Botulin toxin type A (BoNT-A) has been demonstrated as an effective prophylactic treatment of primary headache disorders.\(^1\) The results of the experimental studies of Durham et al suggested that the efficacy of BoNT-A in the management of migraine is due, in part, to its capacity in blocking the release of calcitonin gene-related peptide (CGRP) from the trigeminal neurons.\(^2\)

In his commentary, Blumenfeld pointed out that other studies showed that BoNT-A inhibits the release of substance P and glutamate neurotransmitters responsible for nociception.\(^3\) Therefore the nociceptive effect of BoNT-A may, in part, be explained by an inhibitory mechanism of neurotransmitters of nociceptive neurotransmission from the periphery to the cortex.

In our previous articles we had referred the hypothesis that therapeutic blockade of greater occipital and supraorbital nerves “might have resulted in an inhibition of the constant trigeminal hyperexcitability present in headaches by not only locking the conduction of the noxious stimuli but also by blocking the antidromic flow of substance P and CGRP, mediators of axon reflexes that are the basis for perivascular neurogenic inflammation. The consequent vasodilatation and the extravasation of the above peptides, local reinforcing factors of the algogenic stimulation might have been interrupted by the anesthetic with subsequent normalization of the response threshold to the stimuli of the nociceptors.”\(^4\) The action of inhibition of axonal transport of local anesthetic had long been shown.\(^5,6\) Repeated anesthetic blocks could produce a long-lasting effect of hypostimulation on the peripheral nociceptors, thus rebalancing their threshold of activation and consequential arrest of induction of neuroplastic mechanism of central hypersensitization that may clinically produce chronicity of pain.

This course of multiple anesthetic blockade of nerves, even if it is purely without any influence of the “primum movens,” would interfere in the central pathogenetic mechanism of the formation and transmission of the trigeminal nociceptive stimulus of a migraine crisis.\(^7\) The observations published by Durham et al are of great interest and very stimulating, and can be applied similarly to local anesthetics.

It can also partly confirm the eventual common pharmaco-dynamic mechanism of the two substances like BoNT-A and local anesthetic and explain the clinically demonstrated efficacy of their use in migraine. I would like to ask Dr. Durham if his elegant experiment could be applied to local anesthetics. The valid experiments supported by encouraging clinical observations can open new and interesting clinical horizons in the treatment and prophylaxis of migraine also in its chronic form.

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Does Single-File Botox Injection Really Work for Primary Headache?

In their study of the efficacy of single-site injection of botulinum toxin type A (BoNT-A) for the therapeutic management of migraine trigger points, Behmand and colleagues\(^1\) report that injecting each of the corrugator supercilii muscles bilaterally with 25 units (for a total dose of 50 units) produced significant benefit. We have several comments on this interesting article.

First, this is a high dose of BoNT-A relative to the small size of the corrugator muscle. In contrast, other studies have used total doses ranging from 25 to 300 units\(^2\) distributed over 11 to 25 injection sites, with 1.5 to 18 units injected into 2 to 4 sites in the medial and lateral corrugator muscles.\(^3\) The delivery of small doses at multiple sites can reduce the occurrence of side effects while controlling pain effectively.\(^6\)\(^7\) It is likely that with a high dose concentrated in one muscle, diffusion of the toxin could increase the risk of adverse events such as ptosis. Behmand et al noted that the frequency of ptosis was 7% in their study, which is higher than the rates observed by Binder et al\(^8\) (2/104 = 1.9%) and Blumenfeld\(^3\) (6/257 = 2.3%), although lower than the rate noted by Silberstein et al\(^4\) (6/42 = 14.3% in the group treated with a total of 25 units of BoNT-A and 7/40 = 17.5% in the 75-unit BoNT-A group).

Second, we wonder whether the injection procedure described by Behmand et al truly reflects a highly localized single-site injection. Given the likely diffusion of that dose of BoNT-A injected into the corrugator muscle and the spread of toxin throughout the belly of the muscle, it is possible that effects of the toxin extended bilaterally in the frontalis, corrugators, and procerus muscles.

Third, patient selection may have contributed to the observed treatment outcomes. Only one patient in this series met the headache frequency criterion for chronic migraine of at least 15 headaches per month, according to the revised International Classification of Headache Disorders.\(^9\) Of the five patients who showed no change or an increase in headache frequency, baseline headache frequency was four headaches per month for one patient and four to eight headaches per month in the other four patients. Patients with less frequent headaches may be less likely to respond to partial trigeminal treatment compared with those with more frequent headaches. This idea is consistent with the suggestion of Silberstein et al, that reduced clinical efficacy in one of the two BoNT-A treatment groups in their study might have resulted from a lower baseline migraine frequency.\(^4\)

Finally, the somewhat shorter duration of efficacy of BoNT-A injections observed by Behmand et al (range 6 to 12 weeks; mean of 8 weeks) compared with other studies suggests that underdosing by injection into only one muscle may have produced suboptimal treatment outcomes. The fact that corrugator hypertrophy was equal in responders and nonresponders argues against a muscle-relaxing effect as the principal mechanism by which BoNT-A affects the symptoms of headache.

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**Opioid Tolerance or Rather Opioid-induced Pain Sensitivity**

Recently, Von Seggeren and colleagues emphasized a common clinical management problem with opioid use and a pitfall of urinary drug screen monitoring for OxyContin. Pressure on physicians to administer opioids has increased considerably and as a result the administration of sustained opioid treatment for patients with pain of nonmalignant origin has increased as well. Saper et al have presented data on a 3 to 5 year observational study in patients administered opioids daily for intractable headache. The study suggests that at least 75% of patients do not do well and that up to 50%, despite careful supervision, misuse their medications.

As physicians in the headache community struggle to better determine best care principles for patients with intractable headache, we would like to remind readers of another important but under-recognized dimension of opioid therapy.

Jainren Mao’s work and literature review illustrate the compelling evidence that chronic use of opioids may, in some opioid-treated patients, enhance pain, a direct result of receptor changes induced by the opioids. This phenomenon, variably termed opioid-enhanced hyperalgesia or opioid-induced pain sensitivity, occurs during sustained opioid therapy. This paradoxical increase in pain appears related to opioid-induced molecular receptor alteration. While tolerance is a desensitizing process, Mao argues that opioid-induced pain sensitivity (OIPS) is a sensitization phenomenon. A physician unaware of this possibility will likely assume that increasing pain during opioid administration is the result of pharmacological tolerance. Because tolerance, as distinct from OIPS, is a well-recognized and accepted consequence of opioid treatment, opioid dose escalation is generally the first response by physicians to patients’ complaints of increasing pain. OIPS must be considered in this setting.

The actual mechanism for OIPS remains unclear. Based upon the data accumulated thus far, Mao suggests that both opioid-induced desensitization (pharmacological tolerance) and opioid-induced hyperalgesia (OIPS) share common glutamatergic cellular activation. Moreover, opioid administration may induce a pronociceptive process through effects via excitatory neuropeptides. Prolonged use of opioid-like substances may promote NMDA receptor-mediated neurotoxicity in the form of apoptotic cell death.

Although certain clinical details may help distinguish the two opioid-induced phenomena, the clinician is confronted by the fact that both result in increasing pain despite opioid administration. Mao emphasizes that tolerance is generally characterized by a return to baseline pain as desensitization occurs. On the other hand, opioid-induced pain sensitivity results in a progressive worsening of pain from the baseline (hyperalgesia). Also, opioid-induced pain appears to involve neural circuits and extensive cellular and molecular changes that, according to Mao, may result in a wider, more diffuse pain field than the original pain pattern. Quantitative sensory testing (QST) might assist in identifying increasing pain sensitivity.

In light of the observations of Mao and others on the possible receptor changes with long-term opioid usage, together with the data by Saper et al, the clinician must pay particular attention not only to the choice of patients to whom to administer opioids but also to the intensity and effectiveness of monitoring...
and clinical surveillance that is required when that choice is made.

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Treatent of Primary Headache in the Emergency Department

The practice of emergency medicine does occur in a relatively uncontrolled environment filled with frequent interruptions and distracting demands. Consequently, identifying potential life-threatening headache etiologies takes priority over the process of IHS headache categorization. Furthermore, since the spectrum of primary headaches share a common pathophysiology and often respond to similar therapeutic interventions, precise headache classification is sometimes less clinically relevant in the emergency department context.

As suggested by Blumenthal et al, sumatriptan and dihydroergotamine (DHE) are not frequently used for treatment of benign headache in the emergency department setting. However, sumatriptan and DHE are not new drugs to the clinical practice of emergency medicine. It is safe to say that the majority of emergency physicians have clinical experience with these drugs. Therefore, we should ask what selective clinical pressures have driven emergency medicine physicians away from the use of subcutaneous sumatriptan and dihydroergotamine (DHE). If asked, emergency physicians will express concern over adverse effects, cost, and perceived drug effectiveness in the emergency department setting. Many of the patients seeking headache pain relief in the emergency department have been ill for 3 to 5 days or longer. These patients have well established central sensitization and cutaneous allodynia. Consequently, they are less likely to respond to triptan therapy and probably DHE and may be predisposed to headache recurrences within 24 hours. A multicenter study involving 12 emergency departments by Akpunonu et al studied subcutaneous sumatriptan against placebo in the treatment of migraine headaches. The response to sumatriptan was excellent with 75% of patients experiencing meaningful relief. However, in this drug company-sponsored study the reported rate of headache recurrence was high with 67% of the patients experiencing a recurrence within 24 hours. Reported adverse effects were also high and 52% of the sumatriptan group reported experiencing dizziness, vertigo, paresthesias, or chest symptoms such as tightness or heaviness.

Finally, we believe that the lower cervical paraspinal intramuscular injection with bupivacaine
described in the same issue of *Headache* has a potential role in the treatment of headaches as well as regional head and face pain in the emergency department.\(^\text{11}\) The Medical College of Georgia emergency department treats over 75,000 patients per year. Each day approximately 10 of these patients present with a headache complaint. During the past 18 months, the headaches of hundreds of MCG patients have been successfully treated with the lower cervical paraspinous technique. Severe migraine headaches along with the associated nausea, vomiting, photophobia, and phonophobia are resolved in less than 5 to 6 minutes following the bilateral intramuscular injections with 1.5 ml of 0.5% bupivacaine for the large majority of patients. Our clinical experience suggests that the lower cervical intramuscular bupivacaine injection may provide another effective headache therapy for the emergency department setting. We hope to confirm these initial impressions with several ongoing experimental investigations.

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**Sympathetic Nervous System Dysfunction in Migraine: Pearls and Pitfalls in the Theorizing Process**

Peroutka proposes that sympathetic nervous system (SNS) dysfunction in migraine relates pathogenetically to an imbalance of sympathetic cotransmitters.\(^\text{1}\) While reduction in sympathetic function in migraineurs is not as consistent or pervasive as one might hope or expect, given the physiologically adaptive role of the SNS in the “flight” or “fight” reactions, theories that implicate the autonomic nervous system in the pathogenesis of migraine work against basic teleologic fundamentals.

The suggestion that migraineurs have significantly lower supine plasma norepinephrine (NE) levels than nonmigraineurs\(^\text{1}\) does not consider the study of Hsu et al, in which plasma total catecholamines and specifically plasma NE were significantly higher in the 3 hours before the subjects awoke with migraine.\(^\text{2}\) The prodrome of migraine is, therefore, clearly associated with catecholamine excess and peripheral sympathoadrenal activation. More importantly, β-blockers do not generally restore or elevate plasma NE levels but characteristically augment peripheral...
adrenergic hypersensitivity (Raynaud’s phenomenon). In inducing SNS hypofunction, β-blockers, thus, replicate precisely the same changes as have been noted in the peripheral SNS in headache-free migraine patients. Propranolol and other β-blockers useful in migraine prophylaxis do not correct the putative SNS disturbance that is regarded by many investigators as a primary and pathogenetic characteristic of migraine. Third, amitriptyline and monoamine oxidase (MAO) A inhibitors can raise circulating and brainstem monoamines that in turn enhance the endogenous pain control system. Fourth, β-blockers generally do not aggravate the orthostatic/relative hypotension seen in migraine patients despite their systemic hypotensive effect. Finally, the physiological role of arousal-related heightened central sympathetic tone in the apparent miosis (iris adrenergic “impairment”) as well as the baseline “Horner syndrome” has not been appreciated. If first-line migraine prophylactic agents have variable influences on the peripheral SNS (propranolol versus amitriptyline) or replicate the same SNS “defect” as is seen between headaches or improve migraine despite a hypotensive effect (β-blockers), it is quite unlikely that such SNS “dysfunction” is etiologically significant.

In effect, Peroutka’s view—revives the vascular theory of migraine, the limitations of which, particularly for the aura, are well known. For evolving the pathophysiology of migraine, it is far more important to discuss mechanistic hypotheses in the framework of prophylactic agents rather than abortive agents, as the latter affect terminal events. Any discussion of involvement of SNS in migraine is incomplete without discussion of possible influence(s) of β-blockers and antidepressants. While atenolol, another first-line prophylactic agent, does not cross the blood-brain barrier and cannot significantly influence brain neuronal function, propranolol-induced brain β-blockade is unlikely to enhance the noradrenergic central inhibitory influence of the locus coeruleus upon the trigeminovascular system. In addition, the locus coeruleus (as also the raphe nuclei) does not directly innervate meningeal tissues, thereby considerably attenuating anatomically its vasospastic role in migraine headache. To sustain Peroutka’s view—as also other mechanistic theories of migraine that involve SNS—the conceptual challenge of the basic sciences must be met.

Stress, the most commonly cited cause of migraine, is a word that generally carries little or no utility, serving mainly as a euphemism for ignorance—a confusing pseudo-explanation confounding rational thought. In migraine pathophysiology, the term “stress” is similarly used to relegate the significance of both poststress aura and headache as well as the typical lateralization (unilateral, bilateral, or side-shift) of headache.

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REFERENCES

Revised Estimates for Probability of Successful Outcome of Pregnancy After Sumatriptan Exposure

A previous article gathered together from four primary studies (n = 327) prospectively observed
pregnancy outcomes after sumatriptan exposure. No evidence for an overall increase in fetal abnormalities was found, and using the norms of an 80% power and a 5% type I error, the sample size was used to calculate what could have been the maximum undetected increment of fetal abnormality associated with drug exposure.\textsuperscript{1} As it turned out, while that report was in press, a further study on the same subject appeared in \textit{Headache}.\textsuperscript{2} This further study found a possible signal for preterm delivery, but, again, no evidence for an increment in fetal abnormality after sumatriptan exposure.

Estimates of spontaneous rates of abnormality can vary according to teratological technique, duration of neonatal follow-up, and international differences in the definition of what is actually “abnormal.” Therefore, the following Table updates the previous estimates, using the new cumulative sample size, and for a range of spontaneous abnormality between 3% and 7% of neonates (which should encompass most local norms).

It should be emphasized that this method delimits overall probability of successful pregnancy outcome. These methods are, of course, inapplicable to particular types of abnormality, which usually arise spontaneously in far fewer than 3% of neonates. Study of particular types of abnormality requires prospective, precise hypothesis-making, in order to avoid random false positives among numerous, repeated statistical tests.

### Revised Estimates of Probability of Successful Pregnancy Outcome After Sumatriptan Exposure (80% Power and 5% Type I Error; Estimates Rounded to Nearest 0.5%)

<table>
<thead>
<tr>
<th>Assumed Spontaneous Rate of Abnormality (%)</th>
<th>Previous (n = 327)</th>
<th>Current (n = 985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&gt;91.5</td>
<td>&gt;95.5</td>
</tr>
<tr>
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<td>&gt;93.0</td>
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<td>&gt;92.0</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>&gt;88.0</td>
<td>&gt;89.5</td>
</tr>
</tbody>
</table>

**Comment.**—I thank Prof. Bengt Källén of the Tornblad Institute, University of Lund, Sweden for a helpful discussion, while, of course, not intending that he should accept any responsibility for this letter.

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