month.

4. Penicillin, streptomycin, bacitracin, neomycin, and erythromycin had epileptogenic properties when applied to the cortex in sufficient concentration.

5. Aureomycin and terramycin, each containing a small amount of sodium glycinate, caused marked depression of the spontaneous electrocortical activity but had no epileptogenic properties. Gross and microscopic cortical damage was severe.

6. Polymyxin B had no epileptogenic properties and did not damage the cortex grossly, but produced depression of spontaneous electrocortical activity.

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REFERENCES


