min range. Mehta et al.\textsuperscript{5} arbitrarily decided to study a 3-min time interval. Clearly, a shorter time interval would be helpful, especially in the urgent clinical situation. Obviously, the precise time interval requires further definition.

Lastly, what is the appropriate intubating dose of vecuronium or atracurium? Schwartz et al.\textsuperscript{2} used only the 0.05 mg/kg and the 0.06 mg/kg intubating dose of vecuronium. Would a larger dose be associated with a shorter onset time? If so, this certainly may be advantageous, despite a possibly longer duration of action. Mehta et al.\textsuperscript{3} utilized a 0.4 mg/kg intubating dose of atracurium. Only 13 of 30 patients had excellent intubating conditions, which suggests that perhaps a larger intubating dose would be more advantageous.

Many of the conclusions of both studies were based on data from anesthetized patients. Although Schwartz et al.\textsuperscript{2} were able to intubate the trachea in 80 s in patients in whom the priming dose was given in the awake state, whether a better priming and intubating dose and time interval between these doses exists remains to be seen. One problem with the Mehta et al.\textsuperscript{3} study is that there was no control group (patients who receive the intubating dose of neuromuscular blocking drugs without the priming dose). In addition, patients in the Mehta et al.\textsuperscript{3} study did not receive the same neuromuscular blocking drug for both the priming and intubating doses.

Despite all the questions listed above, the priming principle clearly appears to shorten the onset time that certainly will help offset one of the few disadvantages of vecuronium and atracurium. Schwartz et al.\textsuperscript{2} and Mehta et al.\textsuperscript{3} are to be congratulated for their extensive studies, which totaled over 200 patients. However, despite the large number of patients studied, the priming dose, the intubating dose, and the time interval between these two doses need better definition. Although the answered questions associated with the priming principle lend themselves to many limited studies, examining only one aspect of this issue, this Editor hopes that investigators will select a more difficult path of performing large and comprehensive studies from which the clinician can better determine the best way to shorten the onset time of vecuronium and atracurium without adverse effect.

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Clinical Implications of the Modulated Receptor Hypothesis:
Local Anesthetics and the Heart

The relative cardiotoxicity of some local anesthetics has been discussed widely at anesthesia meetings and in anesthesia journals in recent years, at first on the basis of case reports\textsuperscript{1} and then on results drawn from animal experimentation.\textsuperscript{2} Before the question was raised as a clinical problem, however, a possible mechanism for selective toxicity of some agents already had been outlined in the basic physiology literature. According to the modulated receptor hypothesis, local anesthetic conduction block is modulated by the conformational state of the sodium channel. The concept of state-dependent channel block in nerves first was presented in a pair of landmark papers in the Journal of General Physiology in 1977\textsuperscript{3,4}; a version of the concept applied to cardiac muscle was introduced almost simultaneously.\textsuperscript{5} State-dependent channel block, when added to restricted access of some local anesthetics to the receptor in the channel, underlies the phenomenon of frequency-dependent (or use-dependent) local anesthetic conduction block. The paper by Clarkson and Hondegem in this

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issue documents the quantitative differences between lidocaine and bupivacaine in their properties of state-dependent channel block and its kinetics. A convincing case is made that the differences are fundamental to the relative cardiotoxicity of bupivacaine when compared with lidocaine.

The ideas basic to frequency-dependent local anesthetic block should be familiar to anesthesiologists. Sodium channels pass through a number of states as they generate the upstroke and a component of the falling phase of the action potential. Of these, the closed or resting state appears to display the least affinity for local anesthetics and similar drugs. The open state and the inactive state, to which channels pass during depolarization, bind local anesthetics more tightly. Thus, given sufficient time, channels recover from block between action potentials and develop additional block each time channels open and inactivate during an action potential. The extent and time course of frequency-dependent conduction block is a function not only of the relative affinity of the various channel states for a particular drug, but also of the ease of access of the drug to the receptor in the channel. The latter determines the apparent rapidity with which various agents bind to and unbind from the receptor. Solubility in the membrane lipid is one property that governs ease of access, because local anesthetics bind to a site within the sodium channel, which can be reached by lipid-insoluble forms only from the axoplasmic surface. As drug-receptor affinity changes with channel state, therefore, hydrophilic charged forms of local anesthetic bind to and unbind from the receptor slowly relative to the channel transitions and thus exhibit pronounced frequency-dependent channel block. Lipid-soluble hydrophobic forms can access the receptor quickly through the membrane lipid, and thus may produce channel block that is either not frequency dependent or requires relatively high rates of channel activation to be revealed as frequency dependent. Under the original form of the theory, extent and rate of frequency dependence were predicted to be correlated with lipid solubility alone; it was an anomaly therefore that the very lipid-soluble long-acting agents such as bupivacaine were found to produce marked frequency dependence at low rates of channel activation. Agents such as bupivacaine and etidocaine, of high potency and long duration of action, achieve the high lipid solubility which confers these properties by the addition of long carbon chains or other lipid-soluble groups to the basic amine or ester prototype anesthetic molecule. This increases molecular size; large molecules also are impeded from rapid binding and unbinding at the receptor site.

The clinical implications of these molecular correlations are that small molecules such as lidocaine, with relatively low pKs and modest lipid solubility, bind to and unbind from cardiac sodium channels swiftly as the channel changes state. The enhanced block due to frequency dependence is therefore not great at the normal cardiac rhythm. Frequency dependence may account, however, for the antiarrhythmic potency of “fast” agents such as lidocaine. A large molecule like bupivacaine, however, dissociates from the channel receptor site slowly. The frequency-dependent component of block for such an agent is large at normal cardiac rates. When combined with a concentration-dependent rapidity of binding, as shown by Clarkson and Hondeghem, the result is a drug that is apparently much more potent in depressing cardiac conduction than predicted on the basis of lipid solubility alone. Once the drug has bound to the channel, it tends to stay there. Factors that come into play during prolonged attempts at resuscitation enhance further the tightness of coupling to the receptor: cardiac cell depolarization, which increases the proportion of channels in the inactive state, to which this agent binds most avidly; and acidosis, which increases the concentration of the charged moiety and further slows the rate of unbinding. As the authors point out, tachycardias also will enhance the apparent potency of this agent.

The relative cardiotoxicity of bupivacaine and the antiarrhythmic properties of lidocaine are only two of the clinically interesting drug properties that may derive from the relative rate and extent of frequency-dependent sodium channel block. First, anticonvulsants such as phenytoin and barbiturates also display frequency dependence. The resultant selective block of rapidly firing nerve cells may be related to their anticonvulsant properties, although the relationship is unproved. Secondly, selective block of certain nerve fiber types by local anesthetics may relate as much to the nerves’ characteristic frequencies of activity as to their anatomic properties. Finally, the widespread existence of channel state-dependent binding among a number of different clinical drug classes should be noted. Although studies specifically investigating interactions are not yet available, it is a priori not reasonable to treat cardiac toxicity due to one frequency-dependent sodium channel blocking agent with another drug, such as an antiarrhythmic agent, having similar properties. The latter may only add to depression produced by the former.

The combination of a very greatly enhanced affinity for inactive sodium channels and a very slow dissociation rate from the resting channel almost certainly accounts in large part for the clinical observations of cardiotoxicity of bupivacaine in comparison with lidocaine. It would be incorrect, however, to single out bupivacaine as unique. This local anesthetic agent differs quantitatively, not qualitatively, from other local anesthetics and illus-
tracts the properties of channel state-modulated binding and frequency dependence common to all those in clinical use. The explication of its quantitative differences from lidocaine in the paper by Clarkson and Hondeghem also illustrates an important case in which the theoretic framework derived from basic research preceded the recognition of the resultant clinical problem.

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Post-Cardiac Arrest Therapy: Calcium Entry Blockade and Brain Resuscitation

IN THIS ISSUE, Steen et al. report improved neurologic function and a reduction in brain histopathology in monkeys treated with nimodipine following 17 min of selective cerebral circulatory arrest.1 Their study gives further support to the hypothesis that pathologic events occurring after resuscitation from a cardiac arrest can increase neurologic damage and that therapy directed toward these events may ameliorate brain damage.2-5 While this study is of considerable practical and theoretic importance, the authors' suggestion that immediate controlled clinical trials be instituted requires further consideration, especially in view of the scientific controversy that encompassed the efficacy of barbiturate therapy after circulatory arrest.6,7 In that situation, clinical trials began before the initially promising results with barbiturates could be tested in other laboratories. This resulted in a negative clinical trial, which actually could have been predicted by further laboratory studies that found no role for barbiturates.7-9

Within the context of the neck tourniquet model for selective cerebral circulatory arrest in the primate, Steen et al. have shown with statistical validity that nimodipine ameliorates brain damage.1 In fact, this study represents a tour de force in bringing together an international team of neuroresuscitative scientists with extensive experience with the model and its enormous intensive care requirements. Additionally, the study was not based upon a shot in the dark, but rather upon the knowledge that postcirculatory arrest brain damage is associated with delayed hypoperfusion, which could be corrected partially by calcium entry blocking drugs.2,3 Based upon their neuropathologic findings of symmetric cortical lesions in arterial border zones, Steen et al. emphasize the importance of calcium penetration into vascular smooth muscle as a possible cause of vasospasm leading to hypoperfusion.1 Some of the brain stem lesions described by Steen et al. fall outside of arterial border zones and may be caused by factors not related to recirculation deficits.10 Since these brain stem lesions apparently respond to nimodipine therapy other mechanisms, explaining its benefits in postischemic brain also may be involved.

Pathologic Calcium Cascades

As noted by Steen et al., an increase in intracellular calcium ion concentration may be a triggering stimulus for a variety of pathologic reactions.1 The central role of calcium as the putative initiator of events leading to