To the Editor.—I’d like to respond to the article by Fink and Cairns: Diffusional delay in local anesthetic block.¹

In the technique used in our two laboratories, Dr. Fink’s methods lead to an apparent increase in local anesthetic (LA) drug potency and a decrease in drug latency and thus makes it more difficult to distinguish differences between A & C fiber response that would make diffusion barriers apparent.

Dr. Fink used a carbonated-Liley perfusing solution. Carbonation increases the potency of LA drugs. He used a high concentration of lidocaine for a short period of drug exposure. Lidocaine is a poor choice of LA to demonstrate lipid diffusion barriers because at pH 7.4 it has a high proportion of uncharged molecules (the membrane permeant form). In addition, its lipid partition coefficient is high (approximately 24.0).

I find a basic misunderstanding of our report² by Fink and Cairns. We attempted to demonstrate that LA block of nerve occurs in two stages: first, the penetration of LA from outside the nerve to the neural excitable membrane, and, second, the efficacy of interaction between the LA drug and the neural membrane receptor in causing nerve block. Only the first is limited by diffusion barriers and it is indicated by rate of block. Use of high concentrations of LA result in equilibration of LA across the diffusion barriers (and thus minimize diffusion factors). The same effect is produced by using highly lipid-soluble LA drugs. Their remarks about time dispersion of the compound action potential following LA drug application apply just as forcefully to drug latency measurements. If enough latency measurements are made, time dispersion would also be evident. I question the validity of lumping all myelinated fibers in one group. The faster the conduction velocity, the larger the fiber and the deeper the diffusion barriers at the nodal membrane. I would like to see a plot of the fastest fibers (25–50 m/s) examined separately. Since the effects of diffusion barriers are apparent soon after drug application, plots of the first 15 min should be expanded.

Let me illustrate some of these points from work in our laboratory:

Our report² indicated the effect of drug concentration on differential blocking of A & C fibers. Bupivacaine HCl at high concentration showed no difference between rate of block of A & C fibers. At low concentration, A fiber response was slow compared with C fiber response. This is to be expected if A fiber nodal membrane diffusion barriers are more protective than those about C fiber. Also see Ritchie et al.³ who, using lidocaine (0.3 mM), showed that the time constant of rate of block of C fibers was more than twice as fast as that for A fibers.

Figure 1 reports studies by Wildsmith et al.⁴ in our laboratory comparing structure-activity relationships in ester chain LA. As lipid solubility decreases and pkₐ increases, the differential effect of LA on A & C fibers becomes more apparent. Note the effect of carbonation.

We believe that the findings reported by Fink and...
Cairns are well done and correct. Our objection is to the limited range of concentrations, the short exposure time, and the choice of lidocaine as the test LA drug. These limitations inevitably lead to a limited (and essentially incorrect) conclusion.

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In reply.—Dr. Gissen objects to our conclusion that differential diffusion within a nerve is an unlikely contributing factor to clinical differential block.1 We welcome the opportunity to clarify the points he raises.

We evaluated differential diffusion by comparing the times required for 95% maximal slowing of conduction in individual axons, when a vagus nerve was exposed to a nonblocking concentration of lidocaine. Dr. Gissen feels that the $pK_a$ and concentration of lidocaine, and the bicarbonate/carbonic acid buffer system used in our study accelerated diffusion to the point of effacing an important differential barrier at the node of Ranvier.

Now the regions the anesthetic molecules had to traverse on their way to the barrier included (in sheathed vagus nerves) about six layers of lipoprotein membrane in the perineurial sheath, followed by the convoluted aqueous endoneurial pathway to the Schwann cell. Beyond the nodal barrier lay the lipoprotein-excitabile membrane itself.

In some of the experiments, we tested the importance of the lipid diffusion barriers by removing the perineurial sheath. This seemed to shorten the 95% equilibration time by about 4 min. Thus, the residual lipid diffusion barrier, consisting of one layer of excitabile membrane, was unlikely to have constituted the major delay in the remaining 13 min required for 95% diffusional equilibrium. The major delay therefore presumably occurred in diffusion through the aqueous endoneurium and between the Schwann cell and excitabile membrane, including the purported barrier in the nodal gap. However, our data showed that the diffusional delay was essentially the same for myelinated and unmyelinated axons and independent of the conduction velocity (or size) of the myelinated fibers. Evidently the substance in the gap at the node of Ranvier had only a quite minor role in delaying the access of local anesthetic molecules, charged or uncharged, to the binding site in the sodium channels. By the same token, the $pK_a$ of lidocaine was probably a relatively unimportant factor.

Was the concentration of lidocaine excessive? The highest concentration of lidocaine used in our experiments was 0.016 g/dl (0.6 mM), a concentration too low to block conduction and deliberately chosen to be so, since our criterion was the time required to approach equilibrium slowing of conduction. The concentration in question was less than one-sixtieth of the 1% concentration commonly used in our clinic.

Dr. Gissen’s request for information on individual fibers conducting in the velocity range 25–50 m/s cannot be met from our study on the vagus because the highest velocity observed there was 29.5 m/s. However, we have recently submitted for publication data from individual axons in the rabbit recurrent laryngeal nerve, conducting at 32–57 m/s. The responses of these fibers did not differ materially from those of the slower myelinated axons observed in the vagus.

As to the effect of our buffer system, we believe Dr. Gissen errs in equating it with that of carbonation. Carbonation involves a $P_{\text{CO}_2}$ approaching one atmosphere,2 or nearly twenty times that of our solutions, where the $P_{\text{CO}_2}$ was strictly physiologic throughout. Dr. Gissen’s text figure indicates experimental conditions that were very different indeed from ours and did not include lidocaine, but they did include procaine, and, in that case, it is interesting to note the concentration was 0.6 mM, exactly that of the strongest lidocaine in our study.

It happens that all the workers cited by Dr. Gissen in support of his position studied compound action potentials; the potentials were obtained at temperatures 10 or more Celsius degrees below mammalian body temperature. Our data were from one axon at a time, at 37° C. Besides the question of temperature, there is the problem of interpreting changes in the amplitude of compound action potentials. Decreases in amplitude may indicate block of some fibers or they may indicate differential slowing of conduction, on occasion without block of any fibers at all. This ambiguity was not present in our study. Thus, we feel that until tested further our conclusion may be regarded provisionally as correct.