A Brief History of the North American Malignant Hyperthermia Registry (NAMHR)

*Marilyn Green Larach, MD, FAAP
Director Emeritus of the NAMHR*

The North American Malignant Hyperthermia Registry (Registry) was founded in 1987 following an idea that David R. Larach, MD, PhD planted in his wife’s, Marilyn Green Larach, MD, FAAP, mind. David was never one to abide whining and complaining. After wading through various malignant hyperthermia (MH) patient files from her initial MH research project, Marilyn was spending too much time complaining about how difficult it was to read frustratingly incomplete anesthetic and hospital records of individuals who had suffered fulminant MH events. David said, “Enough. Stop complaining and set up a registry so that MH events can be reported in a standardized manner, entered into a computerized database, and analyzed in a scientific fashion.” The details were worked out in a series of spousal conversations amid the traffic jams besetting the construction zones of the Pennsylvania Turnpike.

Together, they figured out how to:
- Create multiple linked standardized report forms.
- Preserve patient’s and reporting health care provider’s anonymity for initial reports.
- Improve individual MH-susceptible patient care by acquiring, analyzing, and disseminating data to providers via a one-page MH Hotline summary report on individual anesthetics as well as diagnostic evaluations.
- Organize a searchable database to support rigorous scientific study of MH epidemiology, diagnosis, and treatment.

The logistics tackled included creating patient consent forms (to allow for the generation of MH Hotline Reports) and obtaining Penn State College of Medicine Institutional Review Board (IRB) approval for the Registry. It was given an exemption by the Penn State IRB for the first 10 years of its existence. When it moved west to Barbara Brandom in Pittsburgh, the Registry was supervised by the University of Pittsburgh Medical Center IRB under expedited procedures. Now that the Registry is housed at the University of Florida, Gainesville, it is supervised by Dr. Nikolaus Gravenstein.

Although Dr. Marilyn Larach initially met with Dr. Henry Rosenberg of the Malignant Hyperthermia Association of the United States (MHAUS), MHAUS was unable to provide financial or administrative support for the Registry at that time. MHAUS was still in its own formative stage, although many MHAUS officers and professional advisory council members actively participated in the Registry’s early governance and research activities. Thus, Dr. Larach’s departmental chair at Penn State University College of Medicine, Dr. Julien F. Biebuyck, became her mentor in all things organizational as well as most things scientific. The Registry was established as an independent 501(c)3 organization under the auspices of the Penn State Department of Anesthesia. Dr. Larach became the originating Registry director and served in that position for 10 years until her move to Baltimore. Subsequent directors included Dr.
Gregory C. Allen (1997-1999), Dr. Sheila Muldoon (1999-2000 as acting director), Dr. Barbara W. Brandom (2000-2016), and Dr. Nikolaus Gravenstein (2017-present). In 1995, to share scarce resources, the Registry became a subsidiary of MHAUS.

The first MH Registry board chair was Gerald A. Gronert, MD (1987-1992), with Thomas E. Nelson serving as Secretary-Treasurer. Those serving on the original Registry board included Gregory C. Allen, MD; Julien F. Biebuyck, MB, DPhil; Beverley A. Britt, MD; Gerald A. Gronert, MD; J. Richard Landis, PhD; Marilyn Green Larach, MD; Sheila M. Muldoon, MD; Thomas E. Nelson, PhD; Henry Rosenberg, MD, and Denise J. Wedel, MD. Subsequent chairmen included Drs. Nelson, Landers, and Muldoon. Initially, there were 17 participating U.S. and Canadian MH diagnostic centers that contributed both data as well as financial support to the Registry (Table 1). Unfortunately, the number of active MH diagnostic centers has decreased over time to just four (Table 2).

Beginning in 1987, MHAUS held a series of conferences to discuss the development of a standardized protocol for skeletal muscle contracture testing using caffeine and halothane (CHCT). The Registry’s first research project was to acquire and analyze data submitted by The North American Malignant Hyperthermia Group’s active biopsy centers to validate the North American protocol for caffeine halothane contracture testing. This task was undertaken with the cooperation of the American Society of Anesthesiologists, the North American Malignant Hyperthermia Group (U.S. and Canada), MHAUS, and the Malignant Hyperthermia Association (Canada).

With the support of the Penn State Department of Anesthesia and MHAUS, the Registry hosted multiple MH Biopsy Standards Conferences in which Registry CHCT data analysis was presented and discussed. An analysis of caffeine halothane contracture responses in low-risk subjects was published following the submission to the Registry of at least 10 control subject outcomes from each MH diagnostic center. The Registry led the effort to create a comprehensive MH clinical case definition using the Delphi method to achieve consensus among an international panel of 11 experts on MH. The consensus process required seven separate written information exchanges transmitted by facsimile over 18 months because electronic communications on the Internet were not yet commercially accessible. The resulting definition became known as the MH clinical grading scale (CGS).

All active MH diagnostic centers submitted detailed reports to the Registry on every CHCT they performed. Using the CGS, the Registry staff identified every “almost certain” MH event reported for a biopsied patient. A subcommittee of the North American Malignant Hyperthermia Group confirmed the “almost certain” MH designation in these patients. The subcommittee was blinded to CHCT outcome.

The Registry then was able to evaluate both the sensitivity and specificity of the CHCT and suggest appropriate tests and diagnostic thresholds for clinical and research use. At the Fifth MH Biopsy Standards Conference in 1994, it was agreed that the Registry would use thresholds of ≥0.5 g for 3% halothane and ≥0.3 g for 2 mM caffeine for
investigations that required maximum test sensitivity (97%; 95% CI 84-100%) while accepting a lower specificity of 78% (95% CI 69-85%). It was suggested that genetics investigators might wish to use thresholds of ≥0.7 g for the 3% halothane contracture test, ≥0.3 g for the 2 mM cumulative caffeine contracture test, or both, which have a sensitivity of 88% (95% CI 71-97%) and a specificity of 81% (95% CI 73-88%). An equivocal range was identified to give individual biopsy centers more latitude in diagnosing persons as MH susceptible. Diagnoses via caffeine-specific concentration and a halothane caffeine-specific concentration were no longer used.

With support from both MHAUS and the Penn State Department of Anesthesiology, the Registry hosted the Sixth International Malignant Hyperthermia Workshop in Hershey, PA, in September 1992. This conference was chaired by Drs. Allen, Larach, and Nelson, and featured extensive discussions of the ryanodine receptor amid a cornucopia of chocolate desserts.

Dr. Gronert was instrumental in obtaining significant funding support for the Registry from the American Society of Anesthesiologists from 1989 through 1991. Also helpful was grant support obtained from the Foundation for Anesthesia Education and Research, Sharn Inc., Norwich Eaton Pharmaceuticals, and Procter & Gamble. When the Registry moved to the University of Pittsburgh, Dr. Brandom obtained support from MHAUS and the Department of Anesthesiology in the University of Pittsburgh. Now that the Registry is located in Florida, it is supported by MHAUS and the Department of Anesthesiology at the University of Florida.

The Registry was situated in office space provided by the Department of Anaesthesia at the Penn State College of Medicine until its move to the Department of Anesthesiology at the University of Pittsburgh Medical Center in 2000. In 2017, the Registry moved to the Department of Anesthesiology at the University of Florida in Gainesville, Florida.

From its inception, the Registry collaborated closely with Penn State’s Center for Biostatistics and Epidemiology, now the Department of Public Health Sciences. Dr. Larach’s epidemiologic and biostatistical mentor was J. Richard Landis, PhD. Other biostatisticians that worked closely with the Registry included A. Russell Localio, PhD; Joan Schaeffer Bunn, BS; Allen R. Kunselman, MA; and Erik B. Lehman, MS. The original programmer was Mr. Wayne Janis. The Registry’s first database manager was Dr. Marcela Diaz. Subsequent database managers included Mrs. Linda Fuhrmann, Ms. Cindy Brubaker, and Mr. Michael C. Young. Since the move to Gainesville, Patrick Tighe, MD, MS, has been the database manager. Administrative assistants have included Pamela Myers (Penn State) and Kristee Adams (University of Pittsburgh). The current Registry manager is Amy Gunnett, RN, CCRC (University of Florida).

As of March 2018, the Registry has enrolled more than 725 individuals (see Table 3 for number and type of report forms). To date, the Registry database has supported the publication of 25 peer-reviewed articles that have been cited 1,880 times (Table 4). Registry research reports have addressed MH diagnosis, epidemiology, presentation (including “awake MH”), recrudescence, and complications, including cardiac arrest and
death, treatment (including dantrolene dosage and complications), and phenotype/genotype studies. Current research projects include continued efforts to correlate MH phenotype with genotype, to compare chronic pain in MH-susceptible versus MH-negative subjects, and to determine the long-term sequelae and morbidity of an MH event as reported by the subjects registered in the NAMHR.

We thank all of those who have mentored the Registry directors and its researchers over the years. The Registry would not exist without the many anesthesiologists, intensive care physicians, surgeons, nurse anesthetists, pharmacists, and patients who have submitted their data to this database.
**Table 1. Participating MH Diagnostic Centers (1987)**

- Cleveland Clinic Foundation
- Hahnemann University Hospital
- Mayo Clinic
- Ottawa Clinic Hospital
- Presbyterian University Hospital, Pittsburgh
- Toronto General Hospital
- Uniformed Services University of the Health Sciences
- University of California, Davis
- University of California, Los Angeles
- University of Iowa Hospitals and Clinic
- University of Manitoba
- University of Massachusetts
- University of Nebraska Medical Center
- University of South Florida
- University of Texas Health Science Center at Houston
- University of Washington
- University of Wisconsin
Table 2. Participating MH Diagnostic Centers (2013)

Uniformed Services University of the Health Sciences
University of California, Davis
University of Minnesota
Wake Forest University
### Table 3. Registry Report Forms

<table>
<thead>
<tr>
<th>Registry Report Type</th>
<th>Number Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMRA*</td>
<td>813</td>
</tr>
<tr>
<td>MH Biopsy**</td>
<td>3521</td>
</tr>
<tr>
<td>AKA***</td>
<td>252</td>
</tr>
<tr>
<td>MHN§</td>
<td>11</td>
</tr>
<tr>
<td>MHS §§§</td>
<td>39</td>
</tr>
</tbody>
</table>

*AMRA is an acute adverse metabolic or musculoskeletal reaction to anesthesia report (submitted by clinician).

**MH Biopsy is an MH biopsy report (submitted by MH biopsy center).

***AKA is a report on an individual who has already been identified as MH susceptible (submitted by the individual with assistance from a clinician when possible).

§MHN is a report on an anesthetic administered to a CHCT-negative individual (submitted by clinician).

§§MHS is a report on an anesthetic administered to a CHCT-positive individual (submitted by clinician).

CHCT, caffeine halothane contracture test.
Table 4. Peer-Reviewed Articles Produced by or Utilizing the North American Malignant Hyperthermia Registry Database

To date, there have been 25 peer-reviewed articles published over the 31-year period of the Registry’s existence, with a total of 1,880 citations. The first article was published within 2 years of the Registry’s founding.

- Larach MG. A primer for diagnosing and managing malignant hyperthermia susceptibility. Anesthesiology 2018; 128:8-10

- Butala B, Brandom B. Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility. Can J Anaesth 2017; 64:396-401


• Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. Anesthesiology 2007; 106:901-6 [Citations: 54]


References


