Transfer of Local Anesthetics to the Subarachnoid Space and Mechanisms of Epidural Block

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Using a physiological preparation in the dog to perfuse the subarachnoid space continuously, the amount of procaine recovered in the spinal fluid was determined after repeated epidural injections of various concentrations (0.5–5%). The studies extended into the post-mortem phase. The subarachnoid transfer of procaine was found to bear a direct relation to concentration. Repeated doses magnified the clinical effect of the previous injections and increased the amount of procaine recovered. This seemed to be due to incomplete vascular removal of the previous dose. Position influenced epidural clearance by allowing a greater paravertebral escape, possibly because of regional differences in circulation. A greater quantity of procaine was recovered from the subarachnoid space in the supine than in the lateral position. Death of the animal did not reduce subarachnoid passage. On the contrary, it prolonged the period of time during which procaine could be recovered.

In correlating these facts with clinical experiences, we suggest that epidural blockade results from a dual mechanism, basically an intradural block, due to direct passage of the anesthetic through the dura, and secondly via an extradural absorption in the paravertebral regions.

AT PRESENT there appears to be little controversy regarding the diffusion of anesthetic solution into the subarachnoid space[1,2,3] and the neuroaxis[4] once an epidural injection is performed. However, the site of passage and the mode of action of epidural anesthesia have not been conclusively elucidated. In order to interpret rationally clinical observations made during epidural anesthesia and to analyze the underlying mechanisms, we have studied the influence of different concentrations of procaine on the passage into the subarachnoid space.

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Material and Methods

In 51 mongrel dogs with mean body weight of 13 kg. (range 9–20 kg.) endotracheal intubation was performed under thiopental anesthesia (30 mg./kg.). Mean arterial blood pressure was monitored by means of a polyethylene catheter inserted into the femoral artery and a mercury manometer. Because of the small amount of the cerebrospinal fluid in the dog and to facilitate serial sampling a modification of Rudin's perfusion system was used (fig. 1). In this method a radiopaque catheter was introduced through a Touhy needle into the cisterna magna. Correct placement of the catheter was confirmed by noting movement of the auricular and cervical muscles upon stimulation of the corresponding nerve roots. The catheter was then connected to a perfusion system which contains Ringer's solution dripping at a rate of 0.4–0.7 ml./minute. The lumbar dural sac was exposed through a laminectomy at L5–L6. Through this a second subarachnoid catheter, 1 mm. in diameter, was introduced cephalad and used to collect the perfusion solutions; an epidural catheter was then introduced and placed at the same level as the lumbar subarachnoid catheter. The localization of the catheters was confirmed radiographically.

Once the rate of infusion of the Ringer's solution was stabilized and an initial sample collected from the lumbar subarachnoid catheter, we injected into the epidural space 0.5 cg./kg. of procaine in concentrations ranging from 0.5 to 5.0 per cent. In 5 dogs procaine solutions containing epinephrine 1: 200,000 was used. Every 3 minutes, for 50 minutes, samples were collected. A second injection in the same dosage was then given and collections performed in the same way.

In addition, in 10 animals, a third dose was used. At this point all animals were exsanguinated and one or two doses of local anesthetic were injected post mortem.

In 27 dogs the perfusion was performed in the left lateral position and in 24 animals the supine position was used. Arterial blood samples were drawn in order to measure the levels of procaine and its metabolites with a modification of Banffi's method.[5] In all cases a curve was drawn plotting drug recovery against time. Mean recovery, expressed in μg./ml./minute, was correlated with concentration, volumes and absolute dose injected.

Results

Physiological Effects. The first doses usually produced hypotension, bradycardia and bradypnea. These were most evident when high concentrations of procaine were used.

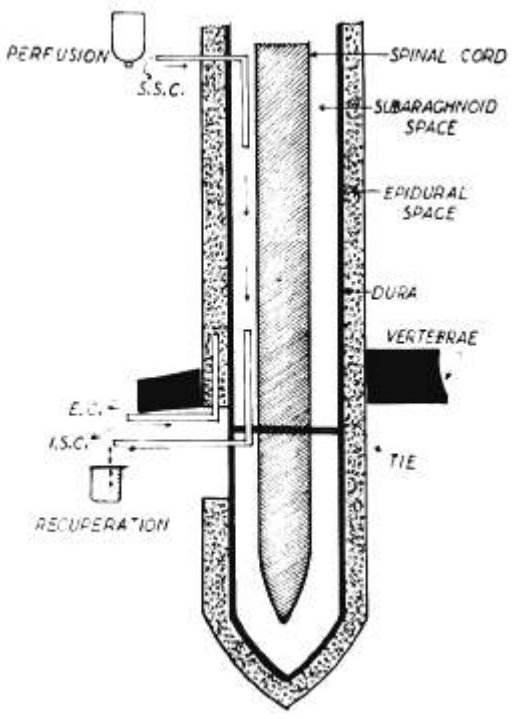

FIG. 1. Method: SCC: Superior subarachnoid catheter introduced via cisternal puncture for the perfusion solution. ISC: Inferior subarachnoid catheter placed under direct vision after lumbar laminectomy for recovery of subarachnoid perfusion solution. EC: Epidural catheter placed at the same level as the lumbar subarachnoid catheter for injecting the anesthetic solution.

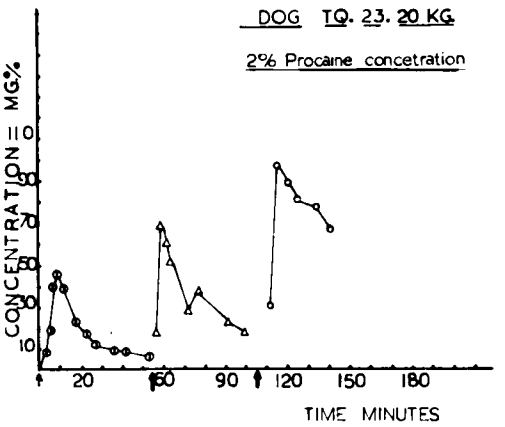

FIG. 2. Subarachnoid recovery of procaine after the epidural injection of the same dose of 2 per cent procaine. The arrows indicate the time of epidural injection. The appearance of procaine in the subarachnoid space and the time of the peak are similar. There is an increase in transfer after each dose. Observe double peak after the second dose.

With subsequent doses the arterial blood pressure fell even further and some animals developed respiratory paralysis.

Recovery Curves. In all animals, variable though significant amounts of procaine were obtained in the perfusion samples. The highest levels were obtained between 5 and 25 minutes, with a mean of 15 minutes. The time was not significantly different after injection of successive doses. An early rise was followed by a two-stage fall, a fast and a slow one, tending to become asymptotic to the time axis (fig. 2). In some cases a double peak recovery curve was observed, the second peak appearing around 30 minutes (fig. 3).

Total Recovery. Recovery increased significantly with successive doses (P-0.001), ranging between 1.6 and 15.3 per cent for the first, and from 3.0 to 18.9 per cent (mean 7.3 per cent) for the second dose.

The Mean Recovery Value of Procaine. This is used as the basis for discussion because it is the most unbiased value.

Influence of Concentration of Injected Solution. The quantity of procaine recovered in the subarachnoid fluid after epidural injection was related to the concentration of the procaine solution injected in the epidural space. Comparing different groups of experiments it

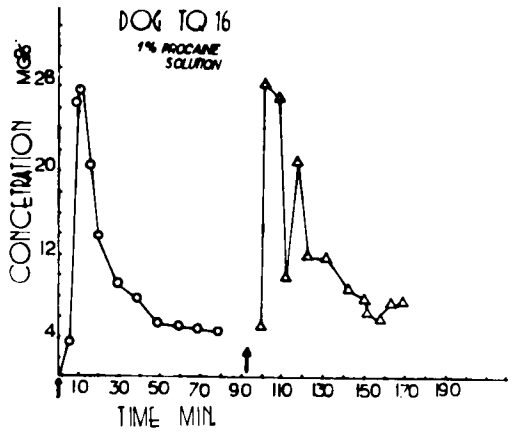

FIG. 3. Subarachnoid recovery of procaine after the epidural injection of repeated doses of 1 per cent procaine. The arrows indicate the time of epidural injection. Here the height of the peaks is similar but the amount of anesthetic transfer is greater after the second dose. Thirty minutes after the second dose there is a second peak. Maximal concentrations found after the injection of 1 per cent procaine, 28 mg. per cent, are lower than observed in figure 1, after 2 per cent procaine.

was seen that concentration was more important than volume in relation to recovery. When higher concentrations (3–5 per cent) were injected, the mean recovery figures were significantly higher (table 1) than with lower concentrations, despite the lower volumes (fig. 4). In the groups with 3, 4 and 5 per cent concentrations, the higher the volume injected, the greater was the recovery. This relation was not observed in the low concentration group (0.5–1 per cent).

Successive doses increased significantly (P.-0.001) the mean recovery rates (table 2). This can be seen in the graphs by the higher peaks and the more gradual slopes.

Position modified passage into the subarachnoid space because the animals in the supine position gave higher recovery curves, with significantly greater mean recovery values (table 3) than those in the lateral decubitus.

Epinephrine added to the procaine produced less elevation of the curves and prolonged the time over which subarachnoid procaine was recoverable.

Procaine in arterial blood was detected 2 minutes after epidural injection. The curves showed high concentrations initially and a progressive fall. Successive doses gave similar results.

Observations on Post-mortem Injection. The results were similar to those obtained in live animals. No delay was observed either in the appearance of procaine or in attainment of a peak. The only distinctive finding was a prolongation of the slope of the curve (fig. 5).

Discussion

Clearance of local anesthetics from the epidural space may be influenced by: passage into cerebrospinal fluid, tissue fixation, paravertebral escape, lymphatic absorption and hematogenous removal. The latter four factors modify the first. Some are operative at the start (paravertebral escape and fixation) while others act continuously (hematogenous and lymphatic absorption). Passage into cerebrospinal fluid is influenced by the volume and concentration of the injected solution, the capacity of the epidural space, variability of epidural escape, thickness of the dural sheath, the efficiency of vascular removal which is related to the time of contact between drug and membrane. This relationship may be expressed in the equation:

$$\text{Subarachnoid passage } K = \frac{\text{injected volume} \times \text{concentration}}{\text{epidural capacity} \times \text{vascular removal} \times \text{thickness of membrane}}$$

TABLE 1. Influence of Concentration of Injected Solution of Subarachnoid Transfer of Procaine on 32 Dogs (μg./ml./minute)

Injected Concentration (per cent)	Mean	Standard Deviation	Standard Error
0.5- 2.0	2.25	0.21	0.04
3- 5.0	3.92	0.47	0.1

TABLE 2. Recovery of Subarachnoid Procaine After Epidural Injection in 30 Dogs (μg./ml./minute)

Dose Injected	Mean	Standard Deviation	Standard Error
First dose	2.6	0.86	0.15
Second dose	4.4	0.50	0.09

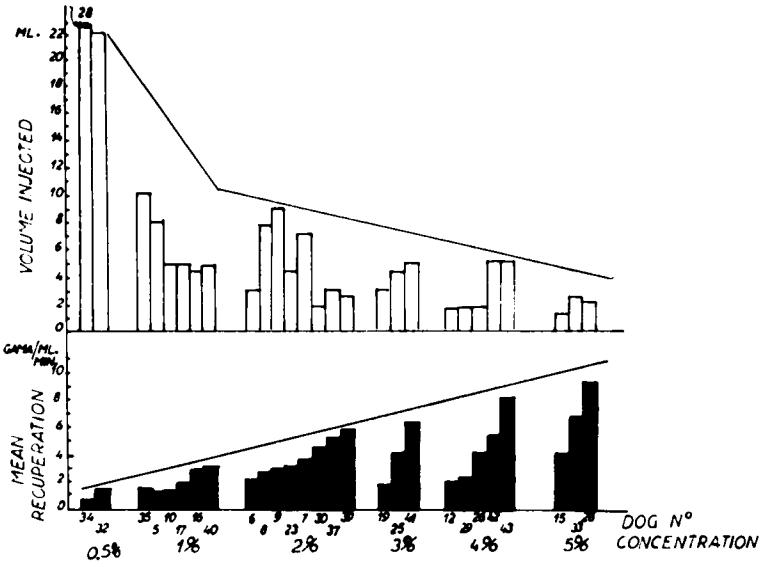

FIG. 4. Mean subarachnoid recovery of procaine according to concentration and volume of the injected solutions. Each column represents one animal, the animals grouped according to concentration of injected solution. The open columns represent the volume injected into epidural space and solid columns the mean recovery of procaine in subarachnoid space. Mean recoveries of procaine were greater when concentration of the injected solution increased in spite of the lesser volumes injected.

where K, the diffusion coefficient, includes properties of the drug such as the dissociation constant, penetrating ability and the like. The relation of injected volume/epidural capacity which represents the effective zone of transfer is valid so long as the injected volume does not exceed the epidural space. If the injected volume overflows the epidural space, as the experience with the larger volumes suggests, dural passage is diminished.

The influence of concentration of the injected solution upon transfer was observed after single and repeated doses. There was an increase in the quantities found in the subarachnoid space which was related to concentration of injected solution, even after death. This demonstrates the permeable nature of the membrane and passive transfer of procaine associated with a higher concentration gradient per unit of surface.

TABLE 3. Influence of Position of the Dog on Subarachnoid Transfer of Procaine After Epidural Injection (μg./ml./minute)

Position	Mean Recovery	Standard Deviation	Standard Error
Lateral D.	2.08	0.25	0.05
Dorsal D.	4.60	0.40	0.11

Anesthetics given epidurally may reach the cerebrospinal fluid through dural passage via the dural nerve root sleeves or by diffusion across the perineurium in a retrograde fashion (fig. 6). The predominance of the concentration effect over volume makes it unlikely that the area of passage is a limited portion of the neural surface such as the perineurium. This is verified by the difference between the 2.2 ml. injection of 5 per cent solution (110 mg.) and the 22 ml. injection of the 0.5 per cent solution (110 mg.). In the former only

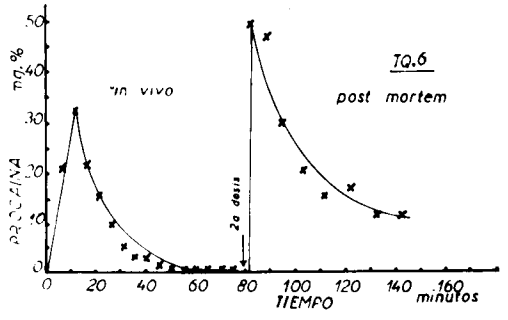

FIG. 5. Subarachnoid levels of procaine after epidural injection *in vivo*, and post mortem. The first curve represents the *in vivo* and the second the post-mortem injection. There is no delay either in the appearance of procaine in the subarachnoid space or in the peak. Observe the prolongation of the slope post mortem, due to the absence of vascular removal.

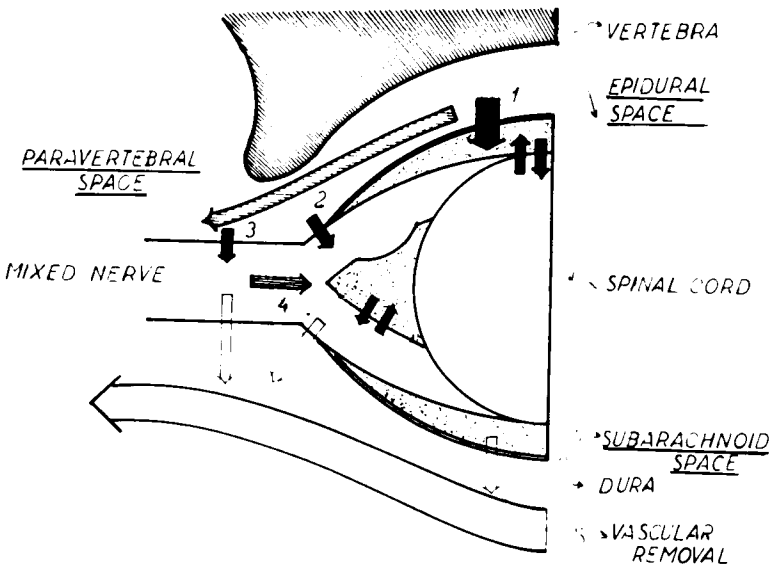

FIG. 6. Clearance of epidural space and mechanisms of epidural block (schematic). The anesthetic injected into the epidural space can traverse the dura (1); traverse the dura sheath (2); arrive in the subarachnoid space by a retrograde neural pathway (4); after paravertebral escape it can make contact with the mixed nerves (3). Outlined arrows indicate hemolymphatic removal. Solid arrows represent blocking mechanisms.

a few spinal nerves could be bathed, but in the latter though the rami of all the spinal nerves are "bathed," recovery of the drug from the subarachnoid space is less. It is likely therefore that subarachnoid passage is a membrane diffusion process with regional variations based upon the characteristic of the membrane.

Vascular removal influences subarachnoid passage by limiting the time of contact between drug and membrane. The importance of this factor is denoted by the prolongation of the time that subarachnoid procaine may be collected after successive post-mortem doses. This may be of importance in patients with less effective circulation as in arteriosclerosis. In these cases, therefore, where less vascular removal can be expected, the epidural doses should be diminished in order to prevent greater spread.

In the production of subarachnoid levels of anesthetics and in relation to duration of the block still another factor must be considered, subarachnoid absorption of the anesthetic. Since there was a greater subarachnoid recovery in the post-mortem experiments, subarachnoid removal must be active, although we believe that the most important route of vascular removal is the epidural rather than the subarachnoid space. Most of the injected drug (82 per cent) remains outside of the dura. This concept is in agreement with clinical experience wherein there are few toxic reactions to the local anesthetic after subarachnoid as compared to epidural block.

Direct transfer of the drug through the dura or via the dural cuffs produces a subdural anesthesia. Paravertebral escape provides a reinforcing action. When the anesthetic leaves the epidural space it not only acts on mixed nerves, but can re-enter the subarachnoid space in retrograde fashion along these mixed nerves. This is evidenced by the fact that thirty minutes after the injection of the second dose some recovery curves show a second peak (fig. 2). This does not seem artefactual or related to the circulation because the blood procaine level at this time is minimal.

We believe that after epidural injection the passage of the anesthetic into the subarachnoid space participates in the production of anesthesia for several reasons. Significant concentrations of procaine are found in the cerebrospinal fluid and manifestations of blockage are associated with this. After the epidural injection of 2-clorprocaine in 12 patients[6] a close correlation was found between the drug concentration in cerebrospinal fluid and the appearance, maintenance and disappearance of anesthesia. This observation disagrees with the results found by Foldes and

Davis.[7] In clinical epidural anesthesia higher blockage is obtained with concentrated solutions.[8] Sometimes, the volume is so small that extension of the block can not be explained by longitudinal epidural dispersion. The present experiments show that there is a close relationship between increasing concentrations, subarachnoid passage and blocking action. When concentrated solutions in small volumes were injected, the block obtained was more extensive. This can only be explained by a greater subarachnoid passage of anesthetic.

Clinical Implications

The difficulties encountered in blocking the lumbar and thoracic dermatomal segments via the caudal route are well known. Because of the large capacity of the sacral space, the easy escape through the anterior sacral foramina and the adhesions between the dural sac and sacrum, large anesthetic volumes are required. If it is valid to explain the lack of longitudinal dispersion of solution, via the caudal canal, perhaps results should be the same in blocking the sacral area through a lumbar epidural puncture. But the latter is not difficult: A block between D12–S5 is easily obtained by injecting 10 ml. of 2 per cent lidocaine between L2–3. This volume rarely flows beyond the first sacral vertebra, as corroborated radiographically, because the radio-opaque-anesthetic solution spreads predominantly towards the thoracic segments. A subdural mechanism of block must then account for the lower sacral block.

The influence of position on the extent of the block has been pointed out.[8] Injection in the lateral position diminished anesthetic requirements by 0.25 ml./segment as compared to the sitting position.[8] In our experiments a significantly higher subarachnoid recovery of drug was found in the supine than in the lateral position. This can be explained by diminution in paravertebral escape and a greater surface area for contact (fig. 7).

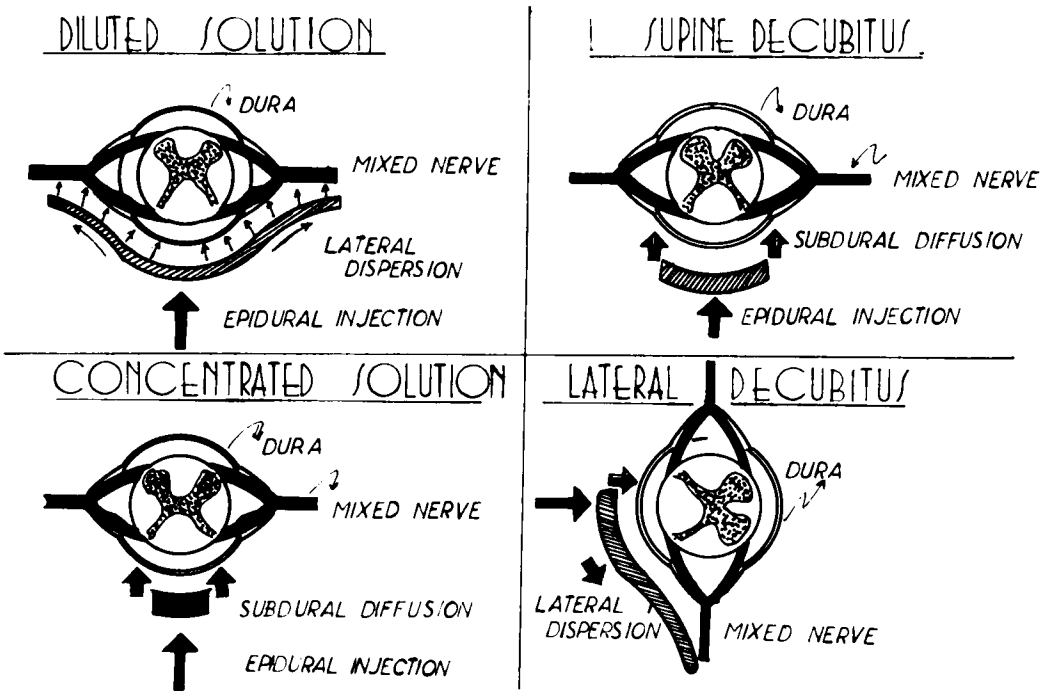

FIG. 7. Influence of concentration of injected solution and position on the subarachnoid transfer of procaine after epidural injection. Injection of concentrated solutions increases the subarachnoid transfer of procaine by a higher diffusion gradient. Lateral decubitus produce greater lateral dispersion in young people and reinforces the block in the dependent part.

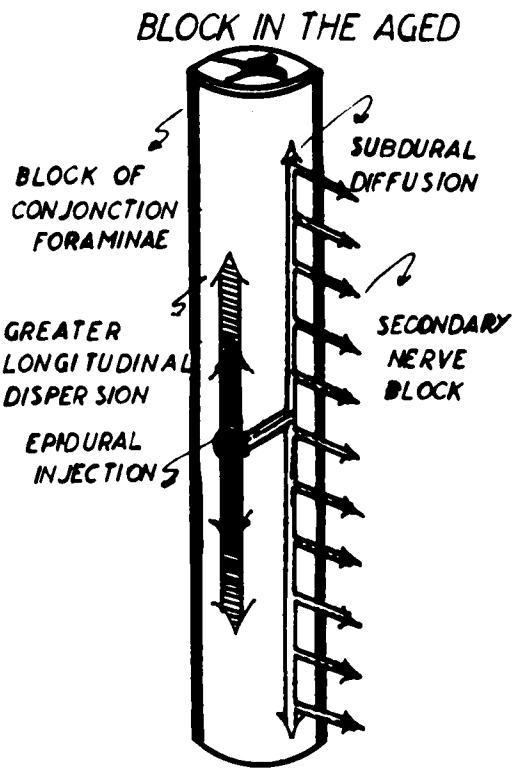

FIG. 8. Characteristics of the epidural block in the aged. Obstruction at intervertebral foramina causes a greater epidural longitudinal dispersion, increases the subdural transfer and the extension of block.

However, the existence of other factors should be considered, because with smaller volumes (which theoretically do not overflow the epidural space) differences also appear. One of these factors could be the dissimilar vascular distribution. There are no posterior epidural veins in the dog; instead there is a rich funicular network laterally.

In the aged, because of the higher epidural dispersion of anesthetic solution resulting from obstruction at the intervertebral foramina, the block is more extensive (fig. 8). If the foramina are indeed obstructed, the mechanism of the block is independent of the paravertebral escape of the solution. Even in the thoracic zone, where the mixed nerves are formed within the intervertebral foramina, there would be a lack of contact with the dural root sleeves and anesthesia results from subarachnoid passage of drug.

In the present experiments the similarity of the shape of the curve, the time of detection of procaine and the height of the peak demonstrate that with repeated doses transfer mechanisms are not modified. The quantities recovered were higher after each injection, producing a step-like curve (fig. 2). This was found even if the concentration of procaine in the subarachnoid space following the first dose had fallen to zero. This suggests a summation of drug effect outside of the dura, perhaps due to a residual of the previous dose below the minimal concentration necessary to establish a gradient. This observation explains why in clinical continuous epidural anesthesia additional injections in the same amount as the initial dose can produce a higher block. In order to maintain a given level it is necessary to reduce the volume or concentration of the subsequent dose.

Summary and Conclusions

Using a physiological preparation in the dog to perfuse the subarachnoid space continuously, the amount of procaine recovered in the spinal fluid was determined after repeated epidural injections of various concentrations (0.5–5 per cent). The studies extended into the post-mortem phase. The subarachnoid transfer of procaine was found to bear a direct relation to concentration. Repeated doses magnified the clinical effect of the previous injections and increased the amount of procaine recovered. This seemed to be due to incomplete vascular removal of the previous dose. Position influenced epidural clearance by allowing a greater paravertebral escape possibly because of regional differences in circulation. A greater quantity of procaine was recovered from the subarachnoid space in the supine than in the lateral position. Death of the animal did not reduce subarachnoid passage. On the contrary, it prolonged the period of time during which procaine could be recovered.

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INTRAVENOUS VITAMIN K Several serious reactions, and one fatality, after intravenous administration of vitamin K, were characterized by dyspnea and chest pain. Whether they were due to the dispersants or the whole emulsion is not known. For less than extreme emergency it is better to give the drug orally or intramuscularly. (*The Medical Letter, Volume 25, Issue 128 (Dec. 6) 1963.*)

CLOSTRIDIAL MYOSITIS Clostridial myositis following parenteral administration of medication is a serious complication with high mortality. Organisms may be introduced with a needle from overlying skin that has not been adequately prepared. Alcohol is ineffective against spore forms; organic iodine compounds may be preferable in preparing the skin for injection. The type of medication administered has had some correlation with the disease, the most prominent offenders being caffeine and epinephrine. Should an ischemic environment be created due to vasoconstriction, direct tissue injury, pressure, or trauma, circulating organisms may well colonize and grow in this site. The course of untreated clostridial myositis is rapid and fatal, symptoms appearing within 10 to 36 hours of the initial injection, and 85 per cent of mortalities occurring within 48 hours. Diagnosis should be confirmed by needle aspiration of the area, the organism being seen on smear. Crepitation may be difficult to elicit, especially in the gluteal region or thigh. Treatment consists of wide excision and debridement of all devitalized tissue, and massive doses of antibiotics together with adequate tetanus prophylaxis. Hyperbaric oxygen should be used when proper facilities and personnel are available. (*Berggren, R. B., and others: Clostridial Myositis After Parenteral Injections, J.A.M.A. 188: 1044 (June 22) 1964.*)