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Malignant Hyperthermia

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History

The first publication describing malignant hyperthermia (MH) concerned a 21-year-old student who had a compound fracture of the right leg. The young man was less concerned about his leg than the risk of general anesthesia, for, since 1922, ten of his relatives had died as a direct consequence of ether anesthesia. He subsequently survived an episode of malignant hyperthermia, and Denborough and Lovell's brief report of accelerated metabolism during anesthesia culminated in a world-wide awareness of the risks of genetic susceptibility to certain drugs and stress.[96] While there had been earlier reports of perioperative hyperthermia, these had been preoccupied with environmental causes and lacked sufficient information to relate these episodes to a specific pathophysiologic entity such as MH.[66,156,290]

Interest in MH in North America began with Locher, in Wausau, Wisconsin,[190] and with Britt, Kalow, and Gordon, in Toronto.[50,51,56,137] Between 1955 and 1958 Locher became involved with the anesthetic care of a family in which 30 members had died in conjunction with general anesthesia. His quest for an understanding of these bizarre incidents led to a relationship with Britt and Kalow, who had experienced several cases of MH in Toronto and were investigating the overall problem. The Wausau amd Marathon County, Wisconsin, area provided a fertile gene pool for Britt and Kalow's systematic human study of MH.[56] Other investigators also contributed to the growing recognition of intraoperative hyperthermia and its possible etiology.[70,349,352,401,415] Evaluation of susceptibility was aided by the recognition of abnormal creatine phosphokinase (CPK) levels by Isaacs and Barlow,[204] and the identification of low-threshold skeletal muscle contracture responses by Kalow and Britt.[227] These pioneering efforts and the unquestioning cooperation of the involved families have made it possible to trace the epidemiology of human MH, to study its pathogenesis and pathophysiology, and to provide safe anesthesia for susceptible patients.

The porcine model of malignant hyperthermia evolved from a report describing pork that was unsuitable for making sausage.[192] Ludvigsen later described a muscular degeneration in pigs, in 1953,[266] and subsequently demonstrated its genetic relationship.[267] This entity became important to swine breeders because the stresses related to slaughter resulted in accelerated metabolism and deterioration of the muscle of susceptible pigs, with the resulting production of pale soft exudative (PSE) pork.[35,106] Unsuitable pork was seldom obtained from normal swine because the time required for slaughter, cooling and processing of the animal was not long enough, nor the me-

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tabolism sufficient, to produce the marked acidosis and higher temperatures peculiar to the susceptible animals.[35,309] The incidence of PSE animals increased with breeding patterns designed to produce pigs with rapid growth rates, good feed efficiency, and superior muscling.[69] This increased incidence led to the term "porcine stress syndrome" (PSS).[219,309,393] Any stress to which these pigs were subjected, *e.g.*, separation, shipping, weaning, fighting, coitus, or slaughter, might lead to increased metabolism, acidosis, muscle rigidity, high temperature, and death. In 1966, Hall reported MH induced by halothane and succinylcholine in stress-susceptible swine.[167] The descriptions of the biochemical processes in PSE[35,309] and PSS[124,181,309,382,393] animals leave little doubt that MH in swine is an anesthetic manifestation of a generalized susceptibility to stress. The porcine models of malignant hyperthermia have provided an ideal means for investigation of the pathophysiology and identification of susceptible individuals.[181,382] Investigations of animal models have helped pinpoint the major metabolic defect, now recognized as being in skeletal muscle.[23,143,181,382] They led to the early therapeutic trials with procaine[176,381] and dantrolene,[178] as well as to the identification of various triggering agents.[181]

While stress and its associated sympathetic responses were known to play a role in porcine MH in the absence of anesthesia,[35,219,309,393] direct sympathetic involvement in inducing human MH was suggested by Wingard[418] at a symposium in 1974. Based upon the higher incidence of sudden death in susceptible families,[417,418] he proposed human myocardial and sympathetic malfunction during the stresses of everyday life. These concepts have led to a closer examination of the role of the sympathetic nervous system in MH in general.[149,265,408]

The Syndrome of Malignant Hyperthermia

While one cannot say that the intracellular or membrane defects responsible for MH are identical in swine and human beings, the extracellular manifestations—changes in vital signs, metabolism, acid–base balance, and temperature—are remarkably similar. Both swine[5,23,24,147,164,181,217,218,264,382,395] and people[50,51,337,349,352,377,415] respond to certain anesthetic agents and drugs with a striking increase in metabolism, both aerobic and anaerobic, resulting in intense production of heat, carbon dioxide,[256] and lactate. Malignant hyperthermia can be triggered by any potent volatile agent,[45,71,94,137,151,166,181,318,415] but the onset is usually more abrupt when succinylcholine is used as the trigger, either by itself[100,152,264,311] or in conjunction with volatile agents.[100,147,164,166,181,264] Once initiated, the response cascades into a fulminant and vicious circle in which body temperature may increase 1 degree C every 5 minutes. It is not uncommon to see a temperature greater than 43 C (109.4 F), an arterial blood carbon dioxide tension greater than 100 torr, and an arterial blood *p*H less than 7.00. This syndrome is generally accompanied by tachycardia and other signs of circulatory and metabolic stress. Almost all pigs[5,23,24,147,151,152,181,217,218,264,382] and about 75 per cent of people[50,137,413] in whom MH is developing show signs of muscle rigidity, which is a contracture rather than a contraction.[51,151,195] A contraction is contractile activity associated with a propagated wave of depolarization; it is brief and reversible. A contracture is nonpropagated, prolonged, and reversible.[150] Active MH results in increased permeability of muscle: increased serum potassium,[23,24,36,50,93,147,151,152,164,217,218,264,327,395] ionized calcium,[12,149,153] CPK,[50,93,217,218,277,318,395] myoglobin,[50,349] serum sodium,[23,24,147,151,152] decreased[36,50,327,352,371] or increased[23,24,36,395] total serum calcium, and marked muscle edema.[50,51] There is probable eventual metabolic exhaustion with a more generalized increase in permeability.[120] Should the episode of MH not be fatal, upon recovery the muscles may be edematous and tender,[23,50,51] and the CPK may take ten to 15 days to return to normal from levels as high as 100,000 units.[50,248] In human beings this syndrome was identified as MH because of the precipitous rise in temperature and because of mortality rates of 60–70 per cent despite symptomatic therapy.[50,241,248,415] Recently (1976) the mortality rate was estimated to be 28 per cent.[39]

The clinical and laboratory findings in human and porcine MH have led to the *theory* that control of intracellular ionized calcium levels[115,330] is abruptly lost, resulting in a rise in intracellular calcium. Increased aerobic and anaerobic metabolism result from attempts to reverse these increases in calcium.[22,26,36,38,51,306,380] Metabolic and respiratory acidosis are consequences of the increases in metabolism, as are the changes in cellular permeability with the associated movement of water, ions, CPK, and myoglobin. The evidence also suggests that MH may involve a generalized disorder of membrane permeability affecting calcium movements.[38,203,337] It is probable that this includes specific enzyme defects that vary in different species or in families within species. These intracellular defects could result in similar extracellular manifestations, *e.g.*, increased metabolism and temperature, acidosis, and sympathetic stress responses. Study of porcine isolated actomyosin suggests that the contractile proteins function normally in susceptible animals.[138] A similar theory explaining muscular dystrophies proposes a slower process, eventually

resulting in calcium accumulation in intracellular organelles, with ultimate dissolution and muscle damage.[102] Confirmation of increased intracellular free ionized calcium levels awaits mammalian application of various intracellular measurement techniques, such as that using aequorin.[27]

Occasional episodes of human MH occur in the absence of significant fever.[25,360] This may be due to the rapid onset of severe acidosis with accompanying acute circulatory failure, or to heat loss greater than production. The former would be associated with profound susceptibility and/or the use of a potent trigger, and the latter would be more commonly expected in young children. With or without increased temperature or acidosis, there must be evidence of increased aerobic or anaerobic metabolism to support the diagnosis of malignant hyperthermia. Increased temperature is usually benign,[126] does not necessarily produce acidosis,[16] and, for example, may be observed in patients with osteogenesis imperfecta with or without anesthesia.[369]

There are several *variant responses* to succinylcholine: 1) muscle contracture, as in myotonia,[83,201,322,332,391] in which the related increase in muscle metabolism is easily tolerated; 2) changes in cellular permeability in the absence of contracture, as observed with loss of CPK and myoglobin;[25,28,284,288,348] 3) an increase in metabolism, as in MH, resulting secondarily in contracture and increased permeability.[152,264] Myoglobinemia and increased CPK values induced by nonanesthetic drugs or stress that are not associated with changes of metabolism or temperature are considered[288] at most a variant unrelated to MH (an "abortive" form).[25,284] Even in normal patients, release of CPK and myoglobin from muscle cells results from the use of succinylcholine.[281,348,386] This is exaggerated in the presence of halothane[3,13,25,200,385] and attenuated by *d*-tubocurarine.[387] Loss of CPK and myoglobin may be pronounced in some individuals subjected to anesthesia,[13,201,284,288,355] other drugs,[235,366] or exercise stress.[199,244] While it is rare for anesthesia to produce such an uncontrolled state, other conditions that predispose to or resemble this loss of control include porphyria,[374] thyroid storm precipitated historically by surgery and anesthesia,[376] the catatonic state produced by ketamine,[374] and hyperkalemia following succinylcholine administration.[150]

Specific Tissues and Organs

Skeletal Muscle

Myopathy. Most MH-affected people and their families appear normal and lead an active life, and their myopathy is detectable only by specific testing;[54,56,92,171,202,204,206,207,209,211,232,294,337–339,375,392] however, some have obvious musculoskeletal abnormalities.[206,242,375,392] It has been suggested that some disorders of muscle, such as muscular dystrophy,[29,136,230,236,284,402] myotonia,[83,286,322,332,352,391] and central core disease,[91,116,125,208] may result in susceptibility to MH, but there is insufficient (and conflicting)[116,284] evidence to confirm their direct association with MH.[51,56,202] Central core disease is a benign congenital myopathy in which longitudinal foci devoid of mitochondria or of oxidative enzymatic activity extend virtually the entire length of the fiber.[125] These cores may resemble targetoid fibers, which are seen more frequently in MH muscle.[172] An extensive histologic study of susceptible families did not disclose evidence of central core disease.[170,172]

Muscle CPK values, when determined in a resting, fasting state without recent trauma, generally reflect muscle membrane stability and are elevated in about 70 per cent of affected people[1,41,47,93,112,171,185,204,205,207,425,426] and most swine.[6,106,187,217,395,404,423] Some prefer determinations of pyrophosphate in testing for myopathy, but data are insufficient to confirm its superiority over CPK.[4,388,396] Pyrophosphate levels may rise with hypermetabolism or increased production of cyclic adenosinemonophosphate (AMP),[388] but this reasoning does not account for its elevation at rest.

Susceptibility in swine is particularly associated with breeding for accentuation of certain muscle groups, as well as for rapid growth and development to marketable weight. This inbreeding has apparently altered muscle enzyme or membrane responses.[69,251,309,393]

Histologic examination of porcine and human susceptible muscle discloses either no abnormality or protean nonspecific pathologic changes that are so variable that one cannot determine whether they are primary or acquired.[170] The fact that they are not seen in children less than 5 years old,[170] or in swine,[316,397] which are marketed at a young age,[316] in general, suggests that the various morphologic changes are acquired.[92,170,171,202,204,209,210,316] A freeze-fracture study proposes that the initial changes may involve phospholipids.[358] Histologic changes include internal nuclei, moth-eaten fibers, supercontracted myofibrils, and less often, target fibers, marked variation in fiber caliber, necrosis and regeneration, mitochondrial rupture and inclusion bodies.[7,170–172,186,202,204,209,338,339,357,375]

Muscle *contracture* responses, determined in studies of biopsy specimens of muscle fragments,[8,9,14,40,45,48,54,113,114,131,140,224,226,227,254,293,295–297,300–304,312] intact tendon-to-tendon muscle fibers,[130,131] or skinned fibers,[384,422] confirm the presence of abnormal re-

sponses in skeletal muscle from susceptible people or swine. The amount of tension developed by fragment specimens is much less than that developed by intact fibers,[131,297,350] but the latter are rarely obtained from human beings,[350] and responses of the two are qualitatively similar for swine[131] and people.[297] However, responses may vary due to differing involvements of various muscles within the same pig.[131,251] Exposure to any of various drugs in a temperature-controlled bath demonstrates an increased sensitivity or decreased threshold in susceptible muscle. These drugs include caffeine, halothane, their combination, potassium, and succinylcholine. While these tests have been relatively standardized, there are differences in results from various laboratories throughout the world.[203] For example, muscle contractures with halothane occur reproducibly and reliably in several laboratories,[8,9,14,32,113,114,293,295,296,300–304,312] but inconstantly in others.[54,140,224,226,227] Similarly, there are differences in results with caffeine, or with the combination of caffeine and halothane, in that some laboratories have reproducible and reliable results[54,140,224,226,227,312] and some have greater variability.[8,9,14,113,114,293,295,296,300–304]

Britt *et al.*[48] suggest that this variability is associated with gradations of clinical MH. Thus, muscle from patients with severe episodes of MH developed contractures upon exposure to halothane alone, as well as to caffeine alone and to halothane–caffeine. Muscle from patients with moderate episodes developed contractures with caffeine alone and with halothane–caffeine, and muscle from patients with mild episodes developed contractures only when exposed to halothane–caffeine. They relate these variations to a genetic spectrum[48,223] of susceptibility. Unfortunately, they do not correlate specific contracture responses with the clinical MH data, admittedly difficult and tedious, but necessary for support of their proposal. Furthermore, episodes of MH in swine vary in relation to adjunctive drugs[151] or prior exercise,[21,395] suggesting that genetic predisposition may be considerably modified by environment.

The lower threshold to potassium-induced contractures in susceptible muscle[131,294,312] suggests a lower mechanical threshold as a part of the disorder of MH. Results with succinylcholine are puzzling. Denborough's laboratory is consistently able to identify susceptible muscle contracture responses using succinylcholine.[14,294,312] However, others do not observe contractures in biopsy specimens exposed solely to succinylcholine.[226] One would not expect chemical depolarization of a specimen dissected to several bundles and mounted in an organ bath, because of the absence of end-plate areas and the associated chemically sensitive membrane of the receptor sites.[150] Ellis' laboratory combines succinylcholine with caffeine to provide the graded response lacking in their halothane-induced contractures.[169]

Kalow and Britt differentiate MH into two types, rigid and nonrigid, based upon gross observation of skeletal muscle tone during MH in human beings,[50,227] and supported by differing contracture responses.[224,226] They correlate this distinction with caffeine- and caffeine–halothane-induced contracture threshold responses that are significantly less than (rigid) or greater than (nonrigid) the threshold responses of normal muscle.[226] Clinically, the nonrigid cases differed from the rigid ones, manifesting *e.g.*, an absence of tachypnea, tachycardia, dysrhythmias, cyanosis, and acidosis.[50] Kalow and Britt also base their expanded and more complex genetic analysis in part upon the variations in contracture responses.[48,225,226] Other investigators support the concept of decreased thresholds in people and swine for MH susceptibility in general, but have not observed a correlation with thresholds greater than normal in patients whose episodes of MH do not include rigidity. However, not many laboratories have examined as many caffeine-initiated contractures as have Kalow and Britt, and interlaboratory comparisons may therefore not be valid. Nonetheless, Kalow and Britt's large variability in normal threshold responses is inconsistent with their theory of nonrigid MH in association with above-normal contracture thresholds. They estimate the normal caffeine threshold as 8 mM,[226] but their thresholds for known normal muscle range from 2[226] to 32 mM[197] caffeine, or more. The latter value is greater than that specified in their definition of nonrigid (insensitive) caffeine-induced responses.[226] This degree of variability has not been found in other examinations of normal thresholds.[141, 295, 304] Rather than invoke additional genetic differences, the author believes that all MH is potentially rigid, but that there are modifying factors (also suggested by Kalow and Britt[223]), and that muscle tension is ultimately related to intracellular calcium levels,[115] energy stores,[87] genetically determined responses of specific enzyme systems or membranes, the potency and duration of the initiating agent, modification by treatment, and probably other environmental factors not yet identified. Metabolism can be greatly increased by intracellular free–ionized calcium levels that are insufficient to activate contractile mechanisms to the point of observable rigidity.[27,79,368] One could argue that the nonrigid episodes reported by Britt may not have been MH

at all, for the laboratory data suggest that metabolism was not increased and that there was no acidosis,[50] *i.e.*, the hyperthermia was due to some other factor.

Measurements of depletion of adenosinetriphosphate (ATP) as an adjunctive test of susceptibility were introduced by Harrison from study of swine,[181] based on the premise that the greater metabolism in the halothane-triggered MH muscle results in a greater reduction in energy stores as compared with normal halothane-exposed muscle.[23,24,81] Pieces of muscle weighing 100–300 mg are exposed to either carbogen or carbogen plus halothane in an organ bath at 37 C for 30–45 minutes, following which they are assayed for ATP. Some,[46,181,310] but not all,[140] laboratories have found that determination of the ATP depletion ratio is a valid test for differentiating susceptible from normal human beings or swine. There may be considerable variation in individual values, making interpretation difficult due to overlap of values between normal and susceptible individuals.[140] Since the bath provides substrates and oxygen, normal muscle should maintain energy stores better than should susceptible muscle. However, the central core of the muscle is probably poorly supplied with oxygen and other substrates, and the muscle bundles may be damaged during preparation. Assay values thus may be skewed downward a variable amount. Values of ATP depletion probably fluctuate more due to experimental than due to biologic variability.

The *metabolic responses* of susceptible skeletal muscle are also greater than those of normal muscle, in both *in-vivo* and *in-vitro* preparations. Virtually all of these studies are necessarily in swine, and the susceptible responses are equivalent in a variety of preparations. The responses include approximately threefold increases in oxygen consumption, increases in circulating lactate to as much as 30 μm/ml (15–20-fold) and associated acid–base imbalances.[5,81,143,147,149,151,152,264,395]

The earliest detectable changes in MH appear in the venous effluent from skeletal muscle, as decreases in pH or P_{O_2} or as increases in P_{CO_2}, lactate, potassium, or temperature.[133,151,264] These changes in muscle metabolism and acid–base balance have profound effects upon the systemic circulation, because skeletal muscle comprises about 40 per cent of body weight. Careful examination of the time courses of these changes has shown that the increase in lactate occurs before there are obvious signs of tissue hypoxia, as evidenced by decreases in venous effluent P_{O_2}. These presumed nonhypoxic increases in lactate indicate greatly increased energy demands, for a decrease in ATP tends to alter the balance between NAD and NADH (oxidized and reduced forms, respectively, of nicotinamide adenine dinucleotide), forcing an increase in lactate production.[22–24,151,228] The increase in aerobic and anaerobic metabolism has been shown to occur prior to the increases in temperature, heart rate, and circulating catecholamines.[151,259,264] When the increase in metabolism is halted (by specific treatment of MH in swine,[148] or following a period of severe exercise in a healthy person[30]), blood lactate slowly returns to normal over a period of approximately 30 minutes.[30,148] The metabolic acidosis during porcine MH is primarily due to lactate production,[23,24,146–149,151–153,264,395] and individual case reports indicate that lactate is also the main factor in the metabolic acidosis of human MH.† One study of isolated human muscle fibers did not demonstrate increased lactate production upon exposure to halothane, but the reasons for this difference are unknown.[20] Increases in aerobic metabolism of skeletal muscle that are extrapolated to the whole body agree with observed increases in whole-body oxygen consumption, and support the premise that these are due solely to increases in skeletal muscle oxygen consumption.[143] However, the increases in oxygen consumption are smaller than the maximal increases possible, such as those seen in exercise,[342] and are paradoxically small considering the measured acid–base and temperature aberrations. Possible explanations for this are discussed under Mitochondria.

Sources of *heat* during active MH include aerobic metabolism, glycolysis, hydrolysis of high-energy phosphates involved in ion transport and contraction–relaxation, and neutralization of hydrogen ion.[23] Heat production in porcine MH is initially accounted for by increased aerobic metabolism and later, as aerobic metabolism decreases, by lactate production.[23,24,158] Precise calculations are difficult,[87] in part due to unsteady metabolic and circulatory states, measurements in only a few animals, variable and uncontrolled heat losses, and production of heat by neutralization of acid.

In examining *mitochondria* isolated from skeletal muscle, investigators have found various differences in mitochondrial function in susceptible people or pigs as compared with normal individuals. Some of these differences may be due to technique: study of pigs[24,43,62,75–78,95,108,142] or human subjects[52,54]; temperature of 25 C,[52,54,62,75,108] or 37 C[62,76–78,142]; measurement of calcium release in the absence of oxy-

† Kolb ME: Norwich Laboratory evaluation of intravenous dantrolene in humans (personal communication).

gen[75,77,78]; measurement of the concentration of halothane in liquid medium.[142] Several investigators have compared values between susceptible and known healthy subjects,[52,54,76,108,142] but others have not mentioned values from healthy subjects,[24] have not identified screening methods,[43,62,75,95] or have compared values with those obtained from unrelated swine rather than littermate normals.[43,62,75,78]

In human subjects, Britt *et al.*[52,54] found no difference between normal and MH mitochondria in regard to respiratory function, and halothane decreased state 3 respiration (oxygen consumption in the presence of a phosphate acceptor, *i.e.*, adenosinediphosphate, ADP) similarly in both. In contrast, the same group[43] reported increased respiratory function in mitochondria from MH pigs and decreased capacity for calcium uptake. Denborough *et al.*[95] found no difference in mitochondrial respiratory function between normal and MH-susceptible Landrace pigs, but, in comparison with unrelated pigs, exaggerated depression by halothane. Several groups[24,62,76,108,142] have in general found reduced respiratory and calcium-binding activities of MH porcine mitochondria. Some of these investigators also saw depressant effects of halothane upon NAD-dependent respiratory function,[24,62,108] without evidence for calcium release by halothane.[142] Cheah and Cheah reported that halothane enhanced calcium efflux from MH mitochondria under anaerobic conditions[75,77,78]; this is probably not related to initiation of MH, but could be a factor in the full-blown syndrome.

These reduced mitochondrial functions do not explain the functional and metabolic derangements observed in MH, but they are consistent with the proposal that MH is a myopathy. Reduced mitochondrial respiration is a feature of muscular dystrophy[324] and of experimental dystrophy such as that due to vitamin E.[273] Also, abnormal mitochondria have been observed in ultrastructural examination of human MH muscle.[186,198,202,210,357] The mitochondrial alterations are probably nonspecific manifestations of the disease process. Mitochondrial uncoupling had initially been proposed as a cause of MH,[416] but this has been theoretically[401] and empirically[51,142] discounted. Animal models based on uncoupling are discussed on page 408.

The diminished aerobic response[23,24,143,146,147,151,152,264] in MH, in the face of apparent marked demands for energy, is not explained by the mitochondrial deficiencies. Differences in muscle type also do not explain this aerobic deficiency. White (fast) and red (slow) muscle differ in regard to capillary structure and aerobic capability: white muscle is more dependent upon glycolysis for increased energy demands, and accordingly has a more sparse capillary network.[123,282,334] However, these muscle types are apparently equally affected in porcine MH, and histologic evidence does not support the involvement of white (fast) muscle in MH.[7,84,353] The porcine longissimus dorsi muscle lumbar segments[251] and forelimb extensor muscles,[131] respectively, show greater MH abnormalities than do thoracic segments[251] and intercostal muscles.[131]

Evaluation of the function of the *sarcoplasmic reticulum* (SR) is complicated by the use of a variety of techniques examining a physiologic process the mechanism of which is not yet known, and which involves release and reaccumulation of calcium so rapidly as to make difficult accurate measurement.[115] Also, calcium binding to SR vesicles isolated from skeletal muscle is assumed to reflect the calcium binding affinity of intact SR, although isolation itself may somehow alter function.[115] Nonetheless, SR binds calcium at accepted physiologic concentrations more effectively than do mitochondria, suggesting that the latter have at most a reserve function in this regard.[115,142,144] Calcium binding by SR is estimated by the rate and capacity of calcium accumulation in the absence of oxalate. However, the performance of these vesicles does not approach that of intact SR; this deficiency is corrected in part by oxalate.[115,144] When oxalate is added to the medium, the duration of binding, as well as the capacity, is greatly increased, and it is called calcium uptake for isolated vesicles of SR under these conditions. It bears no relation to the mechanism or character of calcium "uptake" by SR *in situ*.[144] Calcium release is difficult to measure because of problems inherent in loading SR with sufficient labeled calcium.[144]

As with mitochondrial data, varying results have been reported for SR functions.[24,44,54,63,95,98,100,144,186,210,211,227,280,303,310,347,378] This may be in part because most investigations have used calcium concentrations above the estimated physiologic range. In most studies, SR transport functions for calcium appear to be diminished in both human and porcine susceptible subjects, but, as with mitochondria, the differences from normal may not be large. Calcium binding and uptake are diminished about a third in susceptible pigs compared with normal pigs,[144,186,303] and halothane stimulates calcium binding in both normal and susceptible isolated SR in concentrations of about 0.5 to 1 per cent.[144] Halothane progressively depresses binding of both types of SR as the concentration is increased above clinical levels. Release of calcium by MH and normal SR is minimal with clinical concentrations of halothane, and marked with concentrations above clinical levels.[98,144]

These findings in regard to intracellular organelles are consistent with the diagnosis of a myopathy;

however, they do not reflect changes severe enough to account for the MH syndrome, nor does the effect of halothane explain its triggering action.[144] The specific action of dantrolene in preventing or reversing MH suggests that the lesion in MH is in part located at the link between the transverse tubule and SR, the terminal cisterna of the SR, or both.[60,289,300]

Examination of function of porcine *muscle cell membranes* also discloses differences between normal and susceptible muscle.[130,155] Halothane acts beyond the neuromuscular junction[300]; it produces contractures via mechanisms apparently involving surface membrane calcium equilibria.[155] It produces a depolarization, 5–10 mV, of susceptible skeletal muscle, but not of normal muscle (with one reported exception in the rat),[234] and this depolarization is returned towards the resting potential by dantrolene.[130] This finding suggests a common mode—depolarization—of initiating MH by volatile agents and succinylcholine. One would not expect a small depolarization, in contrast to the greater depolarization by succinylcholine, to reach mechanical threshold (fig. 1) and start the chain of events leading ultimately to contractile activity. However, susceptible porcine muscle has a lower mechanical threshold than does normal muscle,[64,294,312] implying that slight depolarization is sufficient to initiate contractile activity. I cannot speculate as to the mechanism by which this abnormal response triggers MH at the level of the SR.

In most evaluations of MH or of the metabolism of stress responses, the muscle is a "black box," and one cannot infer where specific enzymatic disorders may be located. These could involve calcium pumps or adenylate-cyclase and cyclic AMP mechanisms.[38,327,380,414] Variations from normal may not be functional and detectable unless MH has been triggered,[121] and measurements of muscle metabolites provide valid clues[87] only when the muscle biopsy specimen can be frozen rapidly, *e.g.*, using supercooled clamp forceps.[245] Several investigators have examined mechanisms of abnormal metabolism. In a family with a history of two deaths due to MH, Schmitt *et al.* demonstrated adenylate kinase deficiency within skeletal muscle biopsy specimens, but not within erythrocytes, of two of four close relatives.[361] Adenylate kinase reversibly catalyzes the reaction 2 ADP ↔ ATP + AMP.[407] If its action is adequate, increased muscle metabolism should result in increased tissue levels of AMP; if inadequate, increased levels of ADP. While intracellular pathophysiologic mechanisms in susceptible human beings and swine may differ, the only data that define adenylate kinase function, albeit indirectly, are porcine. Neither ADP nor AMP levels were elevated during MH,[81,228] leaving the question unanswered. These porcine studies also demonstrated

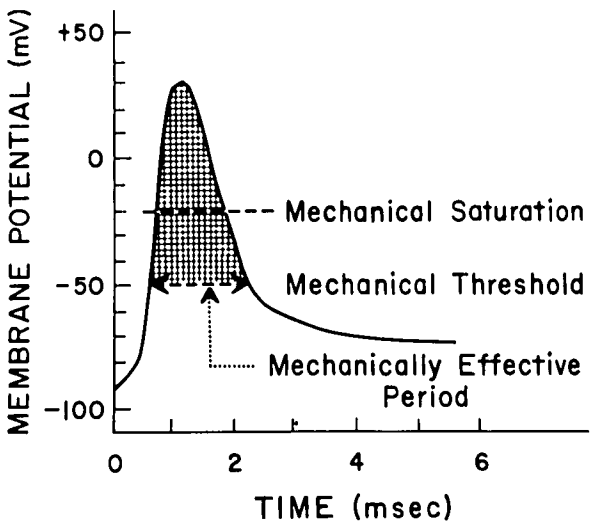

FIG. 1. Mechanical threshold is the membrane potential at which just-visible muscle contraction occurs. In normal muscle this requires a depolarization from the resting potential of approximately −90 mV to −50 mV. In susceptible porcine muscle the mechanical threshold is decreased, perhaps to −70 or −80 mV. A modest depolarization by halothane of about 10 mV approaches the mechanical threshold and can stimulate muscle metabolism. (Reprinted from Fed Proc 24:1116–1123, 1965, with permission.)

stimulation of glycolysis, in particular accelerated substrate cycling, as a possible mechanism for markedly increased heat production.[81] This occurs normally in bumblebee flight muscle, whereby metabolic recycling of fructose-6-phosphate warms muscles to temperatures efficient for flight.[80]

All of the above-mentioned responses of skeletal muscle, while decidedly greater in susceptible than in normal swine, probably represent an exaggeration of normal, rather than different, responses.[291] They occur more readily with greater environmental stress, *e.g.*, the incidence of slaughter PSE muscle is greater in summer than in winter[35]; halothane produces more marked or quicker changes after exercise[21,395]; PSE muscle develops more rapidly when the animal is exercised prior to slaughter.[35] Similar reactions occur in the so-called capture myopathy (overstraining disease) of wild animals after prolonged chase.[183,184]

Other Tissues and Organs

Heart. Myocardial function is altered during human and porcine MH, as evidenced by the early appearance of tachycardia and dysrhythmias and, later, by hypotension, declining output, and eventual cardiac arrest. Myocardial physiologic abnormalities during porcine MH include a fivefold increase in myocardial oxygen consumption and an eightfold decrease in myocardial efficiency, as measured using a right-

heart-bypass preparation.[153] These changes were mediated by beta-sympathetic agonists, as they were blocked by continuous infusion of propranolol, 40 μg/kg/min. This study did not evaluate comparative responses to beta stimulation of heart muscle specimens from normal and susceptible animals, and therefore one cannot state whether these beta-mediated changes were a normal adrenergic response to marked stress or an exaggerated adrenergic effect due to a myocardial abnormality. However, the heart did not show evidence of active MH, as there was neither myocardial lactate production nor potassium loss during whole-body MH.

Specific myocardial abnormalities have been found in three people who died during malignant hyperthermia.[119] The case histories are incomplete with reference to agents and drug therapy, but all apparently died during hyperthermia, acidosis, shock, and hyperkalemia. The combination of these factors is not often seen at death, and one wonders to what extent these account for the subsequent findings of fiber lysis, sarcolemmal disruption, and contraction bands adjacent to areas of over-stretching. Myocardial histologic features of other MH nonsurvivors have been reported to be normal.[337]

While the heart could be primarily involved in MH because of its similarities to skeletal muscle, cardiac function would be expected to be altered in MH because of activation of the sympathetic nervous system and the associated increase in circulating catecholamines.[147,151,152,259,264,395] Pigs and people maintain remarkable cardiovascular stability during active MH,[264] but episodes of sudden death in members of susceptible human families[418,421] and otherwise unexplained nonspecific cardiomyopathies and abnormal thallium scans have been suggested as evidence of direct myocardial involvement.[40,197] Cardiac abnormalities or dysfunction may occur during periods of emotional stress, or secondary to sympathetic hormones,[65] but one cannot differentiate primary changes in human myocardial function from those that might have occurred secondary to adrenergic stimulation during otherwise undiagnosed stress-induced MH in the absence of anesthetic drugs (see below for awake human MH). The associated sympathetic stimulation might alter cardiac function in any one of several ways,[65] *e.g.*, acute dysrhythmia, nonspecific cardiomyopathies or coronary vasospasm[193,255] in the event undiagnosed episodes occurred intermittently and repeatedly in awake human beings.

Central nervous system. Involvement of the central nervous system during human fulminant MH appears to be secondary to increased temperature, acidosis, hyperkalemia, and hypoxia.[36,50,248,249,337,352] The extreme clinical picture resembles acute cerebral edema with coma, areflexia, unresponsiveness, and fixed dilated pupils.[72,88,233,349] There is a variable recovery, which appears to be related to early diagnosis and the severity of the MH episode. A severe fever may result in a virtually flat electroencephalogram and coma, but recovery is still possible.[67] A most unusual response to succinylcholine, given during controlled observations, has been observed in a single susceptible child. It resulted in the acute onset of upper motor neuron lesions.[248,249] This patient was given 5 mg succinylcholine (0.1 mg/kg) injected into one arm isolated by a tourniquet: the succinylcholine produced apparently normal relaxation. When the tourniquet was deflated, fasciculation occurred, and the patient became apneic, with development of hypertonicity of the legs, hyperactive tendon reflexes, and extensor plantar reflexes. The latter neurologic findings gradually disappeared over the next 48 hours. Succinylcholine crosses the blood–brain barrier with difficulty, if at all, and it is therefore hard to explain these results.

Histologic examination of human muscle has disclosed signs of neurogenic atrophy in intramuscular axons with degenerating and regenerating fibers; other neural abnormalities are suggested by fiber-type grouping and targetoid fibers.[186,202,210,232,248,249,337–340] Although early data suggested that the increase in CPK was predominantly of the BB (brain) isoenzyme,[336,373,425,427] an indication of neural involvement, more recent reports fail to confirm this, and describe increases in CPK primarily of the muscle type.[1,185,277,283]

Britt *et al.* using the technique of motor unit counting in peripheral muscles, have found lower values in a high proportion of susceptible human subjects.[57] Unfortunately, the interpretation of these differences is complex. The technique of motor unit counting has yet to win general acceptance[325] and, in their paper, the actual data are blurred by statistical methods and difficult to evaluate accurately. Because of these studies suggesting motor nerve dysfunction that could include denervation of muscle, Moulds compared abnormal responses of denervated mice and human MH-susceptible muscle.[292] He found that the corresponding abnormalities were different, in that the effect of denervation was limited to the development of extrajunctional cholinergic receptors, while the abnormality in MH muscle occurred at a later step in the excitation–contraction coupling mechanism.

Kerr, Wingard and Gatz suggested that the nervous system plays a role in porcine MH because epidural anesthesia in susceptible swine prevented muscle

rigidity induced by halothane in the anesthetized limbs, but did not prevent rigidity in the unanesthetized limbs.[238] Other studies contradicted these data, in that conduction anesthesia did not prevent the metabolic changes induced by halothane.[149] Discussions with Wingard‡ have disclosed that mechanical stimulation, *e.g.*, incision or needle puncture, resulted in immediate rigidity in their pigs, suggesting that the prevention or delay of halothane-induced rigidity by epidural anesthesia did not signify blockade of MH responses.

Brain involvement during MH is unlikely, for *in-vivo* measurements of porcine cerebral oxygen consumption and lactate production show no increase during whole-body MH.[12] Other evidence against neural initiation of MH is provided by the lack of rigidity in a limb isolated by a tourniquet during episodes of human whole-body MH otherwise associated with rigidity.[101,354]

Sympathetic nervous system. Controversy exists as to whether sympathetic responses are abnormal in MH, and whether they help to initiate MH.[139,149,260,265,408,409,417,418,421] The sympathetic nervous system is obviously intimately involved with MH, as evidenced by the following: 1) MH develops in stress-susceptible pigs[35,69,309,393]; 2) the "fight, fright or flight reaction" can initiate an episode in swine in the absence of triggering anesthetic agents[35,309,393]; 3) typical signs of sympathetic stimulation are observed during active human and porcine MH.[35,353] Circulating epinephrine and norepinephrine increase markedly during MH from control levels of less than 1 ng/ml to levels as high as 30 ng/ml; however, these levels increase following the changes in metabolism and acid–base balance,[147,151,264,395] and their elevation is not essential to the development of halothane-induced MH.[149] They probably produce the hyperglycemia and the early,[164] but not the late, hyperkalemia; the later rise is apparently due to efflux from muscle.[151] Potassium efflux from muscle occurs much sooner when the course of MH is rapid, *e.g.*, with the use of succinylcholine.[147,152]

Under certain circumstances, sympathetic agonists trigger what appear to be legitimate episodes of MH in susceptible swine. Alpha-agonists were more effective as a trigger than were beta-agonists, and the single clear instance in which an alpha-agonist, phenylephrine, was demonstrated to initiate MH also gives a clue as to why the mechanism appears to be secondary.[162] Earlier studies from the Bristol laboratory had shown that the initiation of MH by succinylcholine resulted in an increase in lactate production prior to an increase in temperature.[264] In the study involving phenylephrine, the rise in muscle temperature preceded the increase in lactate.[162] This strongly suggests that the mechanism was due to muscle or cutaneous vasoconstriction, resulting in ischemia or decreased heat loss. Thus, hypoxia[262,353] or increased temperature[124,146,221,270] may have produced the MH response in susceptible muscle.

Williams also argues for sympathetic activation of MH, via vasoconstriction by norepinephrine.[408] The mechanism would be expected to be physical, that is, changes in blood vessel diameter and perfusion, with secondary effects upon muscle oxygen supplies and heat loss. This is supported by the recognition of the triggering action of hypoxia[262,353] or of increases in temperature *per se*.[124,146,221,270] Williams believes that awake susceptible pigs are hypertensive[412,413] and always produce more heat due to their constantly greater metabolism,[410,411] and that this is generally counterbalanced by greater heat loss. A vasoconstrictive event "tips the balance" in favor of heat retention,[299] followed by increased temperature, and progression into the cascade of events leading to fulminant MH.[299,309] Other investigators have not observed greater basal oxygen consumption in sedated susceptible swine as compared with normal swine,[147,151,152,264,383] suggesting that the unusual experience of being placed in a whole-body calorimeter while awake may evoke stress responses in the susceptible animal.[410]

Further examination of sympathetic initiation of MH involved the use of the alpha- and beta-agonists, phenylephrine and isoproterenol, in an isolated perfused preparation of porcine skeletal muscle.[146] Phenylephrine did not increase either oxygen consumption or glycolysis, but did result in tissue edema at roughly similar doses in both susceptible and normal muscle. Isoproterenol did not increase oxygen consumption of either susceptible or normal muscle, but did similarly increase lactate production in both. Others also observed that beta-agonists did not trigger MH[181] or result in PSE muscle.[35] There are thus no indications of differing responses to sympathetic agents.

The use of sympathetic antagonist drugs has suggested protection or amelioration during episodes of MH,[35,259,261–263,266,408,412] by lowering temperature and modifying the acid–base changes. However, not all studies have demonstrated this,[181,405] and, in those that did, large doses of alpha-antagonists and/or adrenalectomy were necessary to provide variable protection.[259,261,263,408,412] This improvement has been somewhat uniformly interpreted as an effect upon

‡ Personal communication.

"sympathetic-induced MH."[259,260,265] However, alpha-antagonists may increase heat loss and can potentially increase muscle perfusion by eliminating alpha-agonist-induced vasoconstriction, thus minimizing ischemic hypoxia. Beta-antagonists have attenuated metabolic and temperature responses, but insufficiently to improve survival.[181,261] In large doses, they completely block the stimulation of myocardial metabolism observed during porcine MH.[153] However, the mechanisms of these modifications appear to relate to recognized actions of propranolol in blocking beta-mediated stimulation of the myocardium and beta-induced vasodilation[18] or stimulation of glycolysis[146] in skeletal muscle. Effects upon muscle blood flow during MH are indirectly supported by the observation of decreased vascular resistance during isoproterenol infusion in perfused isolated skeletal muscle.[146]

Evidence against sympathetic initiation of porcine MH during anethesia is provided by a study utilizing total spinal blockade.[149] The accompanying sympathetic denervation failed to affect the onset, development, or characteristics of halothane-induced MH, while the increases in circulating epinephrine and norepinephrine were completely blocked.

Neurotransmitters and relaxants. Carbachol, a long-lasting laboratory equivalent of acetylcholine, has effects similar to those of halothane and increased temperature *per se* upon isolated perfused porcine skeletal muscle, *i.e.*, it increases oxygen consumption approximately threefold and stimulates lactate production markedly.[146] Succinylcholine is structurally related to acetylcholine and also has similar effects.[152] An earlier study did not demonstrate this stimulation by succinylcholine, but that was apparently due to measurement of muscle tone and temperature without associated measurements of metabolism and acid–base balance.[309] Nondepolarizing relaxants such as *d*-tubocurarine and pancuronium block the effects of succinylcholine or carbachol§ in triggering MH, but do not block the triggering effects of halothane.[160,173,176] Other studies in intact swine have suggested delay or attenuation of the effects of halothane by nondepolarizing relaxants,[160] but similar delay has been observed with thiopental[151] and the mechanisms are unknown. Pancuronium has been suggested as a trigger in porcine MH, but the concomitant use of halothane in that study makes that interpretation highly unlikely.[74] One case report[403] discusses the possible role of pancuronium in triggering human MH, but this seems unlikely, as it has been used in many susceptible patients without triggering MH. See below for discussion of curare as a trigger in MH.

§ Gronert GA: Unpublished data.

Splanchnic viscera. Increases in hepatic temperature in pigs had suggested that heat production in MH began in the liver, implying a direct involvement of hepatic metabolism.[23,24,36] Measurements of metabolism[58,164,177] of perfused liver *in vitro* and of splanchnic oxygen consumption and lactate production *in vivo*[143,164] contradict this initial impression. Stimulation of splanchnic or hepatic metabolism during exposure to MH triggers was not observed; splanchnic blood flow and metabolism decreased as whole-body MH progressed.[143] However, decreased function has been found in liver tissue from susceptible as compared with normal animals, whether the swine were stressed[99,117] or not[89] prior to death. Findings in the latter study rule out stress responses and the associated decrease in splanchnic blood flow as a cause of the diminished function. The relationship of structural differences in mitochondria of livers from susceptible and normal pigs[63] to these functional differences is not known.

Blood. Abnormal membranes of human or porcine blood cells have been inferred from findings showing variations in permeability[424] or fragility.[77,182,232,337,370] Normally, platelet ATP stores may be depleted during ADP release associated with aggregation.[406] Initial data suggest that halothane may increase ATP depletion in platelets from susceptible people but not in those from normal people,[61] an effect similar to ATP depletion in skeletal muscle. Present data are insufficient to permit estimation of the reliability of platelet ATP depletion as a screening test for susceptibility. Abnormal coagulation during fulminant MH is discussed under Treatment.

Pulmonary. Pulmonary changes during MH include tachypnea, hyperventilation, $\dot{V}/\dot{Q}$ abnormalities, increased arterial blood P_{CO_2}, decreased arterial blood P_{O_2}, and ultimately, pulmonary edema.[23,24,50,70,147,181,217,218,264,275,337,349,352,354,382,395,413] Increased Pa_{CO_2} is due less to pulmonary failure than to increased CO_2 production. In fact, when cardiac output decreases late in MH, $\dot{V}/\dot{Q}$ may be well matched with efficient CO_2 removal. This is demonstrated in figure 2, where mixed venous blood P_{CO_2} had reached 124 torr at a time when Pa_{CO_2} had decreased to 55 torr. In this situation, whole-body carbon dioxide stores are better reflected by mixed venous blood P_{CO_2} than by Pa_{CO_2}.[146,151]

Renal. Renal function during active MH has been evaluated only indirectly; the oliguria and anuria appear to be secondary to shock, ischemia, cardiac failure, myoglobinemia, and myoglobinuria.[349,352,354,413]

Endocrine. Data suggesting that altered human membrane responses may affect calcium transients are provided in the reports that susceptible patients showed a greater increase in plasma insulin concen-

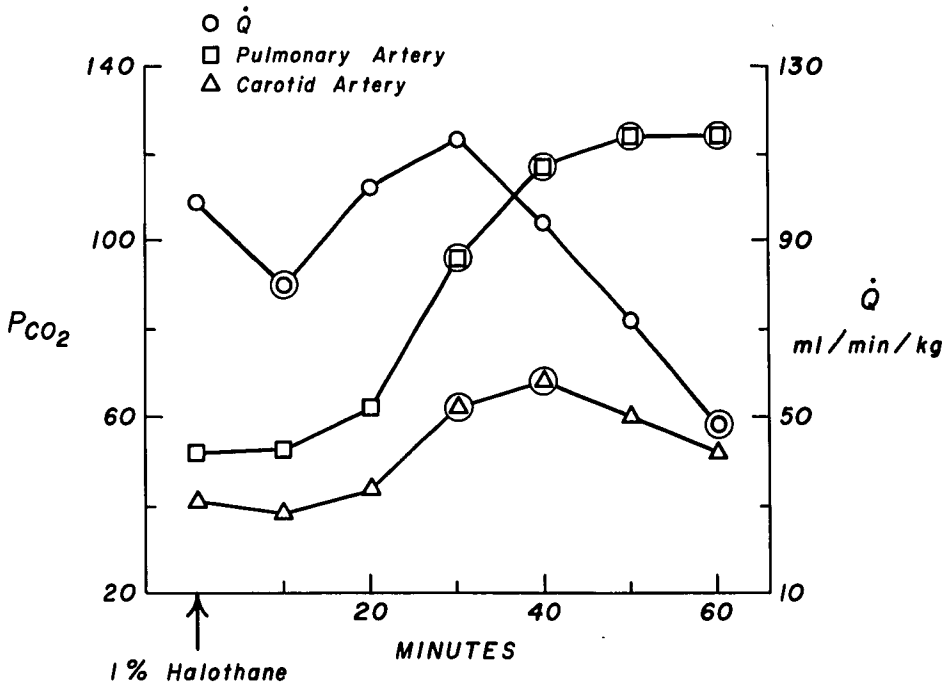

FIG. 2. $\dot{Q}$ and P_{CO_2} of MHS swine with halothane. During fulminant MH and incipient cardiac failure, arterial blood carbon dioxide decreases while mixed venous blood carbon dioxide (pulmonary artery) is still elevated.[151]

trations following a glucose load than did normal patients,[97] and that diabetic MH-susceptible patients may have diabetes that is more difficult to control.[321] While hyperglycemia occurs during active MH, probably due in part to catecholamine effects,[154,164,217,218,264,395] insulin levels remain low to slightly increased; this may be secondary to the associated increase in catecholamines.[164,165] Data from swine evaluating endocrine function initially suggested partial adrenocortical insufficiency.[219,220] Further studies demonstrated adequate adrenocortical function[165,269–272] with increased turnover of cortisone in susceptible animals.[271] This seems likely to be related to exaggerated responses to the stress of handling and sampling that would not be observed in stress-resistant animals. Thyroid function in susceptible animals has been reported as both increased[105] and diminished[35,219,220,258,266]; in one of these studies cautious administration of triiodothyronine was reported to increase survival in stress responses.[258] In these animals, MH was triggered solely by succinylcholine, there were no control animals, and triiodothyronine had a low margin of safety; therapeutic applications appear unfeasible. The catecholamine activity may also diminish thyroid function.[259]

Bone. The calcium content of bone, analyzed by neutron activation, is lower in some, but not all, susceptible patients.[49]

Overview

Alterations in calcium control result in obvious dysfunction in skeletal muscle exposed to appropriate stimuli. Altered calcium control in tissues with more subtle effects upon the whole body may be less apparent. Calcium ion affects the permeability and control of both excitable and inexcitable tissues, but mechanisms within the former may not be relevant to the latter.[330] A wide variety of multi-organ-system defects has been found in susceptible individuals, suggesting that there may be a generalized alteration in membrane properties or permeability. These have been discussed above, and include skeletal muscle membranes, enzyme systems, mitochondria and sarcoplasmic reticulum; heart; central nervous system; liver; blood cells including platelets; endocrine–pancreas, thyroid; bone.

Many of the changes in tissues and organs observed during fulminant MH may be due to blood flow insufficient for metabolic demands, resulting in breakdown of cell membranes, with resultant edema and further loss of perfusion. While not specifically due to MH *per se*, this failure of the peripheral circulation is probably produced by severe acidosis, vasoconstriction, hyperkalemia, decreased cardiac output, and hypotension.

Triggering of MH

The mechanism of triggering in human beings is difficult to examine; in swine it apparently *requires*, at least in part, depolarization of muscle membranes. This reasoning is supported by 1) the muscle end-plate depolarization (and stimulation) of metabolism by carbachol and succinylcholine that is prevented but not reversed by nondepolarizing relaxants, and 2)

the depolarization (and stimulation of metabolism) by halothane that is not blocked by non-depolarizing relaxants but is prevented and reversed by dantrolene.

In swine, increased metabolic responses result from environmental stress such as exercise,[69,221,309,393] heat stress,[124,146,221,270] anoxia,[262,353] apprehension or excitement,[69,309,393] the potent volatile anesthetics,[45,146,147,149,151,335,336,395] and succinylcholine[147,152,167,264] or decamethonium,[90] but not from lidocaine.[166,420] In people, triggering in the absence of anesthetic agents is not proven, but consider the following: 1) susceptible families may have an increased incidence of unexplained sudden deaths[418,421]; 2) susceptible individuals may develop a nonspecific cardiomyopathy[197] related either to unrecognized awake episodes or to primary myocardial abnormalities in MH; 3) (based upon contracture responses) one susceptible patient has had awake febrile episodes (40.6 C) for 10–15 years; these last several days, are related to fatigue or emotional upset, and respond to therapy with dantrolene, but not to aspirin, surface cooling, or other symptomatic treatment.[154,419]

In the absence of anesthetic drugs, the mechanism of triggering in swine is hypothesized from the laboratory findings as follows. Progression of MH results from a hypermetabolic response to the neurotransmitter in association with normal or unchanged responses to sympathetic stimulation. Muscular activity occurs during exercise, excitement, and sympathetic stimulation, *e.g.*, tail twitching, "jumpy." This muscle contractile activity, resulting from end-plate effects of acetylcholine, apparently produces elevated uncontrolled levels of intracellular ionized calcium, the ultimate reasons for which are unknown, but which are related to exaggerated responses to this stimulation of susceptible muscle as compared with normal muscle. Thus, normal muscle undergoing the same degree of activation does not develop metabolic aberrations. The elevation in intracellular calcium results in greater than normal muscle oxygen consumption and lactate production. The beta-sympathetic stimulation accompanying excitement may further increase lactate production.[146] These combined metabolic effects result in respiratory and metabolic acidosis, increased temperature of the muscle venous effluent, and secondary adrenergic stress responses. Alpha-sympathetic stimulation produces vasoconstriction, resulting in decreased heat loss and, possibly, limited muscle perfusion. Increased temperature or relative ischemia resulting from blood flow that is inadequate for the increase in metabolism can exacerbate the metabolic changes and the combined acidosis. These may cascade into a vicious circle of fulminant metabolism, acidosis, and high temperature in association with metabolic exhaustion, failure of cellular membranes, further loss of control of calcium,[129] and cardiovascular collapse. While human beings could have similar responses, one would expect that they would tend to control their emotions and activities more effectively than do swine, and that episodes related to awake triggering might be more subtle.[154,419]

Anesthetic triggering of MH, first by depolarizing drugs such as succinylcholine or decamethonium, would be by effects in people and swine similar to, but more prolonged than, those of acetylcholine. Secondly, triggering by halothane would be due to an action beyond the end-plate.[130,300] There is no information to predict effects of volatile agents upon intact porcine sarcoplasmic reticulum, but at present the data regarding isolated SR suggest that volatile agents do not trigger MH via effects on intact SR. Data about intact human responses to volatile agents at the cellular or subcellular level are not available.

Nitrous oxide and *d*-tubocurarine have been separately incriminated as weak triggers in human MH; the former because it twice produced hyperthermia (blood-gas values not reported) in an 11-year-old susceptible girl who needed dental care,[111] and the latter because it produced hyperthermia in two susceptible children, 8 and 13 years of age (blood-gas values support the diagnosis in one of these cases).[59] These questions cannot be settled conclusively by animal experiments because of possible species differences. At present, few believe that nitrous oxide is a real trigger of MH, because it has been used repeatedly as the basic anesthetic agent for MH-susceptible patients.[37,50,55,68] The hyperthermic episodes have been attributed to residual halothane in the breathing tubes,[247] light anesthesia with multiple reflexes stimulating skeletal muscle,[152] or the belief that nitrous oxide may indeed be a weak trigger easily overridden by barbiturate or opiate depressants.[50,68] *d*-Tubocurarine and metocurine are unlikely MH triggers, based upon known pharmacologic responses in MH, unless this is a side effect unrelated to their action as nondepolarizing relaxants. *d*-Tubocurarine has been associated with greater lactate production in susceptible pigs exposed to environmental stress,[353] but it is not a trigger in susceptible swine.[176] Its effect in these two cases may be attributed to the use of other possible triggering drugs (nitrous oxide or chlorpromazine[344]), or to light anesthesia. At present, pancuronium is the only nondepolarizing relaxant with sufficient use in susceptible patients to confirm its safety (see above in section on neurotransmitters and relaxants regarding pancuronium as a trigger).

Drugs or conditions other than the volatile agents or succinylcholine that have produced human responses remarkably similar to malignant hyperthermia include vitamin E[213] (later retracted when two of the patient's three children had positive contracture responses to halothane),[214] ketamine, phencyclidine, viral infections,[356] lymphomas,[394] some of the tranquilizers,[183,212,298,344] tricyclic antidepressants and monoamine oxidase (MAO) inhibitors.[31,240,246,268,326,372] Ketamine and phencyclidine are structurally related and can increase temperatures of healthy people.[215,314,343] Ketamine has occasionally,[189,287,346,363] but not always,[257,364,399] increased the temperatures of MH-susceptible individuals, but the difficulties in differentiating a benign fever from MH preclude its general use.[252] In large doses MAO inhibitors can produce hyperexcitability and exaggerated motor activity, and, used with diazepam, they have produced heat stroke.[240] While it is likely that these adverse effects could occur in both normal and MH-susceptible people, the risk of these is probably greater in the latter.

Genetics

Initially, human inheritance seemed to be autosomal dominant[51,56,94,205,206,222,242,250,320] with reduced penetrance, *i.e.*, fewer affected offspring than predicted by dominant patterns,[118] and with variable expressivity, *i.e.*, differing susceptibility between families with little variation within a given family.[56,222,320] Some investigators have not seen evidence of reduced penetrance manifested as generation skipping.[110] Others felt that the human pattern of inheritance fit no known genetic system.[232,233] It has recently been proposed that humans inherit susceptibility to MH via more than one gene or more than one allele, and that the pattern of inheritance may thus range from recessive to dominant, with graded variations in between. This is discussed below.

Several years ago, Kalow and Britt[224–226] suggested that caffeine and halothane–caffeine measured different features of muscle responses. Halothane–caffeine thresholds seemed to separate a group of biopsy specimens into control responses (threshold greater than 1.3 mM caffeine) and susceptible responses. The responses to caffeine then divided the susceptible group into a spectrum of susceptibilities. Kalow and Britt further analyzed genetic variation by examining the ratio (threshold to caffeine)/(threshold to halothane–caffeine). High ratios, 17–27, suggested a separate phenotype of nonrigid MH susceptibility.[226] More recently, Kalow and Britt correlated clinical severity of MH with graded contracture responses—the occurrence of halothane-induced contractures as the correlate of greatest susceptibility and severest clinical episode, that of caffeine-induced contractures as somewhere in between, and that of halothane–caffeine-induced contractures as the correlate of least susceptibility and clinical severity.[223] From this they inferred a graded inheritance, and they tended to discount other factors modifying MH episodes. There are not, at present, sufficient clinical data with clear genetic implications because of a lack of control of drug or environmental modifying factors in clinical MH. The theories of Kalow and Britt are somewhat clouded by the variation in contracture responses of normal subjects, whose caffeine thresholds range from 4 to 32 mM or more, and whose estimated threshold ratios range from 4 to 27. However, despite these contradictions, all of their data together suggest genetic complexities, and it seems likely that there is a multifactorial inheritance with a range of susceptibilities.

Ellis and Harriman,[109,110] after extensive examination of histologic features of muscle and contracture responses to halothane, proposed two independent indicators of susceptibility: the histologic presence of a myopathy, and the demonstration of a halothane-induced contracture *in vitro*. However, pathologic features varied, even among siblings, and a diagnostic pattern was not observed. Furthermore, since structural changes may surface later,[170] it may be inappropriate to use histologic changes for genetic interpretations. Since either of these changes or both could be present in susceptible individuals, these investigators also felt that MH is a multifactorial genetic disorder.

With multifactorial inheritance, the offspring tend to be the average of the parents, and there may be gradations of susceptibility among members of a given family. Nonetheless, some families would be expected to have dominant patterns of inheritance. Other myopathies also show patterns of variable inheritance.[317]

Porcine inheritance of MH also originally appeared to be autosomal dominant.[6,217,411,412] Others have proposed a recessive pattern of inheritance with high or complete penetrance,[11,107,313,367,383,404] or a multifactorial inheritance involving at least two abnormal genes or alleles.[53,367] Many of these investigators relied on screening with halothane to identify susceptible animals.[11,107,313,331,367,383,404] This method identifies only those pigs that are most susceptible, and may miss animals with graded and lesser susceptibility.[140,411,412] The latter can be detected by screening with both halothane and succinylcholine,[140,411,412] or by additional screening of muscle biopsy specimens utilizing ATP depletion[217] or contracture studies.[53] These

less susceptible swine are decidedly different from normal swine, and their inclusion in data for genetic analysis could alter the interpretation. Blood groups and certain production traits become associated when swine are inbred.[2] Andresen[10] and Christian[331] have suggested that porcine inheritance is cross-linked with blood type, and Andresen's data further suggest that these may be cross-linked with the locus for 6-phosphogluconate dehydrogenase.[11] Assuming this also represents a multifactorial inheritance, there may be recombinant linkage of these specific factors leading to MH susceptibility in offspring of apparently normal but heterozygous parents. This may also account for sporadic cases of MH susceptibility in swine usually considered nonsusceptible.

Depending upon degree of susceptibility and environmental factors, the ease of initiating MH in human beings or swine could fluctuate. This concept might explain those situations in which known susceptible individuals have shown no sign of MH during exposure to triggering agents.[28,70,86,88,168,329,346] In the event muscle membrane depolarization and decreased mechanical threshold play a role in human MH, as they seem to do in swine, then drug or environmental factors might alter these characteristics, and there may be instances in which susceptibility could be acquired.[356,363,394] With this "acquired" state of susceptibility, exposure to the proper triggers could result in MH. Anesthetic-induced MH, and, in some instances, stress-induced MH, have been reported to occur in the horse,[243,279,400] cat,[90] dog,[15,364,365] deer,[323] birds,[191] and wild animals during capture.[183,184,191] It is not known whether these episodes occur in species that have some form of recombinant or other genetic susceptibility, or whether this is due to environmental or drug-related factors.

Other Animal Models

Animal models have been used to examine abnormal responses and the findings used to study different aspects of MH. Human and frog muscle respond to caffeine and halothane with contractures, and these drugs potentiate each other.[293,345,381] Lidocaine accentuates these contractures and procaine inhibits them,[293] although the latter drug is not effective once the contracture has developed.[381] This then becomes a model of human MH as mimicked by caffeine, and the different volatile anesthetic agents have different effectiveness in augmenting these caffeine-induced contractures.[333] Application of these effects of procaine and lidocaine to human MH is limited because the tissue concentrations of 2–5 mM cannot be achieved without administering large doses.[159,188,293] A similar preparation has been developed using rat rectus muscle,[175] and an *in-vivo* rabbit model closely mimicks MH by using caffeine to produce a response similar to MH upon challenge with halothane.[103]

Models of uncoupling, in general using dinitrophenol,[416] demonstrate lethal increases in temperature upon exposure to halothane at high (25 C) but not at low (20 C) environmental temperatures.[194] These have demonstrated that haloperidol pretreatment antagonizes the hyperpyrexic and lethal effects of dinitrophenol in the absence of anesthetic agents or caffeine.[134] Unfortunately, haloperidol alone may produce fever.[135] Gatz has reported higher temperatures in dinitrophenol-treated rats that breathed oxygen as compared with those that breathed room air.[132] On this basis, and because of oxygen's action in uncoupling nonbiologic systems, he proposed,[132] but could not demonstrate,[237] that treatment of MH using ventilation with air may be more efficacious than ventilation with oxygen. Ryanodine-induced contractures in mice, cats, and frogs have been proposed as an alternative to caffeine; however, dantrolene and procaine are not effective in counteracting this contracture.[73] While all of these models have acquired, rather than genetic, hypermetabolic responses, they nonetheless may help to increase our understanding of the genetic form.[51]

Human–Porcine Differences

Human and porcine MH have several differences: 1) histologic abnormalities are found in people, but seldom in swine; 2) MH can develop in swine in the absence of anesthetic drugs, but this occurs rarely in man; 3) total serum calcium increases in pigs,[36,51,395] while it more often decreases in people.[36,50,51,327,352] The first of these apparent differences may be explained by the observation that the histologic abnormalities may be acquired or secondary and may develop only with time, *e.g.*, they are not seen in young children; swine, because they are marketed at an early age, have not been examined when older. The second difference is more difficult to explain: perhaps people can generally manage their emotional responses so as to avoid prolonged or extreme agitation or excitement, once they realize the intense upset provoked by sympathetic discharges that occur during MH.[154] The third apparent difference is probably due to copious calcium-free intravenous therapy of human patients, and the general lack of therapy of swine. Muscle calcium contents of susceptible pigs[42,309] and people[19,42] are variable, and can be less than[42,309] or not different from[19] those of healthy individuals. Comparisons of blood or serum ionized calcium would probably be more meaningful than those in-

volving total calcium. In swine, ionized calcium increases during MH.[12,149,153] While the two species tend to have similar myopathic deficiencies in mitochondria and sarcoplasmic reticulum, intracellular functions in intact tissues could vary considerably without necessarily altering extracellular manifestations.

Diagnosis

During anesthesia suspicion of MH is aroused by symptoms or signs, including rigidity with succinylcholine,[100,379] that are extraordinary for that patient and procedure.[50,55,137] In susceptible subjects MH may be triggered even in the absence of triggering anesthetic agents when the level of anesthesia is very light and reflex responses are present.[152] In general, though, MH would not be expected to occur in any patient given barbiturate–nitrous oxide–opiate–pancuronium anesthesia.[37,55,68] Using potent volatile agents or succinylcholine, one would be suspicious if there were undue tachycardia, tachypnea, dysrhythmias, mottling of the skin, cyanosis, increased temperature, muscle rigidity, sweating or unstable blood pressure. In particular, rigidity following an adequate dose of succinylcholine correlates highly with susceptibility to MH.[100,379] If any of the preceding abnormalities is present, one must search for signs of increased metabolism, acidosis, or hyperkalemia. Arterial blood analysis should demonstrate metabolic acidosis, and may show respiratory acidosis if the patient is unable to increase ventilation as metabolism increases. In this regard, central venous blood levels of oxygen and carbon dioxide will change more markedly than will those of arterial blood.[133,151] Suggested limits for the diagnosis are a base excess of less than −5 mEq/l and an arterial blood P_{CO_2} greater than 60 torr without reasonable explanation. Increased oxygen consumption is difficult to measure while the patient is anesthetized in the clinical situation. Although CO_2 production can be measured more easily,[256] one must generally rely more upon measurements of P_{CO_2} in relation to the estimated alveolar ventilation. In particular, when the temperature is rising and there are signs of muscle stiffness and acidosis, the diagnosis is established and treatment must be instituted.

Treatment

Malignant hyperthermia is triggered in proportion to the susceptibility of the subject and to the total dose of triggering agent (concentration × duration of administration). Following a brief administration, discontinuation of the agent may be adequate treatment.[55] Also, some drugs such as thiopental appear to slow the development of MH so that termination of anesthetic administration may again be sufficient therapy.[151] While these factors may account for the puzzling instances wherein patients have tolerated triggering agents during prior episodes of anesthesia without observed signs of MH and then experienced fulminant MH during subsequent anesthesia, there remain troubling cases wherein known susceptible patients tolerated prolonged exposure to (adequate doses of) triggering agents.[28,70,86,88,168,329,346]

When MH becomes fulminant—arterial blood P_{CO_2} greater than 60 torr and rising, mixed venous blood P_{CO_2} greater than 90 torr and rising, base excess less than −5 mEq/l and falling, temperature increasing at least 1 degree C per 15 min—adequate therapy is urgently needed for survival.[38,50,336] In some patients the metabolic and acid–base changes occur so rapidly that they markedly diminish cardiac output and result in minimal tissue perfusion and minimal increases in temperature, with rapid demise.

Dantrolene is the only known specific therapeutic drug, but it must be given while there is still adequate muscle perfusion. It is a lipid-soluble hydantoin derivative that acts distal to the end-plate within the muscle fiber, and is specific in preventing or halting porcine MH.[148,161,178,305] A few case reports have begun to confirm its effectiveness in human MH.[118,128,256]¶ Its efficacy in both species suggests that the defect in MH may be located at or prior to its site of action. Dantrolene attenuates calcium release without affecting uptake, by an action upon the connections between the transverse tubules and the terminal cisternae of the sarcoplasmic reticulum, or upon the terminal cisternae directly, or both.[60,289,300] Dantrolene has been demonstrated to be effective in a variety of experimental porcine situations, including contracture studies of isolated muscle,[8,9,14,300,305] and in the intact pig.[122,148,161,178,180,239,305] It controls abnormal metabolic responses and the associated acid–base imbalances, ion fluxes, and sympathetic stimulation more predictably than does symptomatic therapy.[148] It is not useful in screening for susceptibility.[121] It is not associated with serious toxicity at effective doses.

Dantrolene, even in very high doses, does not produce muscle paralysis, although weakness may result.[148] Its one ill effect is hepatic dysfunction, which has not been seen with oral administration of less than three weeks' duration.[362] The porcine minimum effective dose is 3.5–5 mg/kg, intravenously, with attenuation at 1–3 mg/kg.[148,178,305] The human

¶ Kolb ME: Norwich Laboratory evaluation of IV dantrolene in humans (personal communication).

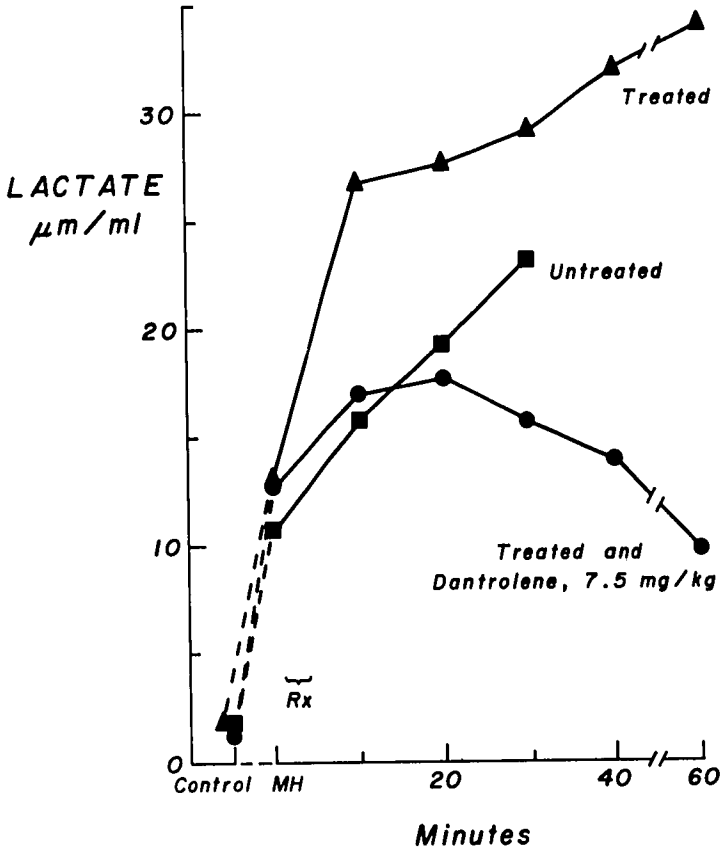

FIG. 3. Arterial blood lactate in MHS swine. During symptomatic treatment of MH, blood lactate continues to rise as a sign of unchecked fulminant metabolism (treated). When dantrolene is used in addition (treated and dantrolene), blood lactate decreases—a sign of dantrolene's specific inhibitory effect upon muscle.

effective dose intravenously is probably 1–2 mg/kg, which may be repeated each 5–10 min, to a total dose of 10 mg/kg.[118,128¶] The dose for effective oral pretreatment with dantrolene in human patients is not known, but is probably in the range of 4–7 mg/kg/day, given in divided doses and started at least 24 hours preoperatively.[127,319] Because dantrolene is poorly soluble, any provision for its rapid emergency use necessitates that the drug and solvents be immediately available in the anesthetic area.[104,145]

Procaine is theoretically effective in the treatment of MH, but is impractical clinically (see above under discussion of other animal models). Reports have both condemned[82,159,166,188] and praised[17,36,173,176,231,293,295,311,379] the use of procaine for the treatment of human MH. Two controlled evaluations of procaine and dantrolene in swine suggest that procaine is ineffective in treating the clinical syndrome and that dantrolene is highly effective.[147,148,304] Procaine may be useful in the treatment of dysrhythmias during the acute episode, and is safer than lidocaine, particularly with the higher blood levels associated with intravenous administration (see above under discussion of other animal models).

Symptomatic therapy for MH, while important, must be used in conjunction with dantrolene, because MH may continue to smolder or become fulminant despite control of temperature and acid–base disturbances (fig. 3). Ventilation should be increased two- to threefold[147,148,237] and sodium bicarbonate, 2–4 mEq/kg, given rapidly intravenously. Arterial blood-gas and acid–base values guide subsequent therapy. Cooling is necessary to lower temperature. Cooling should be aggressive for rapidly increasing temperatures and for those above 40.6 C: surface cooling with the patient packed in ice, gastric or peritoneal lavage, iced intravenous fluids, and pump bypass with a heat exchanger can be used.[347] Cooling should be halted when temperature falls below 38.3 C to prevent inadvertent production of hypothermia.

Urinary output should be measured and diuresis maintained with output approximately 2 ml/kg/hr, using volume loading or diuretics.[257] Initial volume loading would include 2–8 ml/kg balanced salt solution, depending upon the response of the patient. In the event large doses of sodium bicarbonate are necessary in controlling acidosis, furosemide will help to start excretion of the sodium load. Renal failure is primarily prevented by maintaining adequate urinary output. Forced diuresis utilizing either mannitol or furosemide may be necessary as additional therapy. Mannitol may be risky if urinary

output is low because high blood levels of mannitol can be associated with passage across the blood–brain barrier, particularly in association with coma or altered membrane permeability, *e.g.*, Reye's syndrome.[359]

Steroids have been recommended by Ellis for the treatment of human MH, based upon clinical results in nitrous oxide-induced MH and upon human contracture responses.[111] Their efficacy has not been confirmed in porcine MH,[163] and steroid use was associated with a higher mortality rate in a retrospective statistical examination of the treatment of human MH.[55] However, many factors contribute to MH-associated deaths, and steroids are probably helpful during these severe stresses and are unlikely to be specifically harmful.

Based upon retrospective statistical data, and theoretical considerations, Britt suggests that cardiac glycosides may worsen MH[55]; while they have been used in therapy of human MH without untoward effect,[85] their practical application is unknown, and could be hazardous. Deliberate reduction of plasma potassium concentration is at best slow, and the most effective means of lowering it is probably the reversal of the MH process, *i.e.*, effective doses of dantrolene. The administration of calcium to counteract hyperkalemia is risky. Few hospitals have the means to measure ionized calcium levels quickly, and the calcium could conceivably retrigger MH.

Treatment of pulmonary, cerebral, and muscle edema is not different from that used when these occur in association with other disorders. Neurologic sequelae (coma, paralysis) may occur in advanced cases, probably secondary to oxygenation and perfusion that are inadequate for the increased metabolism, as well as to fever, acidosis, and potassium release. Apparently satisfactory anesthesia care may be grossly inadequate in this situation. These neurologic sequelae may persist.

Disseminated intravascular coagulation or consumptive coagulopathy (DIC) may be caused by hemolysis, increased release of tissue thromboplastins due to increased permeability or overt tissue damage, shock secondary to inadequate capillary perfusion, or some rare mechanisms perhaps related to the increased permeabilities present in fulminant MH.[50,86,88,257,275,327,328,349,351,352,413,426] The best treatment is adequate therapy of MH to prevent stagnation of peripheral blood flow and to lower temperature. If the coagulopathy develops and persists despite treatment for DIC, heparinization may be successful in treating it.[285]

One cannot overemphasize the necessity for early diagnosis and early effective treatment to avoid complications.[277] They are all difficult to treat and are associated with serious and sometimes permanent sequelae.[275] Retriggering may occur,[50,55,274] even with dantrolene, as the initial dose of dantrolene is redistributed, metabolized or excreted. Dantrolene has a half-life of about five hours, and its administration should probably be continued for 12 to 24 hours following control of MH, and reinstituted with signs of increased metabolism or acidosis, Dantrolene can be given orally when the gastrointestinal system is functional. The recovering patient therefore needs close monitoring for approximately 24 to 48 hours postoperatively.[50] During this period there should be normal renal function, blood coagulation, bleeding time and blood gases; the neurologic status must include absence of rigidity, and temperature and EKG must be normal.

Lewis, of Children's Hospital in Los Angeles, has proposed that therapy of human MH should include cooling and reversal of acidosis, but that halothane administration should be continued, so as to aid in cooling by maintenance of vasodilation. His approach is based upon the lack of mortality in a series of patients treated for intraoperative hyperthermia at his institution[253]** (discussion following Zsigmond *et al.*[427]). This is not a rational approach to a disorder in which halothane is acknowledged to be a trigger, and animal data contradict its efficacy.[90] In the absence of published data that these patients and their families were susceptible to MH, the author speculates that these patients had fever, but not malignant hyperthermia. At least one other patient has survived the continued administration of halothane during symptomatic therapy for active MH,[276] but at present this is not an accepted mode of therapy. Morphine has been recommended for treatment of human MH despite its lack of effect in porcine MH, but the nonspecific depression by opiates is not likely to be as effective as dantrolene treatment, assuming it is effective at all.[33]

Evaluation of Susceptibility

Evaluation of susceptibility[37,113,203,211,296] to malignant hyperthermia includes a history and physical examination for detection of subclinical muscle weakness or abnormality. A genealogy going back two generations with specific information about anesthetic exposure and, if possible, the agents used, will help in estimating the likelihood of adequate exposure to triggering agents. Measurements of blood CPK are 70 per cent reliable in estimating susceptibility,

** Lewis GB: Current Problems in Pediatric Anesthesia, Review Course, International Anesthesia Research Society, San Francisco, March 1978, Audio-Digest, Vol 20, no. 10, May 22, 1978.

and provide a basic screening tool.[47,112] When CPK is elevated and the subject is a close relative of a known susceptible individual, then he may be considered susceptible to MH without further testing. When the patient is a close relative of a susceptible human and CPK is normal on three occasions, then muscle biopsy is necessary to determine susceptibility. Investigations of the biopsy specimens obtained to detect MH are performed in several centers around the world, and utilize exposures to halothane, caffeine, halothane and caffeine, potassium, or succinylcholine. Such investigations, in conjunction with histologic examinations of muscle and/or measurements of ATP depletion, are perhaps more than 90 per cent reliable in the evaluation of susceptibility, despite a number of differences among the investigators in regard to laboratory technique, preferred triggering agents, and normal values. Porcine data indicate that pretreatment with dantrolene does not alter muscle contracture responses *in vitro* from susceptible to normal, presumably because of washout of dantrolene in the bath.[307] Platelet ATP depletion,[61] skinned fiber responses,[40,422] and a tourniquet test of muscle ischemia and altered twitch responses[341] have yielded data inadequate for evaluation as screening tests. Porcine susceptibility is related at least in part to blood type,[331] but determination of blood type has not yet replaced halothane and succinylcholine challenges as a screening method.[140,412] There is no information regarding human susceptibility and blood type.

Anesthesia for Susceptible Patients

In the preoperative period it is important to avoid subjecting the patient to anxiety and stress, and to reassure the patient that you have confidence in monitoring for MH and in providing proper treatment should it develop.[21,37,55,287,417,421] The patient should be well premedicated, but phenothiazines should be avoided, as they may release calcium from sarcoplasmic reticulum.[344] Atropine is probably best not used unless needed during anesthesia, and then used in small intravenous doses only. It is preferable to give dantrolene orally the day before the surgical procedure, in divided doses that total 4–7 mg/kg/day.[127,180,216,239,319] The safe anesthetic agents[37,55,68] include nitrous oxide, thiopental and other barbiturates, althesin,[174,179,196,389] opiates, droperidol, and pancuronium.[68,335,336] Potent volatile agents, depolarizing relaxants, and ketamine should be avoided.

Stimulation *per se* during light anesthesia may trigger MH responses.[152] Monitoring should include temperature, electrocardiogram, and blood gas–acid–base capability, as well as the usual monitoring done for any patient undergoing anesthesia. Some patients have apparently had MH triggered in the postoperative period, and thus all should be followed for 24 hours.

Regional or conduction anesthesia avoids the use of volatile agents and relaxants,[94,426] but may yet be associated with increased temperatures in susceptible patients.[229,398] Amides such as lidocaine or mepivacaine are best avoided when large volumes are to be used, even though it is unlikely that blood concentrations will be high enough to release calcium from sarcoplasmic reticulum. Dental use of small volumes should not be risky. Esters such as chloroprocaine, procaine, piperocaine, and tetracaine do not diffuse through tissue as well as amides, but are safer for use in large volumes.

Legal Implications[278,315]

Awareness of MH is now generally widespread, as reports concerning it have been disseminated in a variety of journals. Ignorance is therefore not a valid defense against litigation. However, an episode of MH may be a fortuitous event, and one would not incur liability unless he had departed from a recognized standard of care.[390] This should include: family and personal anesthetic history, continuous monitoring of temperature during most anesthesias, avoidance of potent volatile agents and depolarizing relaxants in susceptible patients or in close relatives not evaluated for susceptibility, keeping immediately available resuscitation equipment and drugs appropriate for MH crises, and the use of diligent and due care in the treatment of any such crises. An estimated 1 per cent of cases of MH have involved litigation, but emotional responses of juries make it difficult to predict the outcomes.

Puzzles

1) Why do triggering agents sometimes fail to trigger human MH? Is this due to depression of the initiating process by other drugs? or graded susceptibility associated with complex inheritance?

2) Can triggering anesthetics be used for patients "proven" nonsusceptible by contracture tests of muscle biopsy specimens?

3) Should triggering agents ever be used for susceptible patients who have been pretreated with dantrolene?

4) A reliable screening test for MH that does not involve surgical intervention is needed.

5) The theory of uncontrolled intracellular free ionized calcium levels needs confirmation.

6) Sarcolemmal function in MH-susceptible individuals needs examination.

7) The transfer of membrane depolarization from transverse tubule to sarcoplasmic reticulum in normal muscle is not understood. It is probably involved in the pathophysiologic mechanism of MH.

Summary

In MH, skeletal muscle acutely and unexpectedly increases its oxygen consumption and lactate production, resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. The best-accepted theory is that MH is due to an inability to control calcium concentrations within the muscle fiber, and may involve a generalized alteration in cellular or subcellular membrane permeability. Episodes are predictably initiated in susceptible people and swine by potent volatile anethetic agents or succinylcholine. In addition, in swine, MH is consistently triggered by excitement, apprehension, exercise, or environmental stress such as heat or hypoxia. Several genetic factors probably control the human and porcine inheritance of MH. Sympathetic involvement in MH, while controversial, is probably a response to stress that affects blood flow, heat loss, and myocardial function, rather than a direct sympathetic activation of susceptible muscle. Diagnosis is based upon extraordinary temperature and acid–base and muscle aberrations. Specific treatment is the action of dantrolene upon muscle calcium movements; symptomatic treatment is by reversal of acid–base and temperature changes. Evaluation of affected families is guided by measurements of circulating creatine phosphokinase and by analysis of drug-induced contractures in muscle biopsy specimens. Anesthesia for susceptible patients includes thiopental, opiates, droperidol, pancuronium, nitrous oxide, and preoperative oral doses of dantrolene.

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