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Mechanisms of Differential Axial Blockade in Epidural and Subarachnoid Anesthesia

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The mechanisms of persistent differential blocks that accompany subarachnoid and epidural anesthesia are clarified here with the aid of two principles derived from *in vitro* study of individual myelinated axons: 1) conduction can leap two consecutive blocked nodes but not three, and 2) a fiber length with more than three consecutive nodes bathed by weak anesthetic may block by decremental conduction, the requisite concentration varying inversely with the number of nodes bathed by anesthetic. Principle 1 applies in epidural blockade, where anesthetic bathes only a few millimeters of segmental nerve extradurally in the intervertebral foramen. Here, three-node block will be rare in large, long-internode fibers but likely in small, short internode fibers, thus explaining the differential retention of motor power in the presence of block of pain, which is achieved in epidural anesthesia when relatively weak solutions are used, as in obstetrics. Principle 2 may intervene in subarachnoid blockade where, cephalad to the site of puncture, increasingly concentrated anesthetic bathes increasing lengths of fibers in the craniocaudal succession of spinal nerve roots. This will produce decremental conduction block in increasingly long internode fibers in successive roots, reflected in a corresponding craniocaudal segmental sequence of blocked physiological functions: vasoconstriction, cutaneous temperature discrimination, pinprick pain sensibility, and skeletal motor activity. The segmental *spatial* differential sequence migrates with time but resembles the *temporal* differential sequence of loss seen at the onset of peripheral nerve blocks. Several other previously disparate clinical observations follow logically from the new interpretation. (Key words: Analgesia. Anatomy: segmental nerve roots; spinal dura mater. Anesthesia: mechanisms. Anesthetics, local: differential nerve block. Anesthetic techniques: peridural. Nerve: decremental conduction; differential conduction.)

THE GOAL OF selectively preventing pain impulses from reaching the central nervous system has beckoned physicians for many years. Hope of achieving this with a local anesthetic was stimulated when Gasser and Erlanger discovered a time sequence in the suppression of components of peripheral nerve action potentials by cocaine.[1] This eventually led to attempted differential spinal block[2] and the discovery that persistent differential losses of function were present during the periaxial blockades of subarachnoid[3] and epidural[4] anesthesia. Many efforts were made to explain the persistent differentials in terms of compound action potential physiology and pharmacology, but their outcome was confusing. Later studies of local anesthetic action on individual axons, most recently pertaining to the length of fiber bathed in anesthetic, introduce new elements and make it timely to review their bearing on the mechanisms of differential blockade.

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Physiological Considerations

Both somatic sensibility and motor activity are involved in clinical differential blockade. The sensibilities affected depend on activity in modality-specific primary afferent nerve fibers,[5] the best characterized being cutaneous warmth, coolness, pinprick pain, and mechanoreception (touch-pressure), served respectively by C (unmyelinated), Aδ, Aδ, and Aβ (myelinated) fibers. The motor activities affected are vasoconstrictor and skeletal, served in the periaxial region by Aδ (B) and Aβ myelinated axons, respectively. It should be noted that the differential blockades occur peripherally, in the sense that effects on central processing are not the primary cause of the phenomena. It will be seen that the fibers involved are mainly myelinated and differ in size (inferred from conduction velocity) according to the somesthetic and motor functions involved, although there is sometimes complete size overlap.

In experimental subjects, infiltration of local anesthetic around and into a cutaneous nerve first blocks C fibers and then, after a delay, the A fibers in ascending order of conduction velocity/size.[6] The first sensation lost, along with the C fiber component, is pain, followed successively, as the A delta fiber activity lapses, by warm, pricking pain, and cool. The temporal differentials are temporary; they merge into complete blockade of the nerve and are clearly the product of anesthetic diffusion. Studies of unit potentials have shown that, to block conduction, concentrated drug applied to a myelinated axon has to completely block

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TABLE 1. Transient Differentials: Reported Time Sequence of Functional Impairment at Onset of Blocks

Ulnar (Ref. 10)	Radial (Ref. 11)	IVRA (Ref. 12)	Subarachnoid (Ref. 9)
Vasomotor		Vasomotor	Vasomotor
Warmth and pinprick	Warmth and aching pain		Cold and warmth
Cold	Cold and pinprick	Cold and pinprick	Pinprick
Motor and touch		Motor	Motor

IVRA = intravenous regional anesthesia. Time sequences proceed downward.

at least three consecutive nodes.[7] When left to diffusion, this process requires most time in the fibers with the most widely spaced nodes, that is, in the larger fibers;[8] the distance involved in blocking unmyelinated axons is approximately 2 mm, no greater than for the smallest myelinated axons.[8] This process also accounts for the transient differential blocks at the onset of neural blockade, described in the literature[9–12] and summarized in table 1.

The diffusion metaphor, however, obviously does not account for the persistent differential blocks noted during axial blockades.[3,4,13–15] Rather, the persistent differentials of subarachnoid and epidural anesthesia have been attributed to "absolute" differences in conduction safety ("sensitivity" to conduction block), ostensibly related to fiber size/conduction velocity. This explanation, however, was derived from studies of compound action potentials[16–18] and has become inconsistent with later, more refined data derived from studies of individual axons. The latter reveal no such systematic differences in safety of conduction;[8,19–21] (see reference 22 for a superb review). On the average, the nodes of Ranvier of small myelinated axons are neither more nor less sensitive to block by local anesthetic than the nodes of large myelinated axons in the same population. Hence, other determinants of the persistent clinical differential blocks of axial blockade must be sought.

In subarachnoid anesthesia, the persistent differential losses comprise a failure of temperature discrimination and vasoconstrictor tone extending about two dermatomes higher than loss of pinprick sensibility,[3] which, in turn, extends one or more dermatomes higher than loss of touch sensibility;[13,15] the differential zones migrate upward during onset of and downward during recovery from blockade.[13,15] In epidural blockade, persistent differential loss of function is observed primarily with relatively weak solutions and takes the form of preservation of skeletal motor function throughout the area anesthetic to pain;[4] there is little differential dermatomal loss of temperature discrimination.[14] It may be noted again that most of these differentials involve myelinated axons. As to the sites at which the differential axial blocks develop and continue, there is no certainty. Experimentally, in dog, the drug penetrates the spinal cord,[23,24] but the differences in species size and thickness of tissues, the timing of the observations, and the severely limited dose/effect information hamper extrapolation to humans. In both intrathecal and extrathecal blockade, the weight of evidence and informed opinion clearly favors the spinal nerves,[25,26] that is, sites outside the spinal cord, as the seat of the differential blocks, and this assumption underlies the remainder of this discussion.

To restate the problem, the difficulty is to account for the temporal persistence and segmental distribution of the differential conduction blocks that accompany axial blockades. Recently accrued clues from unit studies with a few types of nerve and molecular species of anesthetic warrant cautious application to the puzzle, but require that due allowance be made for the modulation introduced by the anatomical compartmentation operative in axial blockade.

Recent *In Vitro* Observations on Units

As detailed below, the newly defined differential responses of units fall into four categories, according to: 1) the type of nerve fiber (myelinated or unmyelinated), 2) the molecular species of anesthetic, and 3) the stimulus repetition rate; in addition, 4) in the case of myelinated units, the basis for a differential response exists in the reciprocal relation recently demonstrated between the minimum effective concentration of the drug and the length of fiber (number of nodes, three or more) exposed to the concentration. Number of nodes, in general, scales inversely with internodal length, fiber diameter, and conduction velocity, and so can give the impression that there is a systematic difference in sensitivity to block between thick and thin fibers. The most relevant data from units is outlined below.

1. The ED_{50} of lidocaine, tested by block of conduction in rabbit vagus, was lower for afferent myelinated axons than for afferent unmyelinated axons;[20] Strichartz and Ritchie have suggested that inhibition of potassium channels in slower axons may be a source of such differential blockade.[27]

2. A similar qualitative difference was noted with etidocaine, but the reverse was observed with bupivacaine.[28] The predilection of bupivacaine for unmyelinated axons could contribute to its clinical effectiveness in blocking "slow" burning pain. As already mentioned, the sensitivity of individual myelinated axons to conduction block by local anesthetic does *not* seem to scale with the fiber conduction velocity/size of diameter.[21]

3. The lidocaine ED_{50} for preganglionic sympathetic

myelinated axons was significantly lower than that of vagus myelinated axons, and the incidence of use-dependent (phasic) block at 10 Hz stimulation significantly greater;[28] the possible bearing of this observation on differential block is discussed below, in the section on subarachnoid anesthesia.

4. A reciprocal relation between blocking concentration and length of nerve bathed in anesthetic was first uncovered serendipitously,[29] when it became apparent that the incidence of conduction block in individual mammalian myelinated fibers exposed to one of two near-ED_{50} concentrations of lidocaine increased not only with the concentration, as expected, but also with the length of nerve bathed by the anesthetic (table 2). The explanation offered was that, if successive nodes of Ranvier in a given fiber differ slightly in safety factor (*i.e.*, in "sensitivity" to the drug), increasing the length of axon exposed to a near ED_{50} concentration of the drug would correspondingly increase the chances of blocking three consecutive nodes and therewith blocking conduction in the axon. The reciprocal relation between critical concentration and critical bathed length was demonstrated systematically by Raymond *et al.*[30] working with individual frog axons, and discussed as an effect of decremental conduction;[31] this important idea implies that the block of conduction in an axon under the specified conditions is a direct function of the length of nerve exposed to the anesthetic, as already hinted in the section on decremental conduction in Raymond's and Gissen's review.[22] Regardless of the underlying mechanism, the available results support a simple practical formula given below. When the formula is applied to axial blockade, it leads to a novel hypothesis concerning the mechanism of differential block in subarachnoid anesthesia.

TABLE 2. Incidence of Conduction Block in Individual Myelinated Axons*

Bathed length (mm)	Number of Axons	Block Incidence (%)
Lidocaine 0.3 mM		
15	50	2
23	23	9
25	51	4
Lidocaine 0.6 mM		
5	23	39
15	22	50
23	21	76
25	47	91

* Adapted from reference 29.

Decremental Conduction

Decremental conduction is a phenomenon demonstrated in but not restricted to myelinated axons. It was classically studied in the A component of compound action potentials propagated along lengths of frog nerve.[32] The term refers to cumulative decrease in the currents excited in a series of successive nodes of Ranvier when some agency, such as a low concentration of local anesthetic, diminishes the factor of safety at those nodes (fig. 1). Because of the difficulty of accessing successive nodes in one and the same fiber, it has not been feasible to demonstrate the phenomenon in an individual myelinated axon other than by computerized simulation.[33] In the mathematical model, a decrement in the regenerative current at successive nodes was found to occur only after a certain decrease in safety factor, and the decrement thereafter increased with increasing concentration of anesthetic (*i.e.*, with decreasing safety factor); experimentally, in frog nerve, decremental conduction block was thought to extend over a length of at least 3 cm—the longest length available to the experimenters.[32] The maximum length of fiber, *i.e.*, maximum number of nodes, over which decremental conduction can occur in a mammalian myelinated axon has not been determined.

It is important to note that decremental conduction can stop propagation of an impulse even if none of the nodes in a nerve fiber has been rendered completely inexcitable. Accordingly, the decremental model of conduction block complements or substitutes for the three-consecutive-blocked nodes model proposed by Fink and Cairns.[21] The two models are not mutually exclusive. To assist in focussing ideas, their import may be tentatively summarized in a single statement,

$$S_R = 1/kF(cA \cdot N_A),$$

where overall residual security of conduction S_R (control value, 5–6) in the bathed length of axon is inversely related to a function F (explained below) of the product of cA, the minimum blocking concentration of local anesthetic, and N_A, the number of consecutive nodes (length of axon) bathed by the anesthetic (N_A must be at least 3). k is the potency constant of proportionality of the anesthetic species. Conduction block occurs when S_R falls below unity. The "bathed length" formula is helpful in forecasting the effects of gross neuroanatomy on differential block.

Role of Axial Compartmentation

Axial blockade deposits anesthetic around segmental nerves in one of two distinct compartments, respectively internal or external to the dural sac. In the internal, subarachnoid compartment, between the spinal cord and dural sac, the length of segmental nerve root fibers bathed by the anesthetic increases in successive segments throughout the cervical, thoracic, lumbar and sacral regions (fig. 2).[34] In the external, epidural compartment, extending from the dural sac and lateral end of the dural nerve cuffs to the emergence of the spinal nerves from the intervertebral foramen, the extradural length of fiber

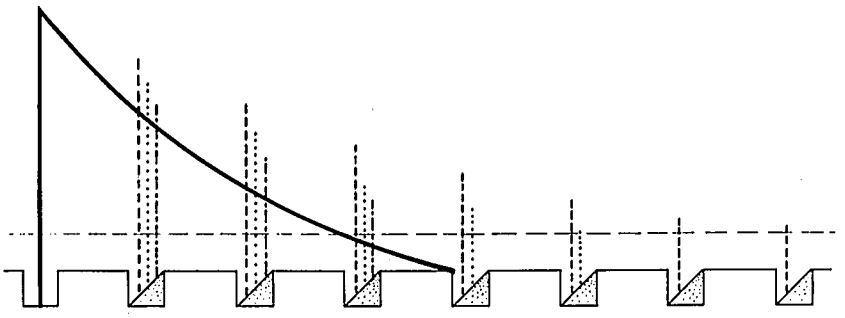

FIG. 1. Schematic diagram to illustrate the principle of decremental conduction block by local anesthetic in a myelinated axon. Based on a computer simulation by Condouris *et al.*[32] The first node of Ranvier at left contains no anesthetic and gives rise to a normal amplitude action potential (solid curve); if the nodes succeeding the first are occupied by a low concentration of anesthetic blocking up to 40% of the sodium conductance, the spikes along the partially anesthetized fiber are of constant but less than normal amplitude or, at slightly higher concentrations, progressively decrease in amplitude to a plateau (not shown). If the anesthetic concentration is high enough to block 74–84% of the sodium conductance (stippling), there is no plateau; the spikes continue to decrease in amplitude at successive nodes (interrupted bars, representing three different concentrations), so that the impulse eventually decays to below threshold amplitude if the series of anesthetic-containing nodes is long enough. Propagation of the impulse has then become blocked by decremental conduction, even though none of the nodes is completely inexcitable. Concentrations that block more than 84% of the sodium conductance at three successive nodes prevent any propagation at all.

bathed in the anesthetic is relatively uniform throughout the entire series of segments from the first thoracic to the second or third lumbar. The anesthesiological import of this anatomy is diagrammed in figure 3.

SUBARACHNOID ANESTHESIA

In figure 3A, schematizing subarachnoid conduction blockade, the density of stippling symbolizes the concentration gradient of anesthetic after injection into the cerebrospinal fluid (CSF). The interrupted line denotes the reciprocal of the security of conduction in the bathed portion of the fibers. Specifically, its height above the base line (in this figure, the spinal cord) indicates that the product of cA and N_A is high enough to block conduction in the represented long-internode and short-internode fibers, taking into account both the ambient CSF concentration of drug and the number of nodes in the bathed length of nerve root. Both of these factors decrease in the cephalad direction. The cephalad decrease in local anesthetic concentration has as pendant a corresponding increase in safety of conduction, and this increase occurs to the same degree in each of the functional populations of myelinated axons of a root or rootlet. The cephalad decrease in root length, however, increases the security of conduction in anesthetic-bathed long-internode fibers more than in short-internode fibers, because the short-internode fibers have more nodes available for consecutive three-node or decremental conduction block. As a result, conduction block in small-diameter, short-internode myelinated pain fibers, for example, and even shorter internode preganglionic sympathetic fibers, will be present at a higher segmental level than conduction block in large-diameter, long-internode fibers, such as touch or skeletal motor fibers. After the injection of the drug, these differential segmental levels are observed to initially migrate cephalad, then to stabilize, and finally to migrate caudad,[13] expressing the shifting balance between diffusion in the spinal CSF, uptake into nervous tissue, and absorption into the circulation. These elements are the major ones subsumed in F in the "bathed length" equation as applied to subarachnoid anesthesia. It may be noted parenthetically that the differential segmental block discussed according to internodal length will also be differential block according to myelinated fiber diameter, conduction velocity, or nodal length, since, as already mentioned, all of these tend to scale linearly with each other.[35,36] The number of nodes per centimeter of fiber increases about fivefold with increase in conduction velocity from 7 to 70 m/sec.[36]

In sum, in subarachnoid blockade, the subarachnoid concentration of anesthetic cephalad to the site of puncture increases craniocaudally and bathes increasing lengths of fiber—and increasing numbers of nodes per fiber—in successive segmental roots, also craniocaudally. In these circumstances, decremental conduction block produces a craniocaudal segmental sequence of loss of physiological function that reflects the increasing internodal lengths of their respective fibers; vasoconstriction, cutaneous temperature discrimination, pinprick pain sensibility, and skeletal motor activity are those best documented. The observed segmental or *spatial* differential sequence[3,13,15] reflects the known fact that these functions tend to be mediated by populations of myelinated fibers of different average conduction velocity,[37] and is essentially the same as the *temporal* differential sequence of loss seen at the onset of peripheral nerve blocks (table 1). Both reflect the same fundamental relation between perinodal anesthetic concentration, number of bathed nodes, and overall residual safety of conduction in bathed lengths of fiber.

The above analysis should further take into account the possibility of use-dependent ("phasic") block in the

various functional fiber groups. This is probably of greatest interest in the preganglionic sympathetic axons, which have a tonic vasoconstrictor function and are continually the seat of physiological repetitive firing activity. In subarachnoid anesthesia, the CSF includes a cephalad zone of low anesthetic concentration where the safety of conduction of the bathed fibers is decreased but still above the threshold for regenerative firing. In sympathetic preganglionic efferent fibers of this group, use-dependent block[38,39] can be elicited by the background repetitive physiological activity in the fibers and will tend to increase the number of dermatomes presenting signs of sympathetic blockade.

Epidural Anesthesia

Figure 3B schematizes how the "bathed length" formula explains the mechanism of differential block; in this case, by calling on the three-consecutive-node rule. The local anesthetic diffusion gradient is primarily situated in the epidural fat; the stippling in figure 3B symbolizes a relatively uniform concentration throughout most of the bathed area. Relatively steep diffusion gradients at the borders of the area restrict or prevent differential functional blocks between affected segments. The thoracic and upper lumbar segmental nerves, however, all traverse an anatomical region that favors the epidural blockade of pain and other small sensory fibers without paralyzing the skeletal motor fibers. In each of these segments, the portion of spinal nerve from the end of the dural nerve cuff to the exit of the nerve from the intervertebral foramen is no more than a few millimeters long.[40,41] When bathed by epidural solution, this distance is hardly enough to accommodate block of three consecutive nodes in Aβ skeletal motor fibers, but more than enough for three-node block of conduction in Aδ and C pain fibers. Epidural infiltration with an appropriate rate of flow and volume of a relatively weak concentration of local anesthetic tends to limit block to this portion of the spinal nerves because it is the portion most directly accessible to the epidural solution. The result will be differential block of pain, but not of skeletal motor activity, in the infiltrated segments. The compartmentation-based differential block limited to small axons will be nullified if additional nodes are blocked by diffusional spread of anesthetic through the dural root cuff or main dural sac[42] or direct spread of solution laterally through the intervertebral foramen.[43] The use of bupivacaine in epidural anesthesia for obstetrics empirically conforms to the differential desiderata,[44] and further sharpens the differential blockade of pain by taking advantage of the drug's low ED_{50} for block of unmyelinated axons.[28]

Some Other Applications of the Bathed Length Principle. Several observers of recovery from subarachnoid anesthesia have detected an unexpectedly early return of sympathetic vasoconstrictor function in the legs by skin conductance, well before the return of cutaneous sensibility and motor power.[45–47] The sequence was noted with surprise, because it contradicted the long-prevalent doctrine that small Aδ and B fibers are *more easily* blocked than Aβ fibers[16] and should recover late. The conclusion was drawn that, during subarachnoid anesthesia with bupivacaine or tetracaine, B fibers were more *difficult* to block than A fibers.[47] *In vitro*, however, as noted above, Aδ sympathetic preganglionic fibers (B fibers) tested in-

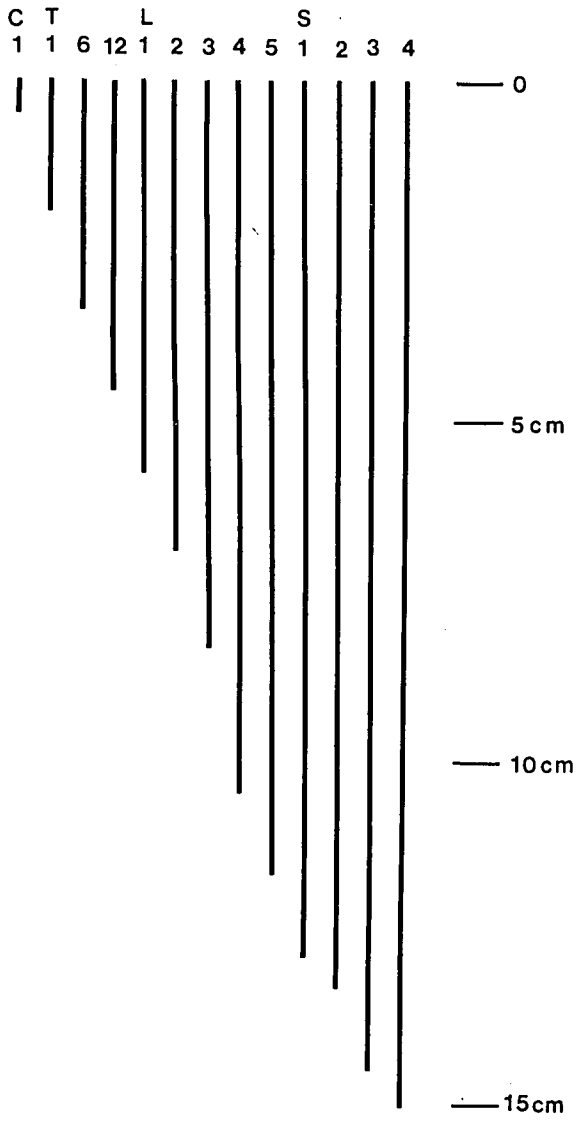

FIG. 2. Relative lengths of the intrathecal portions of spinal nerve roots C1, T1, T6, T12, L1–L5, and S1–S4. The lengths were measured on a photograph of a specimen of brain and spinal cord with attached spinal nerve roots and dorsal root ganglia, seen from the posterior aspect, figure 7.35B in reference 33. The length of S4 in the cadaver would have been approximately 15 cm.

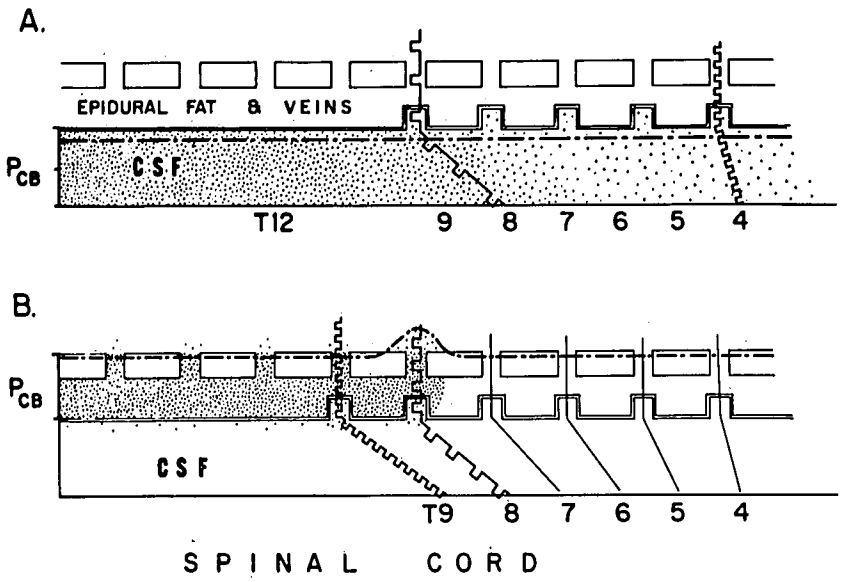

FIG. 3. Schematic diagrams of axial differential block mechanisms in the thoracic region. In *A* and *B*, the two crenated lines represent long and short internode myelinated fibers, respectively, and are intersected by a dashed line at the critical bathed lengths. *A*. Subarachnoid conduction blockade. The concentration gradient of anesthetic in the CSF is symbolized by the density of stippling. The security of conduction has decreased to the same degree in the short-internode fibers of segmental nerve T4 as in the long-internode fibers of segment T8, because the product of node number and anesthetic concentration is the same. Only the short-internode fibers will undergo decremental conduction block at T4. Both the long and the short internode fibers will be blocked at T8. *B*. Epidural conduction blockade. The epidural concentration of anesthetic is approximately the same throughout the affected portion of the epidural space except at the edges of the bathed area. For clarity, long and short internode fibers are represented in different segments, but may be discussed as if present in the same segment because the length of axon between the end of the dural cuff and the exit from the intervertebral foramen is approximately the same and measures only a few millimeters in all the thoracic segments; the number of nodes bathed in the intervertebral canal is not sufficient to establish conduction block in the long-internode fiber, but does suffice in the short-internode fiber. Spread of epidural anesthetic beyond the intervertebral foramina can abolish the differential block, as may diffusion in sufficient concentration through the dura into the CSF and nerve roots.

dividually seemed *easier* to block by bupivacaine than Aδ vagus fibers.[28] The apparent discrepancy is resolved by considering the bathed lengths of the relevant root fibers in the patient's body. Intradurally, roots T12–L2, which contain the lower part of the B fiber sympathetic outflow, are shorter than roots L3–S2, which contain the motor fibers to the muscles of the leg (fig. 2). Therefore, the former have fewer nodes bathed by anesthetic intradurally than the latter. If blood flow and drug absorption rates in all roots are similar, as suggested by recent immunohistological evidence indicating a similar degree of vascularity of all human spinal nerve roots,[48] then the bathed length principle predicts that, in the presence of a waning CSF concentration of drug, conduction block of vasomotor function in the short roots will cease sooner than block of pinprick and skeletal motor function in the long roots. Furthermore, regions innervated by sacral nerves, such as the perineum, should be the last to recover, because these nerve roots have the longest bathed lengths of all. Because the percent difference in length of successive roots intrathecally is less in the cauda equina region than more cranially, there is less opportunity in the caudal region for the development of *intersegmental* differential block based on differences in bathed length.

By similar reasoning, a neurotoxic lesion from an accidental overdose of subarachnoid anesthetic may take the form of a cauda equina syndrome, at least in part, because the cauda equina roots are the longest and have the most sites susceptible to damage. Finally, on a more cheerful note, peripheral nerve blocks take advantage of the bathed length principle by spreading the solution along the targeted nerves.

Historically, the idea that fiber size determines sensitivity to local anesthetic originated with Gasser and Erlanger.[1] At that time, it was believed that the site of action was in the axonal protoplasm, and the higher ratio of surface to volume in small diameter fibers was supposed to make these more "sensitive"—easier to enter and render inexcitable—than large ones.[1] In one form or another, the size principle has influenced studies of differential block ever since. Differential conduction block in a limited sense does depend on fiber size, since, in a short length of nerve, block is less likely in large than in small fibers.[8] But it may be misleading to think of this as size-dependent sensitivity, because, at equilibrium, *in a sufficient length of nerve,* the concentration required for tonic block seems to be approximately the same for all sizes in a given population. According to the new view presented here, difference in the number of nodes bathed by anesthetic is the major determinant of clinical differential block among myelinated axons.

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Appendix

Prediction and Bathed Length Hypothesis

"The true test of a useful hypothesis is its ability to predict results of future experiments."—*Anonymous peer reviewer.*

The hypothesis predicts that any agency that lowers the factor of safety of conduction at a series of consecutive nodes of Ranvier can act like cA in the formula, $S = 1/kF(cA \cdot N)$. Low ambient temperature is such an agency. It can be foreseen that, *in vitro*, in mammalian nerve bathed in a constant ambient cA, a 10° fall in temperature will decrease the critical exposed length by a factor equivalent to the Q_{10} of conduction velocity,[49] which is about 1.6. It can also be foreseen that, during regional cooling of a limb, differential losses of cutaneous sensibility will develop in the same temporal sequence as those caused by local anesthetic blockade, provided the peripheral receptors have the same relative "sensitivity to cold" as their afferent nerve fibers.

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