AETIOLOGY OF MALIGNANT HYPEROTHERMIA

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As in most scientific investigations, research into the aetiology of malignant hyperthermia or malignant hyperpyrexia (MH) has itself been characterized by the oddities of the disorder. Until stressed, the affected organism or tissue is to all intents and purposes normal in structure, function and appearance, with few exceptions, thus complicating the elucidation of mechanism, detection of affected individuals, and establishment of clinical studies. It is with good measure of hindsight (the expert’s privilege) that we recount the major and continuing tasks of MH investigations: (1) to distinguish between primary and secondary roles in aetiology; (2) to discern which conditions are in part the result of acute MH and which are in part the result of an imbalance between supply of substrate and energy consumption.

During general anaesthesia control of body temperature is absent and temperature can therefore drift up or down. Because general anaesthetics result in at most a 10–15% decrease in whole body metabolism [108], heat production is not drastically reduced. Thus it is primarily cutaneous vasodilatation in a cool environment that is responsible for the passive cooling that tends to occur during anaesthesia. If whole body metabolism and hence heat production markedly increase, body temperature can precipitously increase.

HISTORICAL AETIOLOGY

When Denborough and Lovell first described MH in 1960 [26], they had little direct information concerning aetiology, but appropriately surmised that it was a pharmacogenetic disorder. Further case reports added descriptions of muscle rigidity [97,107]. Because there were few actual data other than case reports, and because controlled collection of data was impossible, the questions were overwhelming. Was this a new observation?

Denborough’s original family traced anaesthetic-related deaths to 1922, presumably all associated with diethyl ether. Yet why wasn’t a familial correlation identified and reported sooner? Why did the flood of ominous and frightening case reports only begin in the 60s? Did scepticism in regard to these anaesthesia deaths discourage early reporting and investigation? How much was the apparent increase in MH episodes related to newer anaesthetic agents or techniques? Did the lack of sympathetic stimulation of the new volatile agent halothane upset a necessary balance that ordinarily helped to control muscle metabolism or thermoregulatory balance during anaesthetic stresses? Did the sympathetic stimulation of cyclopropane and ether “tend to prevent” full-blown episodes? In the maturing field of anaesthesia, did the pressures of defining roles in the operating theatre delay the development of observations such as these into organized reports? Did muscle hypertonicity with its associated increase in heat production initiate the metabolic changes, and did the central nervous depression of anaesthesia contribute to it? These and other implied questions confounded observers then, and some of these continue to confound. The number of cases mounted, with a mortality rate of 75%. As Stephen [106] perceived it, some mechanism is set in motion that has “full sway” in the absence of effective thermoregulatory power.

Porcine research fortuitously focused in these same areas. Briskey in 1964 [6] described pale, soft, exudative (PSE) pork that could not initially be distinguished from normal muscle, but became obviously different after it was stressed at slaughter and underwent rapid postmortem change. This finding underscores the difficulties of MH research. Hall and colleagues in 1966 [58] described porcine MH in conjunction with rigidity during suxamethonium–halothane anaesthesia in three littermate swine, and correlated the response with human MH. Topel and colleagues [109] in 1968 confirmed that the porcine stress syndrome
(PSS) was a disorder of muscle. It was obvious that PSE pork was a product of PSS swine that were unduly stressed. In 1969 Harrison and others [61] demonstrated that the muscle ATP depletion test could identify affected pigs. In 1970, Berman and colleagues [5] described the clinical, metabolic and biochemical course of MH in the susceptible pig and further underscored the importance of the pig as an animal model. They clearly demonstrated that metabolic changes occurred first, and that other changes were compensatory. Britt and Kalow in 1970 [11] could exclude central nervous system causes and could incriminate muscle, but they nonetheless described the disorder as “Aetiology Unknown”.

New findings pinpointed skeletal muscle as the major aetiological factor in acute episodes of MH and demonstrated an association with myopathies. Blood concentrations of creatine phosphokinase correlated at least in part with susceptibility, in non-triggered patients as well as during acute episodes [24,67]. Contracture-producing drugs, well known to muscle physiologists, produced lower threshold responses in muscle from susceptible patients [70]. Procaine and lignocaine, perhaps because of effects upon muscle, were noted to be effective in treating clinical episodes [70,71], although lignocaine was later temporarily condemned on theoretical grounds because of its in vitro action in releasing calcium from sarcoplasmic reticulum [8] (see SR: drugs in MH). Suxamethonium could produce violent fasciculations and rigidity. Muscle rigidity (even without the use of suxamethonium) frequently developed during acute MH, but was not a terminal event. Observations in patients undergoing limb surgery with use of a tourniquet confirmed that MH arises in muscle, and that the muscle must be perfused for MH to develop. These patients developed MH involving whole body rigidity while the tourniquet-isolated limb remained flaccid [29,98].

Various theories emerged and diverged. These included loss of control of calcium ion within the muscle cell, myotonia, failing cell membrane function, insufficient ATP, decreased muscle phosphorylase with inadequate ATP production [10,11] and uncoupling of oxidative phosphorylation [116]. This last theory was discounted by the theoretical arguments of Wang, Moffitt and Rosevear [111], who calculated that uncoupling alone would not account for the increased heat production; they did note that muscle contractile activity could result in the requisite amount of heat production.

1971 marked the First International Symposium on MH [41]. This conference summarized findings to date and detailed normal and proposed abnormal physiology. The theory of altered calcium transport within the cell was generally accepted. MH was more or less defined as a genetically determined membrane defect involving the sarcoplasmic reticulum (SR), perhaps at the triad (transverse tubule–SR junction). Other aetiological considerations included inhibition of monoamine oxidase, with a reversal of the trend toward hypothermia usually observed during anaesthesia. The sudden onset of MH suggested a superficial membrane phenomenon rather than a direct effect upon mitochondria. Studies using dinitrophenol implied an alteration in oxygen utilization and a possible toxic effect of increased oxygen tension [39]. However, the contracture related to dinitrophenol was not typical of MH contractures and the number of pigs in the oxygen studies was not sufficient to provide adequate data for definitive conclusions. These proposals were not confirmed by others.

After the First Symposium, theories concerning aetiology included all membranes and tissues of the body, in part because of the involvement of calcium ion in the reactions of virtually every cell in the body [8,9]. Examination of function of intracellular organelles, SR and mitochondria, began to uncover modest alterations in basic functions. Muscle biopsy was becoming accepted as a diagnostic tool; it further demonstrated that muscle was abnormal at the level of the basic regulatory mechanisms of muscle contraction: various contracture-producing drugs, regardless of their mode of action, induced a contracture in susceptible muscle at a threshold lower than that of normal muscle, including the classic potassium contracture [84]. This in part led to the proposal that MH appeared to be an exaggeration of normal rather than different pathological responses [83].

In summary, MH appeared to be a subclinical primary myopathy with secondary systemic pathophysiology; the systemic consequences were marked because muscle comprises about 40% of body mass.

**CENTRAL NERVOUS SYSTEM**

Control of thermoregulation is not disturbed in MH, but there may be a suggestion of CNS
involvement. LaCour, Juul-Jensen and Reske-Nielsen [75] had reported a young boy who developed peculiar central nervous responses after receiving suxamethonium. It had been injected to a tourniquet-isolated limb; after the tourniquet was deflated, peculiar fasciculations occurred, followed by apnoea. This observation has never been satisfactorily explained. Kerr, Wingard and Gatz [73] demonstrated that extradural blockade could prevent the rigidity of halothane-induced MH in the blocked limbs of susceptible pigs. They did not measure metabolic responses, but observed muscle tone and temperature. Gronert, Milde and Theye [48] contradicted their findings and conclusions by demonstrating that the muscle paralysis of total spinal anaesthesia did not block the metabolic responses of MH that were induced by halothane, and that pigs could experience typical episodes of MH during blockade of afferent and efferent central nervous system responses. Britt and colleagues [12], using the technique of motor unit counting in humans, inferred CNS dysfunction. However, the results of the test denote a non-specific myopathy, not necessarily a motor nerve problem, and interpretation of the results may be controversial. Lack of involvement of the CNS was shown by the observations of Artru and Gronert [3]: metabolism of the brain during porcine MH was not primarily abnormal and effects upon it and energy stores were secondary to the temperature, electrolyte, acid-base and cardiovascular disturbances of an acute MH episode.

SYMPATHETIC NERVOUS SYSTEM

Earlier, and now, the major emphases and disagreements concerning the role of the nervous system in MH involve the sympathetic portion of the autonomic nervous system. Wingard [118], at the Wausau symposium in 1974, proposed his theory of stress as a major precipitant in human MH. Susceptible families that he was following had an apparently increased incidence of sudden unexplained deaths, as a result of heart attacks, motor car accidents, etc. Moulds [83] believed that some effect of catecholamines might stimulate MH responses. Britt correlated MH susceptibility in humans with abnormal myocardium (vide infra: myocardium) and with abnormal responses to sympathetic agonists as inferred from increased morbidity and mortality following their use; she summarized others’ findings as suggesting an exaggeration of catecholamine innervation with multiple indirect effects on myoplasmic calcium [8, 9]. Campbell’s group [16, 17] examined sympathetic responses in susceptible unanaesthetized humans under tightly controlled conditions, via measurements of heat production, temperature and blood hormone–metabolite concentrations. There were subtle, but not outstanding, indications that variations in heat dissipation might imply sympathetic dysfunction in susceptible subjects. However, the changes were not marked, and they sometimes were opposite to what one would anticipate—that is susceptible patients, in direct contrast to normal patients, showed a complete absence of exercise-related dietary-induced thermogenesis. It may be more difficult to demonstrate sympathetic dysfunction in the susceptible human, if it is indeed present, because of ethical limitations restricting the degree of stress in a species that is not as genetically pure (and therefore probably not as susceptible) as the inbred susceptible pig.

In the pig model, Williams and colleagues developed an extensive theory incriminating noradrenaline as the major factor in MH, both as a basic abnormality and as a trigger. This theory has not particularly changed over the years [113, 114]: they believe that the susceptible pig has a continually increased metabolism as a result of excessive noradrenaline effects upon its abnormal MH-affected muscle. The pig constantly releases or controls the extra heat and acid by its relatively limited homeostatic mechanisms (swine are unable to sweat). When some factor, such as a hot environment, exercise, fighting, coitus or general anaesthesia suddenly stresses the animal, it cannot control this additional heat production and MH erupts, very much like steam through a pressure control valve. Against Williams’ theory are several observations. The susceptible pig is usually genetically pure and easily triggered by environmental factors; measurement of increased metabolism in a chamber, for example, does not relate to the basal state in the unsedated pig, an observation made by Williams himself [115, 116]. Further, others have not observed increased basal metabolism in the sedated pig [49, 79].

During anaesthesia, the sympathetic nervous system does not have a primary role in porcine MH, for acute sympathetic denervation secondary to total spinal anaesthesia completely prevents the usual increases in circulating catecholamines without altering the MH episode itself [48]. Finally,
Williams [113,114] suggested that the extreme increases in blood concentrations of catecholamines, especially noradrenaline, are further support for his theory. Several authors, however, have not observed triggering in susceptible pigs given infusions of noradrenaline, based in part upon lack of change of temperature [57,61]. Further, Gronert and White (unpublished observations) have used noradrenaline infusions during nitrous oxide–barbiturate anaesthesia to increase blood concentrations to 145 ng ml⁻¹, considerably greater than those generally seen in acute MH, with no evidence for triggering, based upon observation of aerobic metabolism and glycolysis. At the end of the noradrenaline experiment, these pigs were triggered by halothane and suxamethonium.

Lucke, Hall and Lister have favoured a sympathetic mechanism for MH, at least in part. They observed that α-agonists could initiate MH episodes [55], and that α- and β-antagonists could modify these episodes [76]. α-Antagonists did not block initial muscle responses, but altered temperature and arterial pressure phenomena. β-Antagonists modified glycolytic and acid–base changes, but all swine died—that is, mortality was unaffected.

These studies and their modifications are difficult to interpret, because of differences from typical episodes and because of difficulties in preparing stable animal models with various operative and drug-induced situations. As an example, in acute porcine MH episodes initiated by phenylephrine, the increase in temperature preceded the increase in lactate concentration [55], whereas when halothane initiated MH, the increase in lactate concentration preceded the temperature increase [49,79]. This suggests that phenylephrine may have produced environmental triggering as a result of decreased heat loss or ischaemia secondary to vasoconstriction (known triggers of MH or PSS responses), rather than by the direct effect of this α-agonist. In addition, in this same study, noradrenaline increased temperature, but by approximately the same amount in normal and susceptible pigs, a finding confirmed by Gronert and White (unpublished observations). Another study by Lucke and colleagues [78] involved bilateral adrenalectomy and use of adjuvant sympathetic blockers. However, the fitness of these swine following preparation was open to question: of 10 adrenalectomized pigs, six survived for inclusion in the procedure; after the study, it was not possible to extubate the tracheae and four of six died of ventilatory difficulties within 2 h of the end of the experiment. The lack of triggering in these swine is therefore subject to interpretation—was this protection and blocking, or was it borderline survival?

We should note that porcine MH is different from human MH; in the absence of exposure to anaesthetic agents, porcine awake episodes that are identical to classic anaesthetic MH episodes can be predictably initiated with any sort of stress. This is empirical support for any theory involving the sympathetic nervous system. Gronert, Milde and Taylor [46] examined this aspect in the absence of anaesthetic effects, using a mutilating preparation in which one could measure metabolism in the absence of nervous, hormonal or autonomic influences. In this preparation, the pig underwent corporal section at the level of the first lumbar vertebra, with perfusion of the caudal third of the body by a pump oxygenator–heat exchanger. Sympathetic agonists of the α variety (phenylephrine) or β variety (isoproterenol) did not trigger hypermetabolic responses; interestingly enough, the only effective triggers in these experiments were carbachol (depolarization) and increased temperature.

The authors’ overall view is that the role of the sympathetic nervous system in MH is secondary. It is certainly an important part of any MH episode; however, the reaction starts in skeletal muscle and the homeostatic reactions to such a severe response aid in maintaining survival, much as with any other severe stress. α- and β-antagonists modify these episodes in the experimental situation, but without consistently and completely preventing or ameliorating them and, in the case of β-antagonists, without reducing mortality. Central sympathetic findings are variable: Wheatley and colleagues [112] did not find abnormalities in porcine central nervous system bioamines, while Draper and colleagues [28] observed lower concentrations of dopamine in the caudate nucleus of susceptible pigs. They interpreted this as a disturbance of the dopaminergic system of the basal ganglia, with no dysfunction of adrenaline or noradrenaline metabolism. The serotonin inhibitor ketanserin has altered the course of porcine MH in an inconsistent manner [90]. Consistent and reproducible beneficial effects of any drug therapy were not seen until Harrison...
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[59] reported the use of dantrolene. Initiation of MH episodes appears to relate less to sympathetic activation than to depolarization (see MUSCLE: Sarcolemma and Depolarization), although both factors could be involved.

MYOCARDIUM

Britt [7] wrote an editorial in the New England Journal of Medicine that introduced and explained MH as a general medical problem. She referred to MH as a disease of skeletal and cardiac muscle, but she did not describe any specific abnormalities of cardiac muscle per se. This editorial apparently reflected her bias about cardiac muscle and her presumptions that she believed would be confirmed as more data were accumulated. However, supportive evidence is weak. Wingard [118] believed that myocardial problems, either primary, or secondary to sympathetic overactivity, resulted in sudden death, either as a result of “heart attacks” or from a higher incidence of events such as automobile accidents than were seen in the general public. Huckell and colleagues [65] reported life threatening arrhythmias in four susceptible humans, two of whom had a family history of sudden death; these patients had not had awake pyrexic crises. The authors concluded that there may be a unifying concept for various manifestations of MH; that is, there may be abnormal calcium release in the heart also. Huckell and colleagues [64] reported that 26 of 93 patients identified as positive by biopsy (mean age 32-34 yr), had ECG conduction defects, repolarization abnormalities or increased voltage suggestive of hypertrophy. They did not compare the incidence of these findings with that in a control group of normal patients. These authors continued their studies with a series of catheter-guided human myocardial biopsies [80]; these biopsies did not demonstrate MH-related defects, but did show changes consistent with known artifacts of heart muscle following excision, preservation and sectioning. Kawamoto and colleagues [72] demonstrated normal cardiac perfusion in a patient convalescing from an acute MH episode.

The question remains, does the heart have a functional defect which is not detectable structurally, or do these findings signify that the heart is normal? Others have reported changes in myocardium of susceptible pigs. Hartigan and McLoughlin [62] reported ostium primum lesions in a litter of susceptible pigs. Roewer and colleagues [95] measured abnormal excitation–contraction coupling after halothane was administered to isolated heart muscle from susceptible pigs. However, the physiological right heart bypass studies of Gronert and colleagues [50] demonstrated normal sympathetic reflex responses to stress: during whole body MH initiated by halothane and suxamethonium, the sympathetic nervous system produced, via β-agonist effects, major changes in cardiac metabolism. Cardiac oxygen consumption increased five-fold and efficiency decreased about eight-fold, but the responses were completely blocked by large doses of propranolol (40 μg kg⁻¹ min⁻¹ by continuous i.v. infusion). There were no suggestions of MH triggering in the heart: neither lactate nor potassium was released during acute MH episodes in the absence of treatment with propranolol. These responses imply secondary sympathetic effects which then altered myocardial physiology.

Britt [9] has inferred from clinical evidence that cardiac muscle is abnormal and that cardio-active drugs may be harmful in MH. She has developed this position in part because of her unparalleled MH file of human case reports. Her statistical analysis indicates a direct relationship between use of drugs such as digoxin, calcium and adrenaline and increased mortality. She concludes that these drugs can produce MH responses in skeletal and cardiac muscle and that, in the presence of these drugs, the heart may not function adequately for recovery. However, association does not imply cause. We believe that critically ill patients were given more of these supportive drugs and that it is consequently difficult to associate increased mortality with one specific facet of treatment when there are multiple life-threatening factors involved in MH episodes. Gronert and colleagues [43], using a right heart bypass preparation, tested this hypothesis concerning the response to cardiac drugs. This study was relevant to care of humans because the pig is more closely inbred and because there is greater control of genetic factors; therefore drug-related risks should be more obvious in the pig model. Calcium, digoxin and potassium were not dangerous drugs in regard to their effects upon cardiac muscle. All stimulated cardiac metabolism in both normal and susceptible pigs, but none precipitated abnormal responses.
OTHER TISSUES
The foremost and single confirmed representative of a weak list of other tissues and organs which could be primarily involved in MH is porcine red blood cell fragility [63], but not human red cell fragility [40]. While disseminated intravascular coagulation occurs in acute MH episodes, this is not likely to be an example of involvement of other tissues. It is rather more likely to be the result of release of tissue thromboplastins as a result of increased cellular permeability or cell breakdown secondary to the stresses of acidosis, increased temperature and ion fluxes. Platelets have been proposed as being primarily involved in MH because of the presence of a contractile apparatus similar to that of muscle; this has led to the development of a diagnostic test based upon platelet ATP depletion by halothane; this test has not been confirmed by others in numerous studies and the inescapable conclusion is that MH does not directly affect platelets in a way that we can presently measure [13]. A recent abstract reintroduced the concept of platelet abnormalities via a modification of the earlier studies, using platelet ATP depletion in conjunction with electron microscopy [103]. It is premature to conclude that this modification establishes primary platelet dysfunction. Porcine platelet monoamine oxidase activity is not different from that in normal swine [22]. Several articles had suggested that plasma cholinesterase function was deficient in some susceptible families. Subsequent investigation did not confirm this proposal and the consensus is that these families were not representative of MH susceptible families in general [51]. Increases in hepatic temperature that occurred early in porcine MH episodes had been interpreted as primary involvement [5]. Data from Darrah and colleagues [23] on the function of isolated liver slices from susceptible pigs supported this position. However, direct examination of hepatic metabolism did not confirm these inferences, suggesting that the liver is not abnormal in MH susceptible individuals [14, 44, 56]. While calcium is a ubiquitous ion serving as a second messenger or mediator in almost all tissues, and the presumption of a generalized abnormality is therefore attractive, the evidence supporting or confirming such a role is not at hand. Klip and colleagues [74] described abnormal MH-related calcium fluxes in lymphocytes that were isolated from susceptible pigs and exposed to halothane.

Again, we need confirmation—perhaps this will be the breakthrough in regard to abnormalities of other tissues. Direct and consistent support is virtually non-existent for theories involving other tissues and organs.

It appears, and perhaps quite logically, that the genetic selection used to develop porcine skeletal muscle to an extreme has led to abnormal skeletal muscle responses to stress and, since other tissues and organs were not similarly selected, there is no reason to expect them to be abnormally involved in a consistent manner in regard to MH [43].

MUSCLE
General considerations
Skeletal muscle, then, is the principal aetiological focus. Physical responses to environmental stresses indicate that the muscle itself, in the absence of other factors, has exaggerated and magnified stress responses. This is exemplified by the effects of external heating. Intact susceptible pigs exposed to a warm environment have increased stress responses in muscle after slaughter [6]. They also are triggered into MH reactions by heat alone [91]. That this is a direct muscle response independent of sympathetic, hormonal or reflex activity is shown by the response of an isolated perfused caudal preparation [46]. Caudal muscle perfused, oxygenated and warmed by a heat exchanger and external heat lamps responded similarly as did the intact pigs of Ørding, Hald and Sjøntoft [91]: at temperatures greater than 40–41 °C, oxygen consumption and lactate production of muscle from susceptible pigs precipitously increased, an effect not observed in muscle from normal pigs that were equally heated. Heat production during porcine MH episodes is accounted for by stimulation of aerobic metabolism, glycolysis, neutralization of hydrogen ion, hydrolysis of high energy phosphate esters and ion pumping [5, 52]. The increase in whole body oxygen consumption in the intact animal is accounted for by increases in muscle metabolism [44]. It had been proposed earlier that futile cycling of certain metabolic reactions might explain the runaway metabolism of MH [20]. Futile cycling is important in the bumblebee, as the thoracic flight muscles must be warmed to 30–32 °C to be active enough to sustain flight. It consists of cyclical increased metabolic activity unrelated to specific functions or reactions other than those of increasing heat production, until the
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muscles have been sufficiently warmed. The accelerated substrate cycling of glycolysis in MH does not appear to be futile; it is apparently related to a need for additional ATP for calcium pumps, particularly at a time when mitochondrial function may be limited. This is in keeping with recent findings that support the theory of altered calcium control (see MUSCLE: Mitochondria, Sarco-

plasmic reticulum). Studies evaluating the triggering action of calcium, digoxin, potassium and hypercarbia in susceptible pigs demonstrated that potassium was the only factor that would trigger MH responses in skeletal muscle [43]. This effect of potassium is analogous to its actions in vitro [84]. These findings confirm the supposition that calcium will not trigger skeletal muscle, because the gradient from extracellular fluid is huge, at least 10⁸, and because exogenous calcium, even in large doses, would alter that gradient very little. In the cited study, ionized calcium concentrations reached 7.5 mmol litre⁻¹. Hypercarbia, to 21.3 kPa, with its associated respiratory acidosis and sympathetic stimulation, and digoxin at extreme toxic concentrations (50 ng ml⁻¹) were also ineffective in triggering susceptible skeletal muscle. Because of the cardiac toxicity of these drugs when given in high doses, these animals were perfused via cardiac bypass, an advantage which eliminated cardiac depression or toxicity as a factor in evaluating results [43].

Rigid v. non-rigid muscle

Britt and Kalow [10,70] divided MH into rigid and non-rigid classifications, based upon their analysis of case reports; rigid patients had the classic MH symptomatology of acidosis, fever, tachycardia, etc., while non-rigid patients had few confirmatory signs. These classifications did not survive rigorous examination [42]. The use of 37 °C rather than room temperature muscle baths at Toronto led to the demise of this theory. The increase in temperature diminished the number of higher-than-normal threshold responses (which had been associated with non-rigid patients). The present view suggests that rigidity depends primarily upon the intracellular concentration of free unbound ionized calcium; if this approaches 5 × 10⁻³ mol litre⁻¹, or if mechanical threshold is altered, rigidity is likely [8,42].

Sarcolemma

The sarcolemma (surface membrane and transverse tubules) responds to stimuli abnormally. It is difficult to discern whether the abnormality rests with the membrane itself or whether the defect lies with internal sarcoplasmic structures which respond to the transferred signal. These abnormalities are characterized by the following. There is a lower mechanical threshold in susceptible muscle membrane; that is, a lesser degree of depolarization produces a contracture [15,38]. Halothane depolarizes the surface membrane [37] and various methods of electrical stimulation result in exaggerated responses [1,43,93,94]. Because the halothane depolarization of about 7–15 mV develops after 20–30 min exposure, the mechanism could be related to metabolic changes within the fibre proper rather than to a direct membrane effect [37]. Data from multiple pulse stimulation, one to six pulses with a 5-ms interval between each, support the theory of abnormal calcium transients and abnormal excitation-contraction coupling [93]. Each 5-ms pulse basically releases a “pulse” of calcium that activates the contractile mechanism; susceptible muscle responds with a faster rate of increase in, as well as greater, tension. Because of overlap of data, these differences were not dramatic, although mean values differed significantly. The use of dantrolene markedly enhanced these differences and eliminated the overlap of data. Dantrolene inhibits the response of both normal and susceptible muscle, so that both have a lower tension and a slower rate of increase in tension. Presumably the susceptible muscle defect permitted greater release of calcium with multiple pulse stimulation. Therefore the susceptible muscle recovered a significant portion of its responses at a time when the normal muscle was still depressed by dantrolene. These data suggest that depolarization per se, if exaggerated, may be a factor in the aetiology of MH episodes. Steiss, Bowen and Williams [105] noted increased amplitude and duration of motor unit action potentials in susceptible pigs; these findings may further support the theory of increased calcium release with motor nerve stimulation. Nelson, Flewellyn and Arnett [87] observed that the onset of mechanical tension was delayed in susceptible pigs in comparison with normal pigs. However, their stimulation artefact obscured the onset of the muscle action potential, thus weakening their major observation of prolonged electromechanical delay.
Intracellular organelles

Specific intracellular muscle organelles include the mitochondrion and sarcoplasmic reticulum (SR). Both human and porcine preparations have been examined by isolation techniques in numerous reports over the past 17 years or so. The process of isolation may alter the function of intracellular organelles in ways that we do not realize, and we therefore may not be warranted in drawing conclusions based solely upon the response of these isolated fragments. Without presenting a review of the considerable detail and variability of all these studies, the consensus can be said to be that these studies demonstrate changes consistent with a myopathy, that they are non-specific changes, that they are of insufficient magnitude to account for MH, and that they do not define a unique defect attributable to MH.

Mitochondria

Cheah [19] has proposed, and Fletcher and Rosenberg [32] support, a theory that mitochondrial phospholipase A2 is abnormal and that this enzyme causes release of fatty acids which acutely inhibit the function of SR. This in turn causes the characteristic overt malfunctions of MH. The release of phospholipase A2, however, is dependent in part upon release of calcium, which stimulates this entire process. Since MH is thought to be a disorder of calcium metabolism or of calcium transients, it is difficult to determine which is the primary alteration, calcium or phospholipase. The response therefore could be a secondary characteristic of MH; at present this fascinating theory is not confirmed. Could the phospholipase A2 response be a reflection of typical and usual biochemical responses that occur in susceptible cells or organelles that do not tolerate stress? Is this perhaps the result of an imbalance between energy supply and demand because of the limited ability of mitochondria to supply ATP when they are binding overflow amounts of calcium? Stadhouders and colleagues [104] have elegantly demonstrated by electron microscopy–microprobe analysis that mitochondria participate in reserve compensatory responses involved in porcine MH. During acute MH episodes, mitochondria actively sequester calcium ion, an action reversed by treatment with dantrolene. The implication is that mitochondrial function is restricted and limited by the forced compensatory uptake of calcium [27]. This may therefore explain why whole body oxygen consumption does not increase as much during acute MH as one would expect; for example, as much as it does during exercise. This limited increase in whole body oxygen consumption could also be the result of a limited involvement of whole body skeletal muscle—not all muscles might be participating in an MH reaction.

Sarcoplasmic reticulum

SR is the focus of the current theories of malfunction during MH episodes. The clinical course and laboratory data strongly suggest that SR no longer can control intra-fibrillar concentrations of free ionized unbound calcium and that the associated hypermetabolism is a result of compensatory stimulation of calcium pumps. This is specifically supported by the delicate studies of Lopez and his colleagues [2, 77], who measured intracellular ionized calcium concentration using an ion-specific microelectrode (see also reference [104], Mitochondria). They observed increases at rest in humans (intact intercostal) and in pigs. They also saw dramatic increases in ionized calcium in intact pigs during acute MH with reversal of the increase by dantrolene. One aspect of these findings deserves comment. It is paradoxical to find increases in calcium ion at rest; there should be signs or findings related to this increase, in particular an increase in basal metabolism, such as that postulated by Williams [113]. This is not the case. It seems probable, in the absence of confirmatory data or of other supportive findings, that the increase in intracellular calcium ion noted at rest may be artefactual, perhaps caused by perturbation of the cells during measurement with the microelectrode. MH susceptible muscle cells may be unable to tolerate such stress, in contradistinction to the stability of normal cells. The alternative theory is that there has been a resetting of resting ionized calcium to a non-energy-demanding level that is perhaps dangerously close to one which could activate contractile activity.

Crucial to our understanding of MH is a knowledge of basic muscle physiology. At present, muscle physiologists do not yet understand the mechanism by which the wave of depolarization from the transverse tubule is transmitted to the SR or to its triad. Dantrolene acts in this same area of muscle; as a result, its specific action, probably closely related to the mechanism of MH, cannot be used to define the lesion of MH.

Two mechanisms of calcium release are postula-
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Drugs in MH. As an episode of MH progresses and the combination of acidosis, increased temperature and electrolyte imbalances leads to failure of cellular mechanisms, or loss of energy charge, cellular permeability increases and there is a beginning of breakdown of the organism. Dantrolene appears to be specific for treatment, because it rapidly reverses these changes under a variety of experimental and clinical conditions. It is not directly diagnostic of MH, because it can aid in controlling high temperature or muscle rigidity regardless of cause. For example, it reduces contractures because it increases efflux from the terminal cisterna of the SR, thereby increasing permeability to calcium. In the second, an amount of calcium too small directly to cause contraction enters the fibre with depolarization and regenerates a much larger increase in calcium release by increasing the permeability of the SR. Both of these types of calcium release lead to contraction, and the additional free, unbound calcium ion is then taken up and bound by SR. Abnormal patterns of calcium-induced calcium release have been observed in samples of susceptible skeletal muscle. While there is not yet a “normal” skeletal muscle role for this alternate mechanism for calcium release, these studies [81, 89] suggest that calcium-induced calcium release may be a part of the abnormal response in MH muscle. For some as yet undefined reason, there may be a strong enhancement of calcium-induced calcium release in MH.

Calcium-induced calcium release may be relevant in MH only at a time when dysfunction is occurring, or, it may relate only to the abnormality of MH. One factor that has impeded application of this theory to MH is the lack of blocking action by dantrolene on isolated vesicles of SR [81]. This paradox has apparently been solved by Ohta and Endo [89], who determined that dantrolene would block this release at 37 °C but not at 22 °C (a frequently used temperature for these studies).

Depolarization

It is the senior author’s belief that depolarization may be significant in MH reactions, whether these are anaesthetic-induced or “awake” (see Sarcolemma). (1) Halothane depolarizes skeletal muscle membranes. (2) The mechanical threshold of susceptible muscle is lower than that of normal muscle and therefore predisposes to easier development of a contracture. (3) Halothane decreases the mechanical threshold of muscle. (4) Suxamethonium and carbachol depolarize normal and susceptible muscle, and both trigger sus-
ceptible but not normal muscle. (5) Electrical stimulation triggers susceptible but not normal muscle. (6) Non-depolarizing neuromuscular blocking drugs delay MH episodes. Evidence against this theory is the action of 4-aminopyridine, which increases acetylcholine release at the endplate, but does not trigger hypermetabolism in susceptible swine [53]. It appears that extreme muscle activity or tension, either in the awake susceptible subject or in the susceptible individual who has increased muscle tension induced by drugs during anaesthesia, is predisposed to have an exaggerated stimulation of metabolism.

Rhabdomyolysis

Rhabdomyolysis may occur as a disorder by itself, related to exercise, certain stimulating drugs, or suxamethonium; it may, but need not, occur as part of an MH episode. Free myoglobin, the *sine qua non* of rhabdomyolysis, begins to increase in plasma soon after exposure to the causative stress, and several hours before creatine phosphokinase begins to increase [33]. It can be detected in the blood or urine almost immediately. It is cleared quickly, so quickly that in less severe instances the clinician may miss the increase, and think that the episode did not involve muscle breakdown.

**Triggering**

Kalow, Britt and Chan [69] have suggested that an MH episode depends upon three factors: (1) an inherited predisposition; (2) internal and external qualifying factors that establish or protect from vulnerability; (3) the presence of triggering agents or conditions. The term “triggering” is apropos because the reaction is self-sustaining once started. Obviously, a greater influence by any of these individual factors may increase the likelihood of an episode.

Many believe that prior exercise may predispose susceptible individuals to more severe MH episodes if they are anaesthetized immediately afterwards; for example following exercise-related trauma. Briskey [6] and Van den Hende and colleagues [110] reported this phenomenon in swine. The aetiology of this accentuation is not certain; it may result from prolonged increases in intracellular ionized calcium concentrations secondary to multiple depolarizations, a position supported by the attenuating actions of non-depolarizing relaxants in MH [45, 54]. It might in part be related to the increase in temperature that occurs with sustained exercise. Others would suggest that sympathetic stimulation has prolonged effects that could account for this accentuation. A combination of all three may be responsible; based upon physiological mechanisms, this is possible and perhaps likely.

**Associated Disorders**

While an MH susceptible subject is usually normal in regard to history, physical examination and appearance, (there are no obvious signs of the subclinical myopathy), there are some clinical disorders with obvious clinical abnormalities, some of which may be related to MH and some mere speculation. These disorders include myotonia, Duchenne’s muscular dystrophy, central core disease, sudden infant death syndrome (SIDS), neuroleptic malignant syndrome (NMS) and heat stroke. Myotonia involves rigidity with suxamethonium, similar to the response of sustained conscious effort in myotonic individuals. Inbred myotonic goats develop this same rigidity to suxamethonium, but do not develop MH, even when the anaesthetic includes halothane [88]. Duchenne’s is now recognized to involve MH-susceptibility [96]; it has always been known to involve an increased risk for anaesthesia: myocardial involvement, with difficult-to-resuscitate cardiac arrest; acute rhabdomyolysis of skeletal muscle, sometimes in the absence of signs of MH or identifiable changes in metabolism [100]. Central core disease, a clinical disabling myopathy that histologically includes multi-section loss of mitochondria (“central cores”) definitely includes susceptibility, confirmed by reported episodes [34]. SIDS, or cot deaths, statistically correlates with MH [92] and has an increased incidence of positive muscle biopsies, but from only one laboratory [25]. This suggested association requires further analysis for, when directly observed, SIDS does not present as hypermetabolism, but as cessation of breathing during quiet sleep. Furthermore, statistical association can be misleading, for SIDS also correlates with administration of oestrogens to pre-term mothers [31]. Because MH susceptible muscle is more easily triggered into hypermetabolic responses by physical stimuli such as heat, we should expect more cases of NMS and heat stroke to occur in susceptible people—a position supported by the positive muscle con-
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eca and colleagues [18]. However, the present authors believe that NMS occurs predominantly because of the central action of the psychotropic drugs; it may later trigger skeletal muscle (if susceptible) because of the varied temperature, electrolyte and acid–base abnormalities. This is an unsettled area.

ACQUIRED SUSCEPTIBILITY

Is there an aetiological explanation for acquiring susceptibility to MH? That is to say, can MH episodes be induced in non-susceptible individuals? The number of MH episodes reported in patients with various lymphomas almost suggests that there could be a predisposing effect [102]. There are several avenues of speculation, although none is necessarily directly related to lymphomas. Because general anaesthetics non-specifically perturb membranes [82] and because MH may be an exaggeration of normal responses [83], there is the possibility that prolonged exposure to MH triggering agents could eventually or ultimately disturb membrane homeostasis to the degree that MH occurs. One case report [85], in which approximately 26 h of anaesthesia was administered in a 36-h period, may exemplify this. MH involves a diminution in mechanical threshold, a situation in which contractile activation occurs more easily than usual; that is, a lesser degree of depolarization produces a contracture. Thus, a combination of drugs or factors (pore-formers, potentiators) can produce a decrease in mechanical threshold or an increase in permeability to calcium ion. If there is also concomitant depolarization of muscle membranes, there could be massive compensatory hypermetabolism, or an MH-type attack or episode. This perhaps is similar to the situation involving heat stroke, NMS, etc. With a certain amount of thermal insult alone in normal muscle, intracellular control of calcium can be lost [35] and, again, an MH episode could occur secondarily. If a number of the above alterations occurred simultaneously, in conjunction with exercise, increased activity or use of stimulant drugs, or both, MH susceptibility could well occur. Its presence might not be recognized unless the patient happened to receive a triggering anaesthetic.

ENERGY IMBALANCE

Whatever the mechanism or originating stimuli, an MH episode per se represents an imbalance between energy supply and energy demand. The pathophysiological picture of an acute MH episode is identical to that of ischaemia, as described in the brain [101], heart or other tissues or organs. The resulting changes have been well described, and involve scavenging of free radicals, action of quenchers or anti-oxidants, or reducing agents such as glutathione. These interactions could also be responsible for abnormal activity of adenylate cyclase, adenylate kinase, cyclic AMP and other enzymes under a variety of circumstances. The similarities are not complete, for calcium antagonists are not effective in treating MH (vide supra, Drugs in MH). Data are contradictory regarding the role of glutathione in MH—some positive [99] and some negative [30]. Again, even if abnormal activity is confirmed, the continuing difficulty is to decide which responses are primary and which are secondary. Primary dysfunction would occur in enzymes or membranes directly altered by susceptibility to MH, but normal tissues would be stimulated into typical and usual stress responses that occur secondary to abnormal stress responses elsewhere in the body or the cell. Susceptible skeletal muscle is exquisitely sensitive to perturbations and the hypothesized primary abnormal response, an increase in intracellular ionized calcium, would promote a variety of (normal) secondary, and in part compensatory, responses. Further, these secondary responses might be difficult to examine in a situation separate from MH—a normal cell would not react unusually until stress reactions occurred.

In particular, if ATP concentrations tend to decrease as intracellular calcium increases, there may be a loss of normal cell membrane ionic gradients. As the mitochondrion in its reserve capacity begins to accumulate the excess calcium, the enzyme phospholipase A2 may be activated, with a release of free fatty acids. The release of free fatty acids will either alter SR function or add to the inherent SR dysfunction of MH. Mitochondrial calcium binding restricts mitochondrial function, and increases in oxygen consumption may then be limited, exaggerating the energy imbalance. Continuing blood supply to the affected tissues may result in oxidation of the free fatty acids, with the formation of prostaglandins, thromboxane A2 and free radicals. All of these, along with their interactions, alter permeability and conductances of membranes. These multiple events, in conjunction with the hypermetabolism of MH, could cascade into a destructive mayhem. Glutathione and other substances may be inordi-
nately activated to counter some of these reactions. Many of the foregoing may overlap or resemble some of the changes in MH that have been considered as mechanistic. This is likely because of the confusion created by analysis of conditions that are in part the result of acute MH and in part caused by the imbalance between supply of substrate and energy consumption. At times during an MH episode there are elements of both. It is up to the MH “detective” to solve the riddle.

REFERENCES
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