



The Communicator

25th European MH Group Meeting Demonstrates Significant Progress

by Henry Rosenberg, MD

The 25th annual meeting of the European MH Group (EMHG) took place in the lovely Baltic city of Riga, Latvia, May 25-27, 2006. The European MH group is made up of investigators and clinicians interested in MH and central core disease (CCD) who are located in European Countries, New Zealand, South Africa, Brazil and other countries. Dr. Sheila Muldoon and I attended the meeting as guests and participants.

Included in the EMHG are anesthesiologists, molecular biologists, neurologists and other scientists and clinicians. The group has emphasized the advancement of the understanding of the pathophysiology of MH and similar disorders in particular as it relates to diagnostic testing for MH. In contrast, the Malignant Hyperthermia Association of the US (MHAUS) is a patient advocacy organization whose goal is the promotion of educational information about MH to clinicians and patients.

The EMHG, through more than 25 biopsy centers and other investigative units in Germany, Switzerland, France, UK, Ireland, Sweden, Denmark, Italy, Holland, New Zealand, and Brazil have deepened our understanding of laboratory diagnosis of MH, in particular the molecular genetics of MH. In North America there are six biopsy centers in the US and two in Canada. MH research units in North America may be found in Toronto, Canada, Bethesda, MD and, most recently, a consortium of investigators in Boston, Rochester, Sacramento, Bethesda and Houston.

Several themes were explored and developed at the meeting through formal and equally valuable informal meetings and discussions:

- 1.) Interesting and unusual cases presentations
- 2.) Expansion of the role of molecular genetic testing for MH diagnosis
- 3.) Exploration of similarities and differences between Central Core Disease and MH
- 4.) Definition of the significance of many DNA variants found in the ryanodine receptor gene in relation to the pathophysiology of MH
- 5.) Minimally invasive diagnostic test for MH other than molecular genetics

The meeting began with an invited presentation by a guest lecturer (Dr. I. Klavins) speaking on the role of fatty acid inhibitors in the treatment of tissue damage caused by ischemia. A new class of drugs has been developed and is currently being deployed that partially inhibit fatty acid production in the cell. High levels of certain fatty acids are known to produce tissue damage. The partial fatty acid

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Malignant Hyperthermia (MH) is an inherited muscle disorder which, when triggered by potent inhalation anesthetics and succinylcholine, may cause a life-threatening crisis. The incidence of MH is low, but, if untreated, the mortality rate is high. Since the advent of the antidote drug, dantrolene sodium, and with greater awareness of the syndrome, the mortality rate has decreased. Great advances in our understanding of MH have been made since it was first recognized in the early 1960s, but the nature of the fundamental defect(s) is still unknown.

MHAUS advocates that all surgical patients undergoing general anesthesia should receive continuous temperature monitoring, that adequate supplies of dantrolene be stocked near the OR and that thorough family histories be obtained.

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MHAUS Approves \$70,000 Grant For Genetic Testing



MHAUS recently approved a grant for over \$70,000 for “Improvements in Genetic Testing for Malignant Hyperthermia in North America.” This is a study on the genetics of malignant hyperthermia. It is being run by two prominent members of the MH community, Dr. Sheila Muldoon and Dr. Barbara Brandom.

Dr. Muldoon is Vice President of the MHAUS Board, Chair of the North American Malignant Hyperthermia Registry (NAMHR) Advisory Council, and Director of the MH Diagnostic Center at Uniformed Services University of the Health Sciences (USUHS). Dr. Brandom is the Director of the NAMH Registry and a Professor of Anesthesiology at the University of Pittsburgh.

Examination of the entire coding region of the ryanodine receptor gene will be performed by Dr. Nyamkhisig

Sambuughin. Dr. Sambuughin has recently rejoined the research team at USUHS. She has published many articles on ryanodine receptor genetics and MH, most recently in *Anesthesiology*, 2005.

The grant will provide Drs. Muldoon and Brandom the means to contact people in the NAMH Registry who had strongly positive MH Biopsy results on the CHCT (Caffeine-Halothane Contracture Test) and offer them the chance to join this study. If they participate in the study, they will have some blood drawn and sent to USUHS. The grant will cover the cost of the genetic study for these individuals, as well as the administrative costs of contacting these individuals.

It is anticipated that the results of this study will find more sequence variants in the ryanodine receptor gene. This work is a necessary foundation to support adding more exons to the clinically available test of MH susceptibility, and thus increasing the sensitivity of this diagnostic test.

The Malignant Hyperthermia Association of the United States is a not-for-profit organization dedicated to reducing the morbidity and mortality of malignant hyperthermia and other heat-related disorders by: improving medical care related to MH; providing support information for patients; and improving the scientific understanding and research related to MH and other kinds of heat-related syndromes.

For more information or for materials on malignant hyperthermia or MHAUS' programs, call 607-674-7901; write MHAUS, PO Box 1069, Sherburne, NY 13460; or visit us on the Internet at www.mhaus.org.

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oxidation inhibitor drugs (e.g., ranolazine) minimize cellular damage by inhibition of fatty acid production and their entry into mitochondria.

Parenthetically, several years ago research conducted by Dr. Jeff Fletcher and I suggested a role for such fatty acids in the pathophysiology of MH as it was found that certain fatty acids were produced in excess in MH muscle tissue. However, this line of research was not continued for a variety of reasons.

Regarding the interesting clinical reports, Dr. Hannah Brand of South Africa presented a case of MH in a patient suffering from a rare disorder “Hypomelanosis of Ito.” Dr. Brand is working hard to establish an MH biopsy testing center in South Africa.

Dr. Henrik Rueffert of Leipzig presented a case of MH triggered in a 21-year-old man who had undergone nine previous anesthetics without apparent problem. The MH episode occurred three-and-one-half hours after induction of anesthesia and was treated successfully with dantrolene. The patient was found to harbor a known causative mutation in the RYR-1 gene for MH. Of interest, the investigators obtained the anesthetic records of the previous surgeries and demonstrated that there was evidence of hyperthermia and signs of MH toward the end of several of the procedures.

A case was presented from the MH diagnostic center in Brno, Czechoslovakia, of a patient who developed almost certain MH triggered by succinylcholine. The MH center in Brno is the newest center in Europe. The patient suffered significant medical problems because dantrolene was not available for 55 minutes. (Dantrolene is not required to be available immediately in Czech hospitals other than University



Hospital.) They now have the facilities for muscle biopsy testing and the patient will be tested when recovered. The center also operates a hotline and receives at least 10 calls per week.

In Latvia, the meeting host, Dr. Kaulis, is establishing an MH diagnostic center that will offer contracture testing as well as molecular genetic testing.

Dr. Neil Pollock of New Zealand described 53 anesthetics with triggering agents in 28 patients who were found to be MH negative on contracture testing. None experienced clinical problems. It is not clear how many clinicians avoid MH triggers even though a patient may have tested MH negative.

Dr. Werner Klingler of Ulm, Germany, presented studies of the drug MDMA (Ecstasy), known to produce a hyperthermic syndrome. He found that MDMA activates muscle at the neuromuscular junction, not through the direct release of intracellular calcium as in MH. Hence, dantrolene is unlikely to be of benefit in treating toxicity from this

A hotly debated issue is whether a patient who experienced an almost certain MH clinical event...should undergo genetic testing without first undergoing contracture testing. On the one hand, if a known causative mutation is found, a contracture test is avoided. On the other hand, a correlation between contracture and mutation is needed because of our incomplete understanding of the molecular genetics of MH.

drug. Many of the metabolic effects of the drug are blocked by relaxants that block the neuromuscular junction.

One of the main goals of MH research is to develop a DNA-based diagnostic test. Studies to date have shown that mutations in one gene, the ryanodine receptor gene (RYR-1), are causal for MH in perhaps 70% of MH cases. At least one other gene has been shown to be causal for MH in a few families and there are probably several other genes that are involved in clinical MH cases. The RYR-1 gene is very large. It consists of about 159,000 base pairs. About 100 DNA changes have been described in the gene. Of these, 23 have been found to be “causal” for MH and form the basis of the genetic test in Europe. Some of the other DNA changes are also undoubtedly causal, but all of them have not been identified.

Isolated cell systems or cultured muscle cells have been modified to incorporate one of the

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known MH mutations in their DNA. When the cells are exposed to caffeine, chlorocresol and/or halothane, an increase in intracellular calcium can be measured via specific dyes. Studies are underway in such systems to determine which DNA changes lead to such accentuated calcium release. This would indicate that these mutations are likely causal for MH.

Patrick Brooms from Leeds described experiments along these lines with skeletal muscle myotubes (a collection of muscle cells that when grown in culture form tube-like structures). He and his co-workers demonstrated the viability and reproductibility of this technique, showing that known causal mutations induce enhanced calcium release from cellular stores in muscle.

Dr. Wehner and colleagues from Leipzig also demonstrated that myotubes, derived from patients who are MH-susceptible and harbor MH causing mutations, demonstrate increased resting cellular calcium levels and respond with accentuated calcium release on exposure to halothane.

The technique of measuring cellular calcium flux from cultured muscle may be of value in clinical diagnosis of MH in the future. Other investigative centers using similar experimental approaches are located in Basel, Switzerland and Naples, Italy.

There were, however, no presentations utilizing B lymphocytes from MH patients, which also show similar increased cellular calcium release on exposure to MH triggers.

An important issue is the correlation between the contracture test results and the results of molecular genetics. The Swiss experience, based on 299 biopsies with genetic analysis from families with known



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MH mutation showed none of 132 patients with known MH mutations were MH negative on the IVCT. However, 48 of 167 patients without a mutation were contracture test positive. The possibility is that they harbor another mutation(s) that has not been defined.

The group from Leeds, England, showed that of 184 families with MH mutations in RYR-1, five families demonstrated two mutations. In the UK experience with about 1200 samples, 13 patients were found to have an MH mutation, but were MH negative on the contracture test. If one considers the genetic test as being 100% accurate, this implies a 2.5% false negative rate for the contracture test in MH families. Another possible interpretation is the invocation of a two-hit model for susceptibility to MH (i.e., in those families a second gene is needed to be susceptible and these patients did not have the second mutation or they spontaneously mutated the second gene to be a non-responder – a dominant negative

mutation or a “rescue” mutation).

Since it is policy that patients who are not found to have a mutation are never told they are not susceptible to MH, it is possible to use molecular genetic testing for MH diagnosis in families where one member is found to have an MH mutation. To date, 52 MH-susceptible patients were diagnosed as MH-susceptible without recourse to muscle biopsy testing in Swiss families based solely on DNA testing. This number will likely increase with time.

Another interesting study from the Leeds group presented by Dr. Danielle Carpenter showed that 65 of 90 patients diagnosed as MH positive on biopsy without one of the known MH mutations actually were found to have a DNA change cosegregating with disease status. If those changes are proven to be causal for MH, this would expand the panel of mutations and would increase the sensitivity of the genetic test.

A hotly debated issue is whether a patient who experienced an almost certain MH clinical event (such as the Czech patient previously described) should undergo genetic testing without first undergoing contracture testing. On the one hand, if a known causative mutation is found, a contracture test is avoided. On the other hand, a correlation between contracture and mutation is needed because of our incomplete understanding of the molecular genetics of MH.

The European MH Group requires a positive muscle biopsy contracture test prior to genetic testing. The North American group does not have such a limitation, but will review the presumed case prior to recommending genetic testing.

Since it is now clear that improving the sensitivity of the molecular genetic diagnostic test entails expanding the mutation panel

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from the current 23 to 50 or more mutations, cost becomes an issue. The more mutations that one tests for, the greater the cost. With a relatively homogeneous population, such as in Switzerland, a test panel of fewer than 10 mutations may be used to detect most of those at risk for MH. However, in other countries a much larger panel will be needed. The cost for testing 40, 50, or more mutations with current techniques is significant, reaching several thousand dollars. However, a technique devised by a Dutch biologist promises to simplify such testing and reduce cost. The technique, multiple ligation-dependent amplification (MLPA) www.mrc-holland.com detects copy number changes of up to 45 nucleic acid sequences in one simple reaction, hence reducing cost.

As the sensitivity of the molecular genetic test increases, the dependence on contracture testing will decrease, but the high sensitivity and specificity of the contracture test means that it will still be important for many years.

Central Core Disease (CCD) is an inherited myopathy that, in many cases, predisposes to MH. The many causative mutations for CCD are situated close to the C terminal end of the RYR-1 gene. "Cores" or degenerating material found in the muscle cell that give the cell a target-like appearance under the microscope, are found in muscle cells in some MHS patients with mutations in the C terminal end of the RYR-1 gene regardless of whether the patients have obvious muscle weakness. Ibarra presented data from Japan demonstrating that 29/51 MHS patients had RYR mutations (not necessarily causal though) and 15 displayed core-like structures in the muscle cell. The correlation with

clinical signs of weakness was variable.

Tegazzin from Italy described three Italian families carrying the same two novel mutations of RYR-1 gene. However, family members from only one family displayed cores.

Silva from Brazil presented data showing a high frequency of autosomal recessive forms of CCD in Brazil. They also identified novel mutations in several families.

Anetseder has previously shown that intramuscular injection of halothane or caffeine elicits a greater local rise of lactate and pCO_2 in MHS patients and animals compared to MHN patients. Studies in humans and animals presented at this meeting extended the studies in an attempt to clearly separate MHS from MHN patients. Greater separation was achieved in humans using 5 and 6% halothane and in swine using 15% sevoflurane. Technical issues still need to be worked out, however. The test requires two hours to carry out and, at higher concentrations of halothane, have been associated with elevated CK levels to $>800IU$. However, no patients developed signs of MH or muscle symptoms. The technique may eventually offer an alternative to the contracture test.

The European MH group has

embarked on a rigorous quality control program for muscle biopsy centers including on-site inspections, sample collection to quantify halothane and caffeine concentrations in liquid from the muscle bath, as well as rigorous definition of equipment and drug preparation and addition. Sources of variability in drug concentrations from the different labs are currently being explored.

The meeting has demonstrated that significant progress is being made in understanding the pathophysiology, presentation and molecular genetic diagnosis of MH. Members of the international medical and scientific community across many countries have been working together on the goal of eliminating death and disability from MH and to achieve a better understanding of muscle physiology and pharmacology. Despite much progress on these fronts it is clear that MH episodes still occur. Along with clinical and laboratory research into MH and its variants, a program of education as to the early signs of MH, ready availability of a treatment plan and dantrolene are all necessary to accomplish this goal.

Thanks to Dr. Jerry Parness for review and suggestions.

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PreventionGenetics Continues To Expand Testing

by James Weber, President
PreventionGenetics

Abnormalities in the sequence of the RYR1 gene are the primary known cause of MH and Central Core Disease. PreventionGenetics currently tests for about one-third of this particularly large gene. We cover nearly all portions of the gene in which abnormalities have been reported in the research literature. We hope to eventually offer a test for

Have you visited us lately? Log on to www.mhaus.org to get the latest information on MH, order materials, post a message to the bulletin board or learn about the "Hotline Case of the Month."

the entire gene. Please visit the PreventionGenetics web site www.preventiongenetics.com or phone (715-387-0484) for more information.

There are some especially nice features of the DNA test. It's simple, relatively inexpensive, and doesn't require any extensive travel. Patients just have blood drawn in their local doctor's office and shipped to the testing lab. Also, if a positive DNA test result is obtained in one family member, then it is easy to propagate this result throughout the family.

The main drawback of the DNA test is that it is not especially sensitive. This means that only a fraction (roughly 50%) of those that are MH-susceptible will yield a positive DNA test result. The relatively low sensitivity may be because we cover only a portion of the gene and/or because genes other than RYR1 are also involved in MH.

Despite this drawback, I strongly recommend that all families with a clear history of MH undergo the genetic test. The best person in such a family to test is an individual who either has had a positive muscle

biopsy test or an actual MH event. If a causative sequence variant (mutation) is found in this first (index) family member, then we can test other family members, like siblings, parents, and children for only about \$250 per person, far less than the muscle biopsy test.

Our experience with the DNA test for MH has also highlighted the need for additional research into the genetics of this disorder. For one thing, we need to identify other MH genes. We also need to learn if carriers of causative RYR1 mutations always experience MH events when triggering agents are administered and if family members who do not carry the causative mutations are at the general population risk for MH or at higher risk. I urge MH patients and their families to volunteer for new genetic research studies.

Paying for DNA and/or muscle biopsy tests is often a problem. Some health insurance plans will readily cover testing while others will not. MHAUS offers limited financial support for appropriate DNA testing. Families may also consider pooling funds to pay for the test in the index family member.

Center For Medical Genetics Moves Forward With Testing

The Center for Medical Genetics (CMG) at the University of Pittsburgh Medical Center (UPMC) is moving forward with providing genetic testing of the hotspots in the ryanodine receptor type one gene to people from around the country who could be susceptible to MH.

Ms. Deanna Steele, the genetic counselor dedicated to MH at the CMG of UPMC, is happy to discuss this test with both potential patients and their

physicians. She can be reached at (800) 454-8155.

As of July 1, 2006, 13 potentially MH-susceptible people had contacted the CMG to request information about the test, as well as a similar number of healthcare providers. The Diagnostic Genetics Laboratory at UPMC, under the direction of Dr. Jeffrey Kant, has completed testing on a handful of specimens, both for patients who had positive muscle caffeine halothane contracture tests and those who had

clinical MH episodes only.

Known mutations and new variants in the ryanodine receptor type one gene were identified. There were also some results showing no abnormalities. With this test, failure to identify an abnormality does NOT mean that the patient is safe from MH. Only the muscle contracture test can show that a person is NOT MH-susceptible.

Patient Mini-Conference Share Updates on MH

by Dianne Daugherty

MHAUS held a Patient Mini-conference July 15, 2006, in Westminster, MD, at Carroll Community College and Carroll Hospital Center to share an update on MH with the group. The mini-conference was held with 32 in attendance.

Dr. Kaplan covered the many facets of MH and made it interesting and clear to the entire group. Dr. Muldoon's in-depth presentation on the molecular genetics of MH and personal insights opened the door for a review by Deanna Steele, genetic counselor at Magee Women's Hospital of UPMC, of the basics of genetic counseling and the specific needs surrounding those who may be sent for MH molecular genetics.

The question and answer session at the end of the presentations received significant audience partici-

pation. Patients were open about their experience and all seemed to feel free to ask questions and make comments.

I would like to personally thank Drs. Richard Kaplan and Sheila Muldoon and Ms. Deanna Steele for sharing their expertise with the attendees and handling questions at the end of the session with aplomb. We received thank you emails from MH-susceptibles who were grateful for the education provided and left the event with a better understanding of malignant hyperthermia.

Thank you to the presenters, the Patient Liaison Committee members, Lydia Friedman and Mary Masimore, for their unending efforts at the meeting location and with the accreditation process, and to Fay Kellogg in the MHAUS office for her constant coordination and follow-up



The question and answer session at the end of the presentation received significant audience participation.

on the process to make this conference the successful event it was.

Hopefully, we will be able to find a way to plan more of the same in the future. In the meantime, we have audiotaped the session and are planning to put appropriate portions on the MHAUS website in the future as downloads in the iPod section. Watch for it in the months to come!

Contact Registry To Update Information

Are you registered with the North American Malignant Hyperthermia Registry? Have you had an MH Biopsy test and want to see if your results are in the Registry?

If so, please contact us at (888) 274-7899 or fondja@anes.upmc.edu so that we can make sure we have your most up-to-date contact information and make arrangements to receive any updated medical information which you may have.

Please visit the web site www.mhreg.org for a description of the Registry and why it may be important to you.

The Lila and Jerry Lewis Memorial Fund

There are many special people who take the time each year to remember their loved ones in a way that helps MHAUS. The people below have made gifts during FY 05-06 (Oct. 2005 - Aug. 2006) in memory of Lila and Jerry Lewis. We are most grateful for their support and special tribute gifts.

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MH Hotline Activity For Sept. 2005 - Jan. 2006



The call came and was patched through the Hotline nurse to Dr. Brandom from Roanoke, Virginia. The anesthesiologist had an unusual situation: during a “routine” dental operation under general anesthesia

for an eight-year-old, he noticed tachycardia and increasing carbon dioxide levels. Fearing a rapidly increasing metabolism and MH, he obtained a blood gas that showed mixed metabolic and respiratory acidosis. He diagnosed the Malignant Hyperthermia Crisis and gave dantrolene with an expected decrease in the heart rate and carbon dioxide levels. Things seemed to be under control, but, surprisingly, the fever didn't go down. What should he do? What other diagnoses should he consider? How much more dantrolene should he give? Dr. Brandom made her suggestions and stayed in contact through follow-up phone calls. The child did well and Dr. Brandom agreed the diagnosis was MH.

During the fall-winter period in 2005, 21 physicians staffed the MH Hotline. Drs. Adragna, Brandom, Belani, Chapin, Gronert, Herlich, Kaplan, Litman, Lubin, Melton, Miller, Millman, Parness, Rosenbaum, Rosenberg, Theroux, Tobin, Weglinski, Wedel, Wong, and Watson reported 43 significant questions and 76 reports of MH or MH-like episodes. Calls were patched through at all times of the day and night with the support of the Hotline nurse coordinators, providing a unique, volunteer service to help physicians and their patients in North America and elsewhere. While they average about 1-2 calls per day for the consultants on call, more than twice as many are fielded with helpful referrals or immediate answers to more routine questions by Hotline nurse coordinators.

A number of calls concerned worrisome events that looked a lot like MH but, after consultation, seemed more likely to be something else. MH look-

alike conditions included 33 patients who had unusually high post-operative fevers with some hypermetabolism, but not MH, after all the tests were in. In such cases, fever due to infection was present before surgery, the reason for surgery, or had another underlying source that wasn't immediately obvious to the caller. Sometimes the caller wanted advice about use of dantrolene as a non-specific agent to control fever production by muscles and muscle metabolism. A few called for advice about treatment because they were faced with a perplexing clinical situation where MH was one of several possible causes.

Fifteen calls came from anesthesia care givers who needed advice about sorting MH from the other possible causes for an unexplained increase in exhaled carbon dioxide. Carbon dioxide can increase because breathing is ineffective or because the amount being produced in the body exceeds the body's ability to exhale it under anesthesia. Consultants observed that several calls about elevated carbon dioxide levels came because carbon dioxide was used as an inflating gas during minimally invasive surgery. During minimally invasive abdominal, gynecologic, thoracic, urologic, and vascular surgery the surgical site is exposed by pressurized gas pumped into the area of concern. This way the surgeon can see around tissues and organs to the place of concern, and perform surgery using special long-handled tools passed through relatively small holes. Carbon dioxide is safer than air for this because it is absorbed rapidly in the blood and doesn't cause bubbles that can block the flow of blood to a vital organ, potentially causing major problems like a stroke or cardiac event. Distending the abdomen or part of the chest with compressed carbon dioxide can decrease the size of breaths given to patients under anesthesia. Also, carbon dioxide absorption during the surgery increases blood carbon dioxide levels. For these reasons ventilation must increase, sometimes as much as 50-100%, if the patient is to have normal carbon dioxide levels during the procedure.

Recent changes in anesthesia care have made carbon dioxide increases more

likely during other procedures. Mechanical changes that limited ventilation may have been the cause of two calls about high carbon dioxide levels. Nowadays many anesthesiologists use pressure controlled ventilation in order to keep lung inflating pressures from reaching high levels and potentially damaging the lungs. With pressure-controlled breathing, changes in a patient's position or compression of the chest or abdomen during surgery can decrease the size of breaths so that the ventilation pressure is less effective in eliminating carbon dioxide. In other cases, malfunctioning breathing systems may have allowed carbon dioxide accumulation. Also, more children and adults are cared for during anesthesia with spontaneously breathing techniques than in the 70's and 80's. Many anesthesia experts feel that spontaneous breathing through a flexible airway in the lower throat is less traumatic than controlled breathing through an airway tube that must be placed through the mouth or nose into the wind pipe with a rigid metal blade. Spontaneous breathing can be deceptive. While anesthesia care givers know that spontaneous breathing during hypermetabolism with rising respiratory rate and depth can partially disguise increased carbon dioxide production by increasing its excretion, as was the case in years before controlled breathing during anesthesia became so common, other drugs like narcotic pain medicines can impair spontaneous breathing more than expected and result in increased exhaled carbon dioxide levels. Thus, surprising increases in carbon dioxide can be seen that are not caused by the high metabolism we observe in the evolving MH Crisis and, to a lesser extent, infection.

Three callers asked about patients with confusion and agitation in the post-operative period that the consultants felt was not MH. One asked whether a patient who had severe aches and pains several days after getting succinylcholine as a relaxant for removal of a foreign body from the airway might

be having the MH crisis. It was felt that these were the severe late muscle aches and pains following muscle contractures the muscle relaxant, succinylcholine, causes as it stimulates muscles before they relax. A well-known side effect of this drug, post-succinylcholine muscle pain can be very uncomfortable and quite alarming. It gets worse for 2-3 days after drug use and is commonly improved by a week or two afterward. It is less common in recent years because succinylcholine is less often used, except for an emergency.

Hotline questions ranged over a variety of topics from patient referral to biopsy centers to specific diseases and the question of associated risk of MH. Ten callers asked about muscle biopsy referral for patients suspected of MH susceptibility, while nine inquired about biopsy referral for family members of patients who were thought to have had MH in the past. Seven callers asked about the possible association between MH and other unusual inherited conditions like spinal muscular atrophy type No. 3, Poland "S" syndrome, cri du chat syndrome, pseudocholinesterase deficiency, and myotonia congenita. Consultants were unaware of any relationship between MH and these rare disorders, but did note that there are more often reports of MH and MH-like events in patients with muscular dystrophy than the general population. Pseudocholinesterase deficiency, lack of non-specific enzymes in the blood that dismantle succinylcholine, among other drugs, is not uncommon, but causes paralysis and weakness to last longer after succinylcholine, sometimes for hours. One caller asked about a seven-year-old with a complex medical history and diagnosis of mitochondrial myopathy, a little known muscular disease. The child had had muscle injury associated with two previous anesthetics and the caller wanted to know if MH was the cause of these problems. Four callers asked questions about dantrolene administration, stocking, or availability. Three callers asked about trismus, or clenched jaw muscles, following induction of anesthesia. Not all patients with jaw muscle contractures have MH, in fact it is more commonly associated with muscular dystrophy where the jaw muscle

spasm can be a sign of dramatic generalized muscle contractions that are associated with cardiac arrest from high potassium levels, direct muscle, and potential kidney damage. Is someone who has a history of neuroleptic malignant syndrome (NMS) also at risk for MH? The Hotline consultant answered that there should be no connection between the two, since they have very different causes and mechanisms, although the syndromes can look alike because they involve muscle hyperactivity, fever, and signs of elevated metabolism. Another caller, knowing that sometimes the lipid lowering "statin" drugs (given to treat elevated blood cholesterol and reduce heart attack and vascular disease risk) can cause muscle injury as a side effect, wanted to know whether someone with a family history of MH should take one. The consultant and others also asked to comment, were unaware of any connection between susceptibility to MH and the muscle side effects of the "statin" drugs.

Should a patient who has some evidence of muscle abnormality that's revealed by a chronic elevation of blood levels of the muscle enzyme, creatine phosphokinase (CK), be treated as if he/she has MH? CK release is generally associated with muscle cell membrane

injury and muscle damage. The consultant who answered this question pointed out that earlier studies have shown a high percentage of patients with chronically elevated CK have also got MH susceptibility – as high as 40% – so that most anesthesia care givers would treat all such patients as though they had either some form of muscular dystrophy or MH and avoid all potent inhalational anesthetics and succinylcholine.

In this last part of 2005, as in the past, MH Hotline consultants answered questions about MH Crisis management, MH risk, other medical and muscle diseases, and unexpected problems that looked suspiciously like the MH crisis. While calls don't always turn out to be about MH, caller feedback comment continues to show appreciation for Hotline support. We who donate our time to the Hotline know our callers' patients have the benefit of someone whose experience can help their medical team answer important questions and follow their care with them. I also believe that we, who donate in support of the Hotline, can be assured that our support directly helps patient care and often contributes to a better patient outcome.

by Charles Watson, MD

Meet This Issue's Hotline Consultant

Charles B. Watson, MD, FCCM, graduated from the University of Maryland's School of Medicine in Baltimore, MD, and completed anesthesiology residency training at the Penn State University's MH Hershey Medical Center and in the US Navy in Portsmouth, VA, and Bethesda, MD, with post-graduate fellowships in pediatric anesthesia and critical care medicine at George Washington University, in Washington, DC.

Following service on the faculty of the US University of the Health Sciences and as Director of CCM, then Cardiac Anesthesia, and, finally, Assistant Department Chairman of the Anesthesiology Department at the National Naval Medical Center, in Bethesda, Dr. Watson joined the faculty of the University of North Carolina where he worked as an anesthesiologist and intensivist at the NC Memorial Hospital and served as director of the Critical Care Division. Dr. Watson entered the private practice of Anesthesia and Critical Care in Bridgeport, CT, in 1986, and accepted a clinical faculty appointment at the University of CT in Farmington.

Dr. Watson has been the Chairman of the Department of Anesthesia at Bridgeport Hospital since 1989 and presently serves as Deputy Surgeon-In-Chief of that institution, which belongs to the Yale-New Haven Health Network. He and his wife, Masha, live in Easton, CT., and have three adult children.

MHAUS Holds Annual Strategic Planning Meeting

MHAUS held its annual two-day strategic planning meeting July 21-22, 2006. Important accomplishments have been realized during the past year and we are thankful for our many supporters who share their time, their talents and their monetary assistance.

MHAUS is celebrating its **25th Anniversary** this year! To honor this important occasion, we developed an informative, historically accurate 25th Anniversary Commemorative Book. The book will be sent to new and renewing members as our "thank you" for their support. Information about our founders, past presidents, past executive directors, the MH hotline, the Professional Advisory Committee, the history of the Registry and its directors, as well as those involved in the discovery of malignant hyperthermia and the pursuit of ways to recognize and treat the disorder are highlighted within the covers of this one-of-a-kind piece. Those receiving it will have a chance to read personal remembrances of some of the individuals who have been instrumental in the MHAUS journey!

The **In-service Kit** evolved through a revision of the In-service Video and was available in the spring. It remains a very popular item as a regular MH education tool.

The **MH Procedure Manuals** designed specifically for either hospital, ambulatory surgery center or office-based facilities, is an all-encompassing MH education and training tool. It includes flowcharts, color-coded tabs, specific checklists of each staff member's duties, and an event drill to document response time via regular drills.

The **MHAUS Website** continues to grow! We recognize this interest and developed programs for the site to augment the materials

offered via podcast options of multiple audio presentations. This method offers items to download and listen to when it fits your schedule. E-newsletters are the newest way to be "in the know" about MHAUS' education and events. This short reference piece on the latest happenings in the organization and MH community goes out every few months to current members. New members and others can easily subscribe to this tool on the website and can opt to remove themselves at any time. If a challenge intrigues you, check out the "MH Case of the Month." If you like a brain teaser or just want to see if you know all you think you know, log on and give it a try. The correct answers will be posted the following month.

The **MH Speakers Bureau** is a resource of MH experts to speak to the medical community. Coordination of MH speakers' presentations is handled through Al Rothstein, MHAUS Public Relations, at 866-636-3342 or by emailing him at mhaus@rothsteinmedia.com or by calling MHAUS at 607-674-7901.

The board approved funding for complete characterization of the ryanodine gene in 100 confirmed MH patients in the North American MH Registry of MHAUS who are willing to participate in order to improve the sensitivity and accuracy of genetic testing for MH susceptibility. The work will be done over the next two years at the Uniformed Services University under the direction of Dr. Sheila Muldoon and at the University of Pittsburgh under the direction of Dr. Barbara Brandom.

The Patient Liaison Committee coordinated a **Mini-conference** in July in Westminster, Delaware. The meeting featured MH experts and a genetic counselor as speaker with Q&A time with the speakers. An-

other meeting is planned for the Milwaukee, Wisconsin area in the fall of 2007. Watch for more info as it develops!

In the coming year, MHAUS will be developing yet another way to utilize the website through **webcasts**. The development of 90-minute broadcasts of presentations by our MH experts and the opportunity for the viewing audience (participating live via their computer screen) to ask questions and share experiences is of prime interest. We view this as yet another way to broaden our scope to share education and new information on MH to an expansive audience.

Additional areas of focus to pursue in the coming year will be:

- Outreach effort to risk managers, Emergency Department personnel
- Update and improve the MHAUS website to improve access by members and offer all visitors clear options
- Development of a web site dedicated to professional education in MH
- Continue translations of materials into other languages, as needed
- Research into MH genetics
- Development of training modules for recognizing and managing MH using sophisticated manikin simulators.
- MH Expert Conferences to share new research and insight with the MH community
- Webcasts on MH, NMS and other heat-related disorders
- MH articles in risk management and genetic counseling publications
- Continue ongoing efforts to share MH information with the international MH community
- Enhance the NMSIS (Neuroleptic Malignant Syndrome Information Service) web site with slide presentation.
- Development of a professional conference on NMS and serotonin syndrome

Many Organizations Using Services Of Speakers Bureau



The speakers' presentations include topics such as MH Diagnosis and Treatment, a Basic Primer on MH, Lessons Learned from our MH Hotline Cases, and the new

Molecular Genetics Test. Speakers include hotline consultants and members of our Professional Advisory Council. So far we have 12 who have signed up and are willing to share their experience and expertise to further reduce MH morbidity and mortality!

The American Association of Oral and Maxillofacial Surgeons, the American Association of Nurse Anesthetists, and the Illinois Society of Anesthesiologists are already in the

process of scheduling our speakers. Organizations are eager to educate their members during annual meetings or at smaller educational conferences.

This allows us to not only inform medical professionals about MH, but also share information about our educational materials, such as our hospital, ambulatory surgery center, and office-based manuals, which prepare medical professionals for an MH episode. It also allows us an opportunity to speak one-on-one with our seminar participants, following our presentations, about their personal interest in the MHAUS mission.

You can find out more about our MHAUS Speakers Bureau by calling Al Rothstein at (866) 636-3342 or emailing mhaus@rothsteinmedia.com.

Challenge Yourself With The MH Case Of The Month

Have you challenged yourself with the new MH Case of the Month? Visit www.mhaus.org and go to the *Home or Professionals' Info Center* pages to think about the correct way to proceed with these actual MH cases. Answers with narratives are provided for the previous months' cases.

Yes! *I want to support MHAUS in its campaign to prevent MH tragedies through better understanding, information and awareness.*

A contribution of: \$35 (Basic) \$50 \$100 \$250 \$500 \$1000 (President's Ambassador) or (other amount) \$ _____, will help MHAUS serve the entire MH community.

Please print clearly:

Name: _____

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City: _____ State: _____ Zip: _____

Phone: _____ E-mail: _____

I am MH Susceptible I am a Medical Professional

Please charge my Visa Mastercard Discover American Express

Name on card: _____

Credit Card Number: _____

Expiration: _____

Please clip out this handy coupon, or feel free to photocopy if you prefer to keep your issue intact, then mail to: MHAUS, PO Box 1069, Sherburne, NY 13460-1069

MHAUS Happenings, Events and Notices

☐ **THANKS!** MHAUS is grateful for the financial support of the following State Societies of Anesthesiology: **Connecticut, Florida, Maine, Michigan, Nevada, Ohio and Pennsylvania.** Our appreciation also goes to the following state components of the American Society of PeriAnesthesia Nurses: **Arkansas, Delaware, DC, Illinois, Kansas, Maryland, Missouri, New Hampshire, New Mexico, North Carolina, Pennsylvania, Texas, and Vermont.** Call the MHAUS office to ask how your group can help.

☐ **P&GP Establishes Phone System For Ordering Dantrolene In The U.S. & International Markets** For information regarding ordering dantrolene sodium for injection, please contact P&G Pharmaceuticals Customer Service in the U.S. at 1-800-448-4878 or

in Canada at 1-800-265-8676. Requests for information outside the U.S. and Canada can be sent via fax to +49-6151-877-601 (in Germany). Dantrium® IV full prescribing and product information can be found on the Internet at www.pgpharma.com.

☐ **E-Newsletter Available** MHAUS has already published the first two editions of its new E-newsletter. It is delivered every other month and contains the latest information on MH treatment and diagnosis, MHAUS related events, and educational materials of interest. For example, if you want to find up-to-date information about our conference sessions at the upcoming American Society of Anesthesiologists meeting in October, our Silver Anniversary, or our informative MH Mini-

Conference just held in Maryland, the E-newsletter is your source. You can even link, through the E-newsletter, to our latest MH Case of the Month, taken directly from our MH Hotline experiences. The E-newsletter's subscription list is increasing and includes anesthesiologists, nurse anesthetists, families of MH patients, and other MHAUS members and medical professionals. You can easily sign up for the newsletter at www.mhaus.org, where you can also read the latest edition.

☐ **25th Anniversary Book** This year marks MHAUS' 25th Anniversary. To recognize this milestone, we've put together a commemorative book celebrating the past 25 years dedicated to patient safety. While available, this commemorative book will be a gift to all new and renewing members.

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