The following was solicited by the Editor and is included as an additional response to Riopelle’s provocative letter.

In Reply.—Riopelle raises ethical concerns regarding the recent paper by Katz and colleagues describing studies in which autotomy was induced in rats having sciatic nerve section.

Dysesthetic pain states often occur over a period of time after nerve injury. These are important syndromes that represent a significant proportion of clinical cases seen in pain services. Classified by a variety of descriptive adjectives, such as painful phantom, sympathetic dystrophies, or causalgias, these states are particularly insidious because they may display only the most innocuous of superficial signs and may show a typically lengthy temporal progression. Development of successful therapies has been difficult for several reasons: 1) different nerve injuries may yield different pain states; 2) different therapies may have different efficacies in mechanistically heterogeneous populations; and 3) rational development of therapy requires some understanding of mechanism, a situation that until recently did not exist. Development of such mechanistic insight requires the ability to study systematically the changes in anatomy, biochemistry, and function that occur over time after the creation of the appropriate lesion.

The need to provide the appropriately controlled experiments requires development of relevant animal models. In the case of pain secondary to nerve injury, several animal models have been reported with apparent face validity, i.e., they involve systematic creation of a partial or complete nerve injury. The early systematic use of such models led to the fundamental observations that the injured nerve developed spontaneous activity in specific populations of nerve fibers, and these changes were accompanied by distinct changes in the central terminals of the primary afferents. More recently, in these animal models, it has been shown that such peripheral nerve injury leads to prominent transynaptic changes in morphology, transmitter synthesis, and function of the dorsal horn. However, what gives unique significance to these changes in substrate is that these lesions result in well-defined changes in the behavior of the animal.

Early systematic work (see for example refs. 8 and 9) with such interventions led to the observations that animals with peripheral nerve lesion will display a time-dependent increase in the incidence of autotomy of the toes, digits, and in the extreme case, portions of the paw of the denervated limb. Though controversial, the appearance of autotomy in nonverbal species has been interpreted on the basis of several independent lines of evidence as reflecting discomfort referred by the animal to the now anesthetic peripheral dermatomes of the sectioned nerve (for extensive reviews, see refs. 10 and 11). These models are thus believed to represent the corollary to comparable pain states observed in humans. Accordingly, it may be hypothesized that the changes in substrate described above in these animal models may reflect the time-dependent changes in structure and function relevant to a dysesthetic pain state. These studies have led to what appear to be novel insights. There is now, for example, a growing appreciation that agents such as NMDA receptor antagonists may influence the appearance of these nerve injury syndromes. The observation that increased neuronal activity might itself lead to transynaptic changes led to the consideration that adequate blockade of the afferent drive can ameliorate the postlesion syndrome (see citations in ref. 1). The converse of that scenario is the appreciation that increased neuronal activity prior to the lesion leads to an exacerbation of the behavioral consequence of such lesions. The study by Katz and colleagues even indicates that the triggering events occur in the presence of a surgical plane of barbiturate anesthesia. Surely, such behavioral observations in this rodent model must suggest important clinical insight that merit systematic trials in humans.

Though not meant to be an exhaustive overview, it is clear from these limited comments that these animal models provide a method to approach systematically the challenge posed by patients suffering from these disheartening afflictions.

What poses a dilemma and seems to be the thesis of Riopelle’s concern is the question of whether these studies are appropriate, because the lesion presents the animal with a condition from which it cannot escape. Such investigations into “nonacute” pain conditions represent a paradigm that differs fundamentally from that which many in this area have encountered. Acute pain states may be readily studied in humans and animal models. In these models, the animal is exposed to a high-threshold stimulus from which it can escape unimpeached. In the model used by Katz and colleagues and in other models of nerve injury, the development of the pain syndrome, as in humans, occurs over a protracted period of time. The affliction arguably reflects the developing plasticity of the nervous system, leading to reorganization of the mechanisms whereby afferent information arising in the peripheral nerve and spinal cord assumes a noxious component.

Given the above conditions, one readily understands Riopelle’s concern. The insights into the human condition derive from investigations in which the apparent syndrome occurs only, as in humans, as a function of time. It is an issue that does not differ from those faced in many situations, such as the study of the therapy of tumors or infectious diseases: the animal is faced with a condition from which it cannot escape, but to which it must be exposed to generate the state seen in the human condition. Riopelle’s plea that “limits should be placed on how much suffering we inflict” is important. Responsibility for placing such limits and overseeing their implementation reflects a multifaceted responsibility: the investigator, the institutional animal subjects committee that presided over protocol approval, and ultimately, the editors and the referees serve as a final arbiter of the propriety of the work.
that will appear in this journal. Examination of the Materials and Methods section of the paper by Katz and colleagues and others that use such lesion models reveals that such limits are routinely placed. Protocols and designs routinely have limits that may qualitatively define in any of several ways the degree to which an animal may display signs of stress or debilitation. Significant loss of body weight, loss of blood, infection, failure to feed or drink, or in this case, extensive autotomy, are signs to which we must explicitly attend and must represent endpoints that are built a priori into the precise design and analysis of the experiment.

The simplest solution is to do no chronic interventions. Yet, mechanistically, we are faced with the fact that it is only in the presence of the ongoing lesion that we model the human condition. Indeed, it is the strong belief that these models do provide insights into the human chronic pain state that has led to their use. It is my own consideration that it has only been since the widespread appreciation of the difference between acute and chronic afferent drive and the prominent synaptically changes that occur in animals prepared with these lesions that substantive developments in our understanding of dysaesthetic pain has begun to yield rational, testable, and clinically relevant hypotheses. Framing Riopelle's letter is the balance that we all must seek between the work leading to the improvement of the chronic human condition and the consideration of the animal subject. Those involved in such studies must maintain this perspective.

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Neonatal Postoperative Apnea—Unexplained?

To the Editor.—Recently, Coté and Kelly described a 4.1-kg full-term, 16-day-old neonate who received, over a 45-min period, an anesthetic plus 150 ml of intravenous fluid. This is approximately 10 times the hourly maintenance for the child and does not include any moisture absorbed from warm, humidified gases. This neonate then went on to have "periodic-type breathing" with brief apneic spells of less than 10 s duration prior to extubation. While the infant was being breast-fed 45 min later, her heart rate increased to 200 beats/min; respiration increased to 70 breaths/min; and saturation decreased to 85%. The episodes of "periodic-type breathing patterns" returned along with apneic spells (of less than 10 s duration again), and the child had episodes of bradycardia with cyanosis until she was stabilized.

Given Coté's views on preoperative liquids in this age group, one presumes that this child was not maintained non per os after midnight. While maintenance fluids for the non per os period need to be taken into account, it is also accepted that it is hardly prudent to replace all such requirements plus more over the time period described by the authors. This is especially true during a procedure not usually associated with large fluid/blood loss and in an age group peculiarly sensitive to the pulmonary effects of rapid overtransfusion. The subsequent respiratory irregularities noted on the sleep studies are significant and correlated but do not automatically establish a causal relationship with the child's postoperative problem.

Another case of postoperative apnea, described by Karayan et al, was that of a 5.5 week-old, 4.45-kg infant who, in addition to the general anesthetic described, received 2 more central nervous system depressants, namely lidocaine (approximately 3 mg) and bupivacaine (approximately 16 mg). While it is known that the elimination half-life of bupivacaine in infants less than 6 months of age may be as long as 7.7 h, such patients are also known to have lower concentrations of albumin and a1-glycoproteins, which may contribute to a greater risk from bupivacaine. One may argue that in Karayan et al's patient, a...