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Glucose and Heart Surgery: Neonates Are Not Just Small Adults

DESPITE the many advances in cardiac surgery, neurologic complications continue to be recognized postoperatively. Cognitive deficits appear in about one-half of adults after coronary artery bypass grafting and in as many as one-third of children after neonatal heart surgery.[1,2] Preoperative, intraoperative, and postoperative episodes of hypoxia-ischemia all seem to contribute to these complications. Hyperglycemia has been shown to worsen neurologic injury in adult ischemia models.[3] Given the risk of ischemic neurologic injury in neonatal heart surgery and the role of hyperglycemia in ischemic brain injury in adults, de Ferranti *et al.* 's examination of the relationship of blood glucose to neurologic outcome after neonatal heart surgery, published in this issue of the Journal, addresses an important and timely question.[4]

To appreciate the distinction between neonates and adults, it is useful to briefly review their differences in whole body and brain glucose metabolism. During development, brain metabolism changes markedly. Glucose crosses the blood-brain barrier through transporter proteins (GLUT1), and then enters the cell through a second glucose transporter system (GLUT3). Glycolysis then begins with the phosphorylation of glucose by hexokinase I. GLUT3 and hexokinase I increase fivefold from neonate to adult as cerebral metabolic rate increases.[5] The developmental increase in cerebral glucose metabolic rate corresponds with an increase in synaptic activity, synaptogenesis, and myelination of specific brain regions.

Cerebral glucose metabolism yields adenosine triphosphate, which provides energy to maintain ion gradients, support synaptic activity, and preserve cellular homeostasis. Unlike the adult brain, the neonatal brain is able to metabolize ketone bodies (acetoacetate and D-3-hydroxybutyrate) and free fatty acids to generate adenosine triphosphate under physiologic conditions. The neonatal brain is also able to metabolize lactate to generate adenosine triphosphate for up to 60% of its energy requirements.[6] Lactate permeability across the blood-brain barrier is greater in neonates compared with adults, thus supporting brain lactate metabolism and limiting its build-up.[7] During ischemia, the neonatal brain is able to use alternative substrates such as lactate and glycogen for energy.[8]

A wealth of information from animal models and clinical studies implicates hyperglycemia to be detrimental to the adult brain during global and focal ischemia.[3] Although hyperglycemia supports adenosine triphosphate production through glycolysis and delays cellular energy failure during ischemia, the resultant lactic acidosis seems to be toxic to several intracellular processes, thereby hastening cell death and poisoning the repair mechanism of surviving cells.

In contrast to the adult, hyperglycemia in the neonate seems to protect the brain from ischemic damage. In a neonatal rat model of hypoxia-ischemia, Vannucci *et al.* found that low-dose glucose treatment yielding mild hyperglycemia (270–360 mg/dl) did not exacerbate brain damage; unexpectedly, glucose treatment yielding moderate hyperglycemia (630–720 mg/dl) ameliorated the brain damage in this model.[9] Studies in neonatal pigs involving hypothermic low-flow cardiopulmonary bypass or deep hypothermic circulatory arrest also demonstrated less brain damage with higher glucose levels.[10]

There are several reasons why hyperglycemia may help the neonatal brain.[11,12] First, hyperglycemia increases cerebral high-energy reserves and glycogen stores. As a result, high-energy phosphates are sustained longer during ischemia in hyperglycemic compared to normoglycemic neonatal animals. Second, glucose uptake and metabolism is slower and lactate accumulates slower in the neonatal brain compared with the adult brain. Third, lactate clearance is enhanced, thereby avoiding the toxicity of lactacidosis.

Although many studies have related serum glucose levels to ischemic neurologic outcome in adults, only one clinical study pertains to cardiac surgery. Ceriana *et al.* found that hyperglycemia was associated with adverse neurologic outcome in adults undergoing aortic arch reconstruction.[13] As a result, many cardiac anesthesiologists treat hyperglycemia based on clinical studies of stroke or cardiac arrest and animal studies of ischemia. For pediatric cardiac surgery, the role of hyperglycemia in neurologic injury is even less clear. At the same time, neonates are at additional risk for *hypo*glycemic neurologic injury.

In neonates, hypoglycemia during fasting or illness is

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well known and results from several factors. Whole body glucose metabolism corrected for body mass in neonates is up to twice as high as in adults. Hepatic glycogen stores, corrected for body mass, are less in neonates than adults. Gluconeogenic enzymes to convert amino acids to glucose are also inefficient. Neonates suffering from infections or cardiopulmonary disease are at particularly high risk for fasting hypoglycemia. Nicolson *et al.* randomized infants undergoing heart surgery to receive either lactated Ringer's solution or lactated Ringer's solution with 5% dextrose before cardiopulmonary bypass.[14] The group not receiving dextrose had a 5% incidence of hypoglycemia, whereas infants receiving dextrose had no episodes of hypoglycemia. Similarly, de Ferranti *et al.* administered fluids without dextrose while monitoring serum glucose levels and identified a 9% incidence of hypoglycemia. Consequently, during neonatal cardiac surgery, glucose is often infused intravenously, or if it is not infused, glucose is closely monitored to prevent hypoglycemia.

Although prolonged hypoglycemia is known to cause brain damage, transient hypoglycemia has also been associated with neurologic injury in neonates. Kinnala *et al.* compared neonates with a history of hypoglycemia with matched controls and found they were four times more likely to display neurologic abnormalities on magnetic resonance imaging or ultrasound scanning.[15] Thus, in neonatal heart surgery, preventing hypoglycemia may be more important to improve neurologic outcome than preventing hyperglycemia.

Despite the concern over hypoglycemia in neonates, cardiac surgery is usually associated with hyperglycemia related to the administration of glucocorticoids, hypothermia, and the stress response. Nicolson *et al.* found similar increases in blood glucose concentrations during cardiopulmonary bypass and following circulatory arrest in both the glucose supplemented and not-supplemented groups.[14] These findings indicate that the infusion of dextrose-containing fluids decreases the incidence of hypoglycemia without significantly affecting the incidence of hyperglycemia. However, there has been concern about the resultant hyperglycemia and neurologic injury among pediatric cardiac anesthesiologists.

To address this concern, de Ferranti *et al.* reviewed the database of a prospective trial conducted between 1988 and 1992, which compared neurologic outcome following surgery using a low-flow cardiopulmonary bypass or deep hypothermic circulatory arrest strategy for the arterial switch operation for D-transposition of the great arteries.[4] Although the effect of serum glucose on neurologic outcome was not the initial aim of the study, this database is unique in that it provides a cohort of 171 patients undergoing a similar procedure at one institution with uniform clinical practices. The study protocol included determination of serum glucose levels at specific time points, continuous electroencephalogram monitoring, and neurologic and developmental evaluations at 1, 4, and 8 yr of age. The electroencephalogram and neurologic evaluations were performed by blinded observers, and long-term follow-up was excellent. After examining their data in several different ways, the authors found no relationship between high glucose levels and poor early or late neurologic or developmental outcome. In fact, electroencephalogram activity returned more rapidly following deep hypothermic circulatory arrest in patients with higher glucose levels, and lower glucose levels after deep hypothermic cardiopulmonary bypass was correlated with an increased risk for electroencephalogram seizures, suggesting that higher glucose is better for the neonatal brain than normal or low glucose.

This study does have several weaknesses to temper these conclusions. It was observational and was not originally designed to address the impact of glucose management on neurologic outcome. Although electroencephalogram activity returned earlier in patients with higher glucose levels, the correlation coefficients, although statistically significant, were weak. Further, the relationship between return of electroencephalogram activity and neurologic outcome is uncertain in this setting. Given these issues, the conclusion of high blood glucose concentration being beneficial is tenuous. It is also possible that the serum glucose threshold of 150 mg/dl used by the authors to define hyperglycemia was not the proper "hyperglycemic" threshold to test. Management of cardiopulmonary bypass during pediatric cardiac surgery has significantly changed since this study was performed. Many centers now use regional cerebral perfusion or low-flow bypass instead of circulatory arrest, pH-stat instead of α-stat blood gas management during deep hypothermia, and higher hematocrit levels during cardiopulmonary bypass. These factors clearly reduce ischemic neurologic injury and may therefore lessen the importance of blood glucose on neurologic outcome.

Despite these limitations, this study provides evidence for the lack of association between hyperglycemia and adverse neurodevelopmental outcome after neonatal heart surgery. At the same time, hypoglycemia occurs not infrequently during neonatal heart surgery, and transient hypoglycemia poses a risk of neurologic injury to the immature brain. In light of the clinical and experimental evidence available to date, it is wise to administer dextrose-containing fluids during neonatal heart surgery or, if this is not done, to closely monitor serum glucose levels.

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References

1. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344:395–402
2. Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC, Barnes PD, Holmes GL, Hickey PR, Strand RD: Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med 1995; 332:549–55
3. Sieber FE, Traystman RJ: Special issues: Glucose and the brain. Crit Care Med 1992; 20:104–14
4. de Ferranti S, Gauvreau K, Hickey PR, Jonas RA, Wypij D, du Plessis A, Bellinger DC, Kuban K, Newburger JW, Laussen PC: Intraoperative hyperglycemia during infant cardiac surgery is not associated with adverse neurodevelopmental outcomes at 1, 4, and 8 years. Anesthesiology 2004; 100:1345–52
5. Vannucci SJ, Seaman LB, Brucklacher RM, Vannucci RC: Glucose transport in developing rat brain: Glucose transporter proteins, rate constants and cerebral glucose utilization. Mol Cell Biochem 1994; 140:177–84
6. Hellmann J, Vannucci RC, Nardis EE: Blood-brain barrier permeability to lactic acid in the newborn dog: Lactate as a cerebral metabolic fuel. Pediatr Res 1982; 16:40–4
7. Cremer JE, Cunningham VJ, Pardridge WM, Braun LD, Oldendorf WH: Kinetics of blood-brain barrier transport of pyruvate, lactate and glucose in suckling, weanling and adult rats. J Neurochem 1979; 33:439–45
8. Vannucci SJ, Vannucci RC: Glycogen metabolism in neonatal rat brain during anoxia and recovery. J Neurochem 1980; 34:1100–5
9. Vannucci RC, Mujsce DJ: Effect of glucose on perinatal hypoxic-ischemic brain damage. Biol Neonate 1992; 62:215–24
10. Kurth CD, Priestley M, Golden J, McCann J, Raghupathi R: Regional patterns of neuronal death after deep hypothermic circulatory arrest in newborn pigs. J Thorac Cardiovasc Surg 1999; 118:1068–77
11. Corbett RJ, Laptook AR, Garcia D, Ruley JI: Energy reserves and utilization rates in developing brain measured in vivo by 31P and 1H nuclear magnetic resonance spectroscopy. J Cereb Blood Flow Metab 1993; 13:235–46
12. Corbett R, Laptook A, Kim B, Tollefsbol G, Silmon S, Garcia D: Maturational changes in cerebral lactate and acid clearance following ischemia measured in vivo using magnetic resonance spectroscopy and microdialysis. Brain Res Dev Brain Res 1999; 113:37–46
13. Ceriana P, Barzaghi N, Locatelli A, Veronesi R, De Amici D: Aortic arch surgery: Retrospective analysis of outcome and neuroprotective strategies. J Cardiovasc Surg 1998; 39:337–42
14. Nicolson SC, Jobes DR, Zucker HA, Steven JM, Schreiner MS, Betts EK: The effect of administering or withholding dextrose in pre-bypass intravenous fluids on intraoperative blood glucose concentrations in infants undergoing hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 1992; 6:316–8
15. Kinnala A, Rikalainen H, Lapinleimu H, Parkkola R, Kormano M, Kero P: Cerebral magnetic resonance imaging and ultrasonography findings after neonatal hypoglycemia. Pediatrics 1999; 103:724–9

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Rested and Refreshed after Anesthesia? Overlapping Neurobiologic Mechanisms of Sleep and Anesthesia

A RAPIDLY growing field of recent research focuses on the potential mechanistic similarities between the behavioral states of endogenous nonrapid eye movement (NREM) sleep and anesthesia. In this month's issue of the Journal, Tung *et al.* move this field a large step forward, reporting research suggesting that pharmacologic "sleep" may be able to fulfill some functions of natural sleep.[1] The authors previously reported that on emergence from prolonged propofol-induced sedation, no electroencephalographic (rebound increases in rapid eye movement [REM] or NREM sleep) or behavioral signs of sleep deprivation are observed,[2] and that 24 h of sleep deprivation decreases the latency to loss of righting reflex by 40% for propofol and 55% for isoflurane and prolongs the time to recovery from both.[3]

What is the relationship between sleep and anesthesia? Although there are obvious significant physiologic differences between sleep and anesthesia (*e.g.*, the ability to fulfill an essential biologic need, arousability from noxious stimuli, and cyclical variability), the two states have many similarities ranging from a generalized reduction in responsiveness to external stimuli to subtle changes in encephalographic activity. K-complexes (single, episodic, large-amplitude waves), sleep spindles (0.5- to 3.0-s runs of 12 to 14 Hz), and an increasing predominance of slow waves (delta 1–4 Hz and theta 4–7 Hz) are features of both NREM sleep and light anesthesia.

Both human and animal research suggest that NREM sleep and anesthesia may share certain mechanistic features. Labeled positron emission tomography scans of human brains during anesthesia have demonstrated regional changes in brain images similar to those seen during sleep.[4] Positron emission tomography with metabolic scanning[4] and microelectrode recordings of thalamic relay neuronal activity[5] show distinctive reductions in thalamic activity during anesthesia, which are also known to stimulate natural sleeplike changes in thalamocortical electrical activity.

On a neural substrate level, animal experiments[6,7] demonstrate that anesthetic agents that are proved, or postulated, to act on α_2-adrenoceptors (dexmedetomidine), and γ-aminobutyric acid A receptors (muscimol, propofol, and pentobarbital, isoflurane), induce a loss of consciousness, at least in part, *via* activation of endogenous NREM sleep-promoting hypothalamic pathways. Importantly, different classes of anesthetics seem to converge differentially on sleep-promoting circuitry; noradrenergic neurons within the locus ceruleus maintain their "awake" activity during hypnosis produced by γ-aminobutyric acid A–mediated (GABAergic) com-

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pounds but are inhibited during hypnosis induced by α_2-adrenoceptor agonists, whereas histaminergic neurons in the tuberomamillary nucleus appear critical to the hypnotic action of both types of agents.[6,7]

How important is it to understand the overlap between natural and pharmacologic "sleep"? Sleep disruption and deprivation create problems for patients recovering from surgical interventions. Although the causes are multifactorial, appropriate control of pain and anxiety are necessary to prevent the negative consequences that unfavorably affect recovery. However, commonly used medications to treat pain and anxiety may themselves alter sleep architecture and quality. For example, aspirin (acetylsalicylic acid) decreases the duration of slow-wave sleep (stages 3 and 4 NREM sleep) and stage 2 NREM, and it decreases sleep continuity[8]; selective serotonin reuptake inhibitors decrease REM sleep duration and increase REM latency[9]; classic benzodiazepines decrease slow-wave sleep duration, decrease delta power during slow-wave sleep, and increase stage 2 NREM sleep[10]; and opioids increase the duration of stage 2 NREM and decrease slow-wave sleep and REM.[11] Prolonged sleep deprivation alters electrocortical, respiratory as well as carbon dioxide and oxygen homeostasis, and psychiatric and immune functions (all of which are reversible with physiologic sleep), and can ultimately result in death when taken to an extreme in animal experiments.[12] Can we find hypnotic agents to combat these detrimental effects in settings where natural sleep is not possible? Could any of our existing anesthetics/hypnotics be helpful?

The rapid-acting anesthetic *propofol*, originally developed for use as an intravenous anesthetic for outpatients, was recently introduced as a sedative during intensive care. Its rapid onset and offset allows physicians to sedate patients to near unresponsiveness for extended periods while retaining the ability to wake them up rapidly[13]; and these properties have led to the advocacy of its use to promote sleep in the intensive care setting, although there is little evidence to support such a strategy. Propofol is thought to act by binding to the γ-aminobutyric acid A receptor at a site distinct from the benzodiazepine binding site and allosterically enhancing the activity of γ-aminobutyric acid.[14] Does propofol-induced sedation promote or mimic physiologic sleep? Unlike endogenous sleep, propofol sedation does not demonstrate an orderly progression of electroencephalogram states and is not entirely reversible with external stimuli. In addition, little evidence exists suggesting that propofol-induced sedation can satisfy the biologic need for natural sleep. Might prolonged periods of continuous sedation, overlapping with naturally occurring sleep periods, result in sleep deprivation?

Tung *et al.* administered 6 h of propofol anesthesia to electroencephalogram-telemetered rats after inducing 24 h of sleep deprivation by the disk-over-water paradigm (animals are placed on a 45-cm elevated disk that rotates when sleep is detected by computerized electroencephalogram/electromyogram monitoring, causing the rat to wake up to avoid falling in a water hazard[15]); unexpectedly, Tung *et al.* observed that propofol anesthesia induced the hallmark features of natural sleep deprivation recovery (increases in NREM and REM duration as well as NREM delta power). Their results suggest for the first time a functional relevance to the phenotypical, electrical, and neuroanatomic similarities between NREM sleep and anesthesia reported by others in recent years. Might anesthetic practice be refined such that, one day, patients will emerge from anesthesia or prolonged sedation feeling refreshed and rested?

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References

1. Tung A, Bergmann BM, Herrera S, Cao D, Mendelson WB: Recovery from sleep deprivation occurs during propofol anesthesia. ANESTHESIOLOGY 2004; 100: 1419–26

2. Tung A, Lynch JP, Mendelson WB: Prolonged sedation with propofol in the rat does not result in sleep deprivation. Anesth Analg 2001; 92:1232–6

3. Tung A, Szafran MJ, Bluhm B, Mendelson WB: Sleep deprivation potentiates the onset and duration of loss of righting reflex induced by propofol and isoflurane. ANESTHESIOLOGY 2002; 97:906–11

4. Alkire MT, Pomfrett CJ, Haier RJ, Gianzero MV, Chan CM, Jacobsen BP, Fallon JH: Functional brain imaging during anesthesia in humans: Effects of halothane on global and regional cerebral glucose metabolism. ANESTHESIOLOGY 1999; 90:701–9

5. Vahle-Hinz C, Detsch O, Siemers M, Kochs E, Bromm B: Local GABA(A) receptor blockade reverses isoflurane's suppressive effects on thalamic neurons in vivo. Anesth Analg 2001; 92:1578–84

6. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by $GABA_A$ receptors in an endogenous sleep pathway. Nat Neurosci 2002; 5:979–84

7. Nelson LE, Lu J, Guo TZ, Saper CB, Franks NP, Maze M: The α_2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep pathway to produce its hypnotic response. ANESTHESIOLOGY 2003; 98:428–36

8. Horne JA, Percival JE, Traynor JR: Aspirin and human sleep. Electroencephalogr Clin Neurophysiol 1980; 49:409–13

9. Sharpley AL, Williamson DJ, Attenburrow ME, Pearson G, Sargent P, Cowen PJ: The effects of paroxetine and nefazodone on sleep: A placebo controlled trial. Psychopharmacology (Berl) 1996; 126:50–4

10. Risberg AM, Henricsson S, Ingvar DH: Evaluation of the effect of fosazepam (a new benzodiazepine), nitrazepam and placebo on sleep patterns in normal subjects. Eur J Clin Pharmacol 1977; 12:105–9

11. Walder B, Tramer MR, Blois R: The effects of two single doses of tramadol on sleep: A randomized, cross-over trial in healthy volunteers. Eur J Anaesthesiol 2001; 18:36–42

12. Rechtschaffen A, Gilliland MA, Bergmann BM, Winter JB: Physiological correlates of prolonged sleep deprivation in rats. Science 1983; 221:182–4

13. Beller JP, Pottecher T, Lugnier A, Mangin P, Otteni JC: Prolonged sedation with propofol in ICU patients: Recovery and blood concentration changes during periodic interruptions in infusion. Br J Anaesth 1988; 61:583–8

14. Hales TG, Lambert JJ: The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones. Br J Pharmacol 1991; 104:619–28

15. Bergmann BM, Kushida CA, Everson CA, Gilliland MA, Obermeyer W, Rechtschaffen A: Sleep deprivation in the rat: II. Methodology. Sleep 1989; 12:5–12

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Fishing for Genes: Practical Ways to Study Genetic Polymorphisms for Pain

"A FISHING expedition." These three words, uttered during a grant review, seal the fate of the unfortunate applicant. They infer lack of focus, lack of clear preliminary data or thought, and essentially lack of hypothesis. Many genetic studies suffer from this characterization. But it need not be so. The Human Genome Project, along with similar complete descriptions of the genetic makeup of several subhuman mammalian species, provide an incredible opportunity to probe the genetic determinants of acute and chronic diseases.

The current issue of the Journal contains a review on considerations for designing human genetic studies to examine pain mechanisms.[1] It describes how to fish for genes related to pain. It is not written for geneticists, molecular biologists, or laboratory scientists. For the expert, it provides the necessary formulas and rationale to design trials to study novel genes related to development of chronic pain. For the rest of us, it provides a clear framework in which to phrase questions on the genetic basis of pain. If you have any intention of trying to understand the genetic basis of pain in the next 5 yr, I suggest you carefully read and keep this article.

The nature and nurture discussion states that both inherent and environmental factors determine behavioral biology. There are many reasons to attempt to understand the genetic factors that correlate with the development of chronic neuropathic pain, although they tend to fall into two camps. For one, genetic screening of persons with and without pain may identify novel proteins involved in the process of pathologic pain or targets for novel drug development to treat chronic pain. For another, genetic screening may identify groups or individuals at particular risk for developing chronic pain. The former is the basis of multiple large population studies, mostly done by industry and outside the public domain, in which the plan is to generate intellectual property for sale to develop novel analgesic drugs. No such publicly available screening databases are available, although a few are in the process of being generated, including those of the authors of this report[1] and others.[2,3] The latter are apparently of little interest to industry and have attracted little academic interest.

As anesthesiologists, we are interested both in the treatment of acute and chronic pain and in the prevention of the development of chronic pain. Remarkably, a large proportion of patients with complicated chronic pain problems date the onset of their pain to that of surgery,[4] and to a large extent we can predict which surgical populations are likely to develop chronic pain.[5] As a result, we are in a unique position, as those who treat chronic pain and provide treatment to those undergoing surgery, to affect both. Thus, we are also in a unique position to utilize the information provided in the current report[1] to identify novel targets in the pathophysiology of chronic pain and to identify populations at risk for this devastating problem. We care for these patients in the complete sense of the phrase, and we have available preoperative testing, intraoperative care, and postoperative analgesic methods that could be tailored to individuals, based on the tools provided in this report.[1]

Why go on such fishing expeditions? There are two answers to this question, as indicated above. If one wants to drop a line and see what bites, then the key is to use bait that is attractive to anything and everything below. The major focus of the current article, as is especially indicated in its figures, rests on this aspect of global genetic screening. To determine the genetic characteristics associated with chronic pain, the key limitations are the incidence of developing chronic pain in the population and the frequency of the genetic variability (polymorphism) for individual genes. As clearly indicated in the figures, as the number of subjects studied increases linearly, there is an exponential increase in the number of genes that can be screened for a possible association. The "targeted" approach, as suggested in the article, would base the selection of genes in such a scenario on molecules that are considered important in pain processing or in the neuroplasticity of chronic pain. However, as indicated above, a key benefit of this screening approach rests in identifying unsuspected targets and a much larger set of genes than those Belfer *et al.* listed.[1] These types of methods have been applied in the laboratory setting to screen for genes that are differentially altered in rat strains that are susceptible or not susceptible to the generation of chronic pain after nerve injury.[6]

The problem with this approach is, in a sense, statistical. As discussed in the current article, many associations may be related to environmental influences affect-

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ing the development of pain, and these can only be recognized *post hoc*. As one screens for many genes, some associations may appear that relate to processes weakly associated with pain, but not causal or closely linked. For example, using a gene microarray to screen for many genes, a recent study demonstrated that peripheral inflammation in the rat results in an increase in expression of the gene for the protein cystatin C in the spinal cord.[7] A follow-up study in humans showed an increase in this protein in lumbar cerebrospinal fluid in women in labor pain, suggesting that this protein might be used as a biomarker for pain.[8] More complete examination, however, showed no relationship between concentration of this substance in cerebrospinal fluid and pain, whether acute or chronic, in humans.[9] Clearly, identification of a potential cause or diagnostic marker for pain using this approach just begins with the genetic screen, with much validation work to follow.

A second reason to fish is exemplified by the fly fisherman, who, as I am told (not being one of them), knows precisely the target, and imagines, or perhaps hallucinates, the location of the fish to be caught. The current article is a similarly effective guide for such fishing. As clearly demonstrated, the number of subjects required to test the relative risk of a specific gene to pain increases dramatically with the extent to which that gene varies in humans and the incidence of chronic pain in the population. Dramatic results have been achieved with this method in other fields, and current work suggests that at least a couple of targets, such as genetic variation in the promoter for tumor necrosis factor α and catecholamine-O-methyl-transferase, are important to postoperative pain and efficacy of analgesia. This approach strives not to identify new targets but rather to demonstrate the relative importance of suspected targets in the pathogenesis of pain.

The beauty of the current article is that it explains how to go fishing regardless of which approach one chooses. Some may find the explanations and equations arcane. No problem. Simply take this article to your local geneticist or molecular pathologist and report your interest in studying the underlying genetic factors, or a specific factor, as a cause of pain. He or she will find the description perfectly sensible in the language of that field of study, and most likely will be delighted to help.

As indicated above, we as anesthesiologists are in a unique position to study the genetics of pain because we treat patients with various genetic backgrounds who are undergoing standardized injuries. A small number of these patients will experience excruciating postoperative pain, and a small number will develop chronic pain following these injuries. Predicting which patients will have either or both of these problems can be determined by one type of fishing, and deciding whether these two experiences—severe postoperative pain and subsequent chronic pain—are related can be determined by the other type of fishing. Thank you to Belfer *et al.* for once again providing a guidebook to those who want to better understand pain mechanisms in our patients and how to better treat or prevent pain. Isaac Walton would be proud!

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References

1. Belfer I, Wu T, Kingman A, Krishnaraju RK, Goldman D, Max MB: Candidate gene studies of human pain mechanisms: Methods for optimizing choice of polymorphisms and sample size. ANESTHESIOLOGY 2004; 100:1562–72

2. Bragdon EE, Light KC, Costello NL, Sigurdsson A, Bunting S, Bhalang K, Maixner W: Group differences in pain modulation: Pain-free women compared to pain-free men and to women with TMD. Pain 2002; 96:227–37

3. Werner MU, Duun P, Kehlet H: Prediction of postoperative pain by preoperative nociceptive responses to heat stimulation. ANESTHESIOLOGY 2004; 100: 115–9

4. Crombie IK, Davies HT, Macrae WA: Cut and thrust: Antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76:167–71

5. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery: A review of predictive factors. ANESTHESIOLOGY 2000; 93:1123–33

6. Valder CR, Liu JJ, Song YH, Luo ZD: Coupling gene chip analyses and rat genetic variances in identifying potential target genes that may contribute to neuropathic allodynia development. J Neurochem 2003; 87:560–73

7. Yang HYT, Wilkening S, Iadarola MJ: Spinal cord genes enriched in rat dorsal horn and induced by noxious stimulation identified by subtraction cloning and differential hybridization. Neuroscience 2001; 103:493–502

8. Mannes AJ, Martin BM, Yang HYT, Keller JM, Lewin S, Gaiser RR, Iadarola MJ: Cystatin C as a cerebrospinal fluid biomarker for pain in humans. Pain 2003; 102:251–6

9. Eisenach JC, Thomas JA, Rauck RL, Curry R, Li X: Cystatin C in cerebrospinal fluid is not a diagnostic test for pain in humans. Pain 2004; 107:207–12