INVITED EDITORIAL
To Fire the Train: A Second Malignant-Hyperthermia Gene

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> The further nosology is pursued, the more clearly does it emerge that in every case of every malady there are two sets of factors at work in the formation of the morbid picture, namely the internal or constitutional factors, inherent in the sufferer, and usually inherited from his forbears, and external ones which fire the train. (Garrod 1931, pp. 146–147)

This year marks the 150th anniversary of the first public demonstration of the use of anesthesia in surgery. The event was so startling in its lack of antecedents and profound in its applications that, despite the lack of technologies of mass communication, news of William Morton's successful use of sulfuric ether reached the ends of the earth within weeks (Pernick 1985). More than 100 years were to elapse before malignant hyperthermia, a lethal consequence of the use of ether and its related compounds, was first recognized by Michael Denborough, then a medical student in Australia. Denborough's insight was twofold—first, in identifying the disorder as a distinct entity and, second, in apprehending that susceptibility could be inherited (Denborough and Lovell 1960). The curious failure on the part of preceding generations of anesthesiologists to detect malignant hyperthermia arose less from its presumed rarity—or from the intellectual handicap of those attracted to the field—than from the time and collective experience required to learn how to safely administer drugs capable of killing in so many different ways.

In this issue of the *Journal,* Monnier et al. describe the first mutant allele in the second gene to be associated with human malignant hyperthermia on the basis of linkage analysis (Monnier et al. 1997). The gene *CACNL1A3,* which encodes the channel-forming α_{1s} subunit of the skeletal muscle L-type voltage-dependent calcium channel (VDCC) (also known as the "dihydropyridine receptor"), joins the calcium-release channel (also known as the "ryanodine receptor" [*RYR1*]) as a point of entry into the syndrome's pathophysiological cascade. The mutation, an adenine-for-guanine substitution at nucleotide 3333, confers an arginine-to-histidine transition at amino acid 1086. Three previously identified substitutions for arginine residues elsewhere in *CACNL1A3* cause the neuromuscular disease hypokalemic periodic paralysis (HOKPP1) (Jurkat-Rott et al. 1994; Ptacek et al. 1994), which itself may predispose to malignant hyperthermia (Lambert et al. 1994). Publication of Monnier et al.'s contribution provides an opportune landmark for taking stock of research aimed at elucidating the genetic substrate of malignant hyperthermia thus far and for surveying the distance ahead.

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The Malignant-Hyperthermia Phenotype: Clinical Features and the In Vitro Contracture Test

Shortly after Denborough's account, the clinical syndrome was fleshed out in full. Fulminant muscle rigidity, rhabdomyolysis, hypercarbia, and acidosis following inhalation of volatile anesthetics and parenteral injection of depolarizing muscle relaxants are the cardinal clinical features. Elevated core temperature is common, but *normothermia does not rule out the diagnosis. Hyperthermia may be a late sign,* as in the proband described by Monnier et al. (1997), and triggering agents must be discontinued at the earliest suspicion. Hyperkalemia and increased serum creatinine phosphokinase accompany the perioperative crisis but have not proved to be useful markers of malignant-hyperthermia susceptibility. Ventricular dysrhythmia is the proximate cause of death in the acute event, with renal failure and neurologic injury the feared sequelae. The international incidence of malignant hyperthermia is estimated to be 1/50,000 anesthetics. Children are at special risk, with ~1/5,000–10,000 pediatric anesthetics using trigger drugs complicated by a malignant-hyperthermia crisis. A higher incidence is encountered in geographically defined populations—for example, residents of north-central Wisconsin, aboriginal inhabitants of North Carolina, valley dwellers in parts of Austria, and descendants of settlers in Quebec.

Confirmation of Denborough's initial observations left anesthesiologists and their patients with a staggering quandary. The drugs responsible for triggering malignant

hyperthermia had become the preferred components of most general anesthetics. Particularly in emergencies, a family history of anesthetic complications is often unavailable, and susceptible patients may exhibit no specific antecedent phenotype. To make matters worse, a prior history of an uneventful anesthetic using triggering drugs does not assure that a subsequent anesthetic will be safe (Halsall et al. 1979). These uncertainties were resolved in part by introduction of the in vitro halothane contracture test (IVCT) (Kalow et al. 1970; Ellis and Harriman 1973), in which strips of biopsied muscle are suspended in a bath and electrically stimulated. Abnormally high levels of tension in the presence of caffeine and halothane added to the bathing solution are generated in the muscle of individuals susceptible to malignant hyperthermia. The IVCT focused experimental efforts on skeletal muscle as the primary site of the defect, away from earlier theories of neural or endocrine pathogenesis, but it was not until 1984 in Europe and 1989 in North America that test centers agreed on standardized protocols and cutoff points for clinical purposes. Data collected before these dates are contaminated to an indeterminate extent by subjective interpretation, which could underlie the limited genotype-phenotypetype concordance reported for putative mutant alleles in some families (Serfas et al. 1996).

Use of the IVCT for the differential diagnosis of malignant hyperthermia is now fairly uniform, but divergent strategies adopted for ascertainment and genetic counseling are reflected in the subsequent acquisition of molecular genetic data. IVCT centers in the United States often halt testing within a pedigree after identification of the first positive result in the generation of the proband's parents, since malignant-hyperthermia susceptibility is assumed to be rare. In European and Canadian laboratories, efforts are made to perform an IVCT on all of a proband's relatives at risk, laying the groundwork for genetic investigations such as that by Monnier et al. (1997). The IVCT remains indispensible in malignant-hyperthermia diagnosis, counseling, and research (Hopkins et al. 1997); however, it is invasive, costly (as much as $3,000), ill suited for use in early childhood, and not widely available. The dismal record of numerous attempts to improve or replace the IVCT have contributed greatly to interest in the potential of DNA-based approaches. It initially was hoped that hints in the search for the genetic foundations of malignant hyperthermia would be revealed by closer scrutiny of the triggering drugs themselves.

External Factors

All halogenated ethers in contemporary clinical practice (i.e., isoflurane, ethrane, sevoflurane, and desflurane), as well as halothane (an alkane), are potential malignant-hyperthermia triggers. Clinicians are reluctant to abandon their use, because of the precise and rapid control, over depth of anesthesia, that anesthetic vapors provide. As a class, the halogenated agents produce skeletal, cardiac, and smooth-muscle relaxation in normal patients, in stark contrast to the rigidity and contracture observed in those susceptible to malignant hyperthermia. None of the volatile agents depolarize normal muscle, despite small elevations in myoplasmic calcium, and the mechanism of relaxation is not known. Although their lipophilicity assures access to any tissue or subcellular compartment, no protein targets expressed in skeletal muscle that are specific for the volatile anesthetics have been found. The potent agents are metabolized to varying degrees in the liver, but none of the metabolites are noteworthy myotoxins, nor are the responsible enzyme pathways aberrant in malignant hyperthermia. To date, clues to the mechanisms of muscle destruction in individuals predisposed to malignant hyperthermia have not been forthcoming from knowledge either of the pharmacokinetic profiles of volatile anesthetics or of their effects on normal tissue.

Succinylcholine, a depolarizing muscle relaxant, is the other drug capable of triggering malignant hyperthermia, either alone or, as in the present proband, in coadministration with a volatile anesthetic. Quick in onset and short in duration, succinylcholine frequently is used in pediatric anesthesia, to facilitate tracheal intubation after loss of consciousness by inhalation of a volatile drug. It is at this point in the perioperative course that patients susceptible to malignant hyperthermia most often become rigid, with a clenched jaw and rigid chest impairing ventilation. Succinylcholine binds to the neuromuscular junction, initiating a wave of depolarization within the sarcolemmal t-tubule system, seen clinically as muscle fasiculations followed by paralysis. Because succinylcholine is a charged quaternary ammonium compound that cannot enter the cell, depolarization is thought to be directly responsible for triggering a malignant-hyperthermia crisis. The neuromuscular junction has been intensely investigated as a possible site of the malignant-hyperthermia defect, but no abnormalitites of the nerve terminal or motor endplate are found in tissue from malignant-hyperthermia survivors; patients with disorders of the neuromuscular junction (e.g., myasthenia gravis) are not at risk for malignant hyperthermia; and neuromuscular blockade with nondepolarizing muscle relaxants (curare-like compounds) does not prevent or treat the acute event. Succinycholine is catabolized in the plasma by the enzyme pseudocholinesterase. No cases of pseudocholinesterase deficiency, an autosomal recessive disorder with an incidence of 1/3,000, have been reported concomitant with malignant hyperthermia.

Early recognition of a malignant-hyperthermia epi-

sode, as well as prompt intervention with intravenous dantrolene, a hydantoin congener introduced in 1977, is life saving in 90% of victims. Dantrolene is highly lipid soluble, inhibiting calcium release from the skeletal muscle sarcoplasmic reticulum rather than acting directly at the neuromuscular junction or on the t-tubular membrane. A distinct protein receptor for dantrolene recently has been proposed as a possible constituent of the skeletal muscle triad at the site of apposition between the terminal cisternae of the sarcoplasmic reticulum and sarcolemmal t-tubules (Parness and Palnitkar 1996). Isolation of this protein, as well as cloning of its gene, potentially will yield an additional candidate for analysis in malignant-hyperthermia pedigrees. If so, a deeper understanding of the mode of action of the specific therapy for malignant hyperthermia may reveal mutant alleles that have eluded inquiry based on investigation of triggering drugs.

Internal Factors

Thus far, primary genetic approaches have been much more fruitful than deliberation over drug triggers and their antagonists, in directing discovery of genetic alterations associated with malignant hyperthermia. Soon after Denborough's description, meat spoilage in an animal model sharing many features of the human syndrome was reported in strains of pigs bred to produce lean bacon (Hall et al. 1966). Abundant genetic and biochemical evidence pointing to a disorder of the skeletal muscle calcium-release channel kindled a search for a causal mutation in the porcine *RYR1* gene, resulting in isolation of a cysteine-for-arginine substitution at position 615 of the pig RYR1 amino acid sequence (Fujii et al. 1991). This alteration, which is responsible for all malignant-hyperthermia susceptibility in pigs, is found in only a small proportion (5%) of human malignant-hyperthermia pedigrees. Until the present, as many as 12 additional point mutations in *RYR1* are known to cosegregate with human malignant hyperthermia. Some appear in a small subset (2%–10%) of pedigrees, depending on the origin of the screened database; others, including the first definitive report of *RYR1* malignant-hyperthermia homozygotes (Lynch et al. 1997), are confined to a single family. Additional mutant *RYR1* alleles remain to be found, since not all of the original families showing chromosome 19 linkage in the region of *RYR1* (MacLennan et al. 1990) are accounted for by mutations identified to date.

Events during veterinary anesthesia that resemble those in human malignant hyperthermia are reported in a wide variety of other species, including horses, cats, and dogs. In most instances, clinical episodes and IVCT data within a pedigree are not available to confirm a genetic predisposition. One breeding colony of dogs has been established in which malignant hyperthermia is inherited as an autosomal dominant trait in correlation with abnormal IVCT results (Nelson 1991). The pig *RYR1* mutation has been ruled out (Hogan et al., in press). Candidate gene searches and linkage analysis using markers characterized as part of the Dog Genome Project are underway. Whether a mutation in canine malignant hyperthermia or in any other species will correspond to human malignant hyperthermia is unknown.

Abnormal regulation of calcium in skeletal muscle is the sine qua non of malignant hyperthermia; hence, proteins known to participate in myoplasmic calcium homeostasis may denote candidate genes. To initiate contraction in skeletal muscle, calcium stored in the sarcoplasmic reticulum is liberated by conformational changes in the *RYR1* protein that are transduced by the VDCC in response to t-tubule depolarization. The critical role of the VDCC in excitation-contraction coupling motivated earlier investigators to map, clone, sequence, and identify polymorphisms in *CACNL1A3* encoding the VDCC channel-forming α_{1s} subnunit as a candidate for malignant hyperthermia. Although the HOKPP1 *CACNL1A3* mutations appear in regions of the molecule that have been demonstrated, by the construction of experimental chimeral channels, to be voltage sensors, the site of the malignant-hyperthermia mutation that Monnier et al. have found in the intracytoplasmic loop spanning transmembrane repeats III and IV has not previously been assigned a physiological role. Distinct isoforms encode the α_1 subunits of heart, neuroendocrine, and brain VDCCs, which cooperate in the assembly of channels with tissue-specific functional properties. Defects in the α_{1A} subunit of the brain-specific P/Q-type calcium channel gene (*CACNL1A4*) cause familial hemiplegic migraine and type-2 episodic ataxia (Ophoff et al. 1996), intimating that only the surface has been scratched in the isolation of disease-causing mutations in this gene family. Other inviting malignant hyperthermia–candidate proteins expressed in skeletal muscle include calsequestrin, which acts as a calcium buffer in the luminal space of the sarcoplasmic reticulum (Kawasaki and Kasai 1994); triadin, which may physically couple CACNL1A3 to RYR1 (Brandt et al. 1992); the FK506-binding protein (FKBP12), which stabilizes the closed conformation of the RYR1 (Timerman et al. 1993); and aldolase, which copurifies with the triad and causes rhabdomyolysis in deficient patients (Kreuder et al. 1996).

Linkage analysis based on IVCT phenotyping indicates that *RYR1* mutations will not be found in as many as 50% of families with malignant hyperthermia (Ball and Johnson 1993). Evidence for a second malignant-hyperthermia locus at *CACNL1A3* is now firm, but both *RYR1* and *CACNL1A3* have been exluded in other kindreds (Sudbrak et al. 1993). Linkage to a locus on chro-

mosome 3q, with a LOD score of 3, has been reported for a single family (Sudbrak et al. 1995), but no candidate genes are known to reside in the 1 cM of highest probability. As Monnier et al. (1997) point out, a fourth locus on chromosome 7q, in proximity to the gene encoding the VDCC α_2/δ subunit, also has been linked to malignant hyperthermia in a single family, but a causal mutation has yet to be disclosed (Iles et al. 1994). Sequencing efforts in the latter two regions not only have the potential to identify new malignant-hyperthermia loci but may bring to light hitherto unidentified molecular participants in excitation-contraction coupling.

Investigators are divided over how to best categorize malignant-hyperthermia events and positive IVCT results observed in patients with recognizable coexisting neuromuscular diseases (e.g., Duchenne muscular dystrophy, carnitine parmitoyl transferase II deficiency, and Brody myopathy [a deficiency of the Ca^{2+}-ATPase pump]). One opinion holds that, if a myopathy can be diagnosed by signs, symptoms, and clinical tests without an IVCT, it is not "true" malignant hyperthermia and that only otherwise normal individuals with a positive IVCT fit the nosology. Others argue that malignant hyperthermia is a clinical syndrome, not a single disease, with many myopathic disease inlets to a shared pathophysiological pathway that is initated by elevated myoplasmic calcium. In providing the first positive evidence for locus heterogeneity in the absence of a concurrent disease phenotype, the contribution of Monnier et al. (1997) upholds the latter point of view. IVCT results from this family with a *CACNL1A3* mutation are indistinguishable from IVCT abnormalities compiled from families with a disorder of the *RYR1* gene; hence, the IVCT as presently configured fails to discriminate between diseases predisposing to the malignant-hyperthermia syndrome. The practical—and nontrivial—clinical consequence is that all myopathic conditions suspected to be mediated by calcium injury must be considered susceptible to malignant hyperthermia, and selection of the anesthetic technique and management of crises must be handled accordingly. The telling research corollary is that documentation of allelic heterogeneity in both *RYR1* (with mutant alleles causing both central core disease and malignant hyperthermia) and *CACNLlA3* (with mutant alleles causing both HOKPP1 and malignant hyperthermia) compels a search of genes mutated in well-recognized neuromuscular disorders, for alterations that make their presence felt only in environments of triggering anesthetic drugs.

Malignant hyperthermia associated with short stature, myopathy, micrognathia, low-set ears, and variable additional features (e.g., cryptorchidism and pectus carniatum) is recognized as King-Denborough syndrome (McPherson and Taylor 1981). Tragically, the diagnosis of this extremely rare disorder usually is made in retrospect, after an anesthetic death. Although the clinical spectrum of King-Denborough syndrome might suggest a contiguous-gene defect, normal karyotypes in one male and in one female have been reported (Hogan et al. 1994). The *RYR1* R614C mutation was not observed in either child. Events resembling malignant hyperthermia also have been described in a small number of other dysmorphic conditions (Schwartz-Jampel syndrome, Noonan syndrome, and some forms of arthrogryposis), but it is unclear whether these are pathologically related or coincidental associations.

Summing Up

In the search for all genetic alterations taking part in the pathogenesis of human malignant hyperthermia, a single *CACNL1A3* mutation now can be added to a dozen or so *RYR1* mutations already identified. It is highly probable that additional *RYR1* mutations will be characterized in the near future, and it is reasonable to anticipate that new *CACNL1A3* mutations will be detected as inventories are screened on the heels of the present publication. If so, will the tight genotype-phenotype correlation described by Monnier et al. (1997) hold up, or will the story more nearly resemble that described for many of the *RYR1* mutations, in which the extent of concordance varies from family to family, for each mutation? In all likelihood a third locus on chromosome 3q and a fourth on chromosome 7q (the VDCC α_2/δ gene) will yield malignant hyperthermia–associated candidate mutations. Because human malignant hyperthermia is a genetically diverse syndrome with clear-cut evidence of both locus and allelic heterogeneity, genes responsible for otherwise recognizable neuromuscular diseases mediated by calcium-induced injury must be considered possible candidates for additional mutant alleles. Finally, it is too early to tell whether a second animal model will correspond to human malignant hyperthermia, or if a microdeletion will be associated with malignant hyperthermia in patients with dysmorphic syndromes.

When Should Surgical Patients Be Genotyped?

Informed use of the data in the present manuscript, for anesthetic management and counseling of family members at risk, is constrained by the confidence with which the *CACNL1A3* R1086H mutation can be presumed to be causal. Arguments favoring causality for this mutation are based strictly on statistical criteria in the absence of biological evidence. The mutation is described in only one moderate-sized family with a single clinical episode of malignant hyperthermia; the proband could not be analyzed for the mutation; IVCT results are available from just two generations; three of the IVCT results are equivocal; and the "normal" chromo-

somes screened for the mutation were from IVCT-negative patients from other malignant-hyperthermia pedigrees. That the *RYR1* R614C mutation is associated with a similar phenotype in two species argues in support of its causality, but, unless additional animal models of human malignant hyperthermia are discovered, this criterion is too stringent to be met by subsequent mutations. Construction of a transgenic animal for each mutant allele is not feasible, but a comparison of the functional properties of normal and mutant *CACNL1A3* cDNAs, particularly if they are expressed in the presence and absence of triggering agents, will be key to the validation, beyond all reasonable doubt, of the causality of the mutations.

Would a prudent anesthesiologist, given foreknowledge of a causal malignant-hyperthermia mutation segregating in a family, administer a trigger anesthetic to members testing negative for that mutation? I believe not. At present, not only are we ignorant of the total number of predisposing mutations, but the population frequency, new mutation rate, incidence of phenocopies, and extent of penetrance and expressivity for any malignant hyperthermia–associated mutation are unknown. Moreover, alternative anesthetic agents and techniques are available that achieve analgesia, amnesia, and muscle relaxation and maintain physiological homeostasis during surgery, with drugs free of the potential to trigger. Regional anesthesia using local anesthetics for spinal, epidural or direct nerve blockade, or general anesthesia with agents innocent of malignant-hyperthermia potential (e.g., nitrous oxide, propofol, opiates, barbiturates, ketamine, benzodiazepines, and nondepolarizing muscle relaxants) have a cumulative safety record virtually identical to that of the triggering drugs, for most patients and for most surgeries. Choice of anesthetic now hinges more often on price, convenience, training and experience of the practitioner, coexisting disease (e.g., in asthma the smooth muscle–relaxant properties of volatile agents are desired), and restrictions of the surgical procedure (e.g., volatile agents permit spontaneous breathing in bronchoscopic retrieval of intrapulmonary foreign bodies). For these reasons, a ban on the use of triggering agents is unlikely to be a rational option in the forseeable future.

Conversely, in a patient with no family history or other a priori risk of malignant hyperthermia, would the presence of a malignant-hyperthermia mutation known to be causal in at least one other unrelated family override these practical factors in devising the safest anesthetic plan? I believe so. If, as might be argued, the present publication coincides roughly with the halfway point in the search for the genetic alterations predisposing to malignant hyperthermia, and if cost were not prohibitive (i.e., if solid-phase microchip-based PCR was used), would it be worthwhile to screen all patients coming to surgery? Clearly, a patient lacking known mutations is at somewhat less risk than the unscreened population—but also is at risk somewhat greater than zero. Vigilance for early signs of a trigger and immediate access to dantrolene therefore will remain essentials of anesthetic practice, for long into the future. But an individual found to carry one (or more) causal malignant-hyperthermia mutations could benefit in the extreme by selection of an alternative risk-free anesthetic. Estimates of the incidence of known malignant hyperthermia–associated alleles in the general population are crude at present, but barriers to procuring this information are surmountable. The cost of a crisis, long-term care for injured patients, and years of productive life lost to a syndrome that chiefly afflicts the young and fit can be estimated. If savings in morbidity and mortality outweigh the expense of genetic screening, perioperative genotyping for malignant-hyperthermia mutant alleles soon may guide anesthesiologists in judging when to keep their hands off the throttle—and when to pour on the coal.

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