Anesthesiology
47:490–497, 1977

Motor Unit Counting and the Caffeine Contracture Test in Malignant Hyperthermia

Beverley A. Britt, M.D., F.R.C.P.(C), Alan J. McComas, M.B., B.S., F.R.C.P.(C),† Laszlo Endrenyi, Ph.D.,‡ Werner Kalow, M.D.§*

Motor unit counting, a neurophysiologic test, compares the sizes of the potentials of single motor units evoked by weak graded neural stimulation with the response of the whole muscle to a maximal neural stimulus. This test was performed on 1) individuals belonging to families afflicted with malignant hyperthermia (MH), and 2) individuals unrelated to malignant-hyperthermia-susceptible (MHS) patients. The MH status of the patients was confirmed by means of the skeletal-muscle caffeine contracture test. Two or more of the following muscles or muscle groups were examined in each subject: extensor digitorum brevis, hypothenar muscle groups, the thenar muscles supplied by the median nerve, and the soleus. Stimulating electrodes consisting of two silver discs were placed over the end-plate zone of the muscle and a reference electrode at a distance. The repetition rate for the stimuli was approximately 0.7 Hz. When the potentials of 10 or more motor units had been identified on an oscilloscope their mean amplitude and the number of functioning motor units were calculated. Coaxial needle electromyography was carried out on the brachial biceps or the abductor pollicis brevis, and the vastus medialis or the extensor digitorum brevis. Motor unit counts were lower than the cut-off values corresponding to the selected probability levels in a high proportion of MHS subjects. The proportion was larger in tests utilizing pairs of muscles than in those involving the appropriate muscle types alone. A further increased proportion, and thereby more sensitive discrimination, was obtained by a triple combination of muscles. Concentric needle myopathy (EMG) was not as accurate a prognosticator of the MH trait as was motor unit counting.

Motor unit counting confirms that the primary defect of human MH involves motor nerves as well as the skeletal muscle. Motor unit counting also serves as a noninvasive diagnostic test for MH and is only slightly less accurate than the caffeine contracture test. (Key words: Hyperthermia, malignant pyrexia; Muscle, skeletal, electromyography; Muscle, skeletal, motor unit counting; Muscle, skeletal, caffeine contracture.)

MOTOR UNIT COUNTING is a neurophysiological test, originally developed by McComas *et al.*[1] Although the test has yet to win general acceptance, it is being used increasingly in neurologic centers as a research or diagnostic tool.[2–7] The principle of the method is to compare the sizes of the potentials of single motor units evoked by weak graded neural stimulation with the response of the whole muscle to a maximal neural stimulus. The assumptions inherent in the methodology and the accuracy that can be anticipated have been discussed.[1–8] It is relevant that, in experimental studies in animals, the test has been found to be reliable in normal and myopathic muscles,[9] while sometimes underestimating the extent of the neuropathic lesions.[10] Apart from its application in experimental studies of muscular dystrophy and other myopathies, the counting method is of value in clinical electromyography for the detection of denervation in distal muscle of the limbs.[2] In the present study we performed this test on a large number of individuals belonging to families afflicted with malignant hyperthermia (MH), to improve our comprehension of the etiology of MH and to develop a rapid noninvasive tool to aid in its diagnosis. Our values obtained with motor unit counting are compared with those ascertained in the same patients by concentric needle electromyography and by the caffeine contracture test.[11–13]

Methods

Patient Selection

The subjects selected comprised the following groups of patients, all less than 60 years of age. (Persons 60 years old or older were excluded since motor unit counts decline significantly after 60 years of age.)

Group I. Individuals without systemic disease who did not have malignant-hyperthermia-susceptible (MHS) relatives served as controls for the motor unit counting study.

Group II. Individuals without systemic diseases who had no MHS relatives, but were undergoing orthopedic procedures, for example, cup arthroplasty or Charnley hip replacement; thoracic operations, such as transthoracic hiatus hernia repair; or abdominal procedures, for instance, elective cholecystectomy, were the controls for the caffeine contracture test.

Group III. Patients who had previously had MH reactions with or without rigidity (rigid or non-rigid patients).

Group IV. Relatives of rigid or non-rigid MHS patients (MHS) relatives. Both the caffeine contracture test and motor unit counting tests were performed on the individuals in Groups III and IV.

* Associate Professor, Department of Anaesthesia, University of Toronto, Toronto, Ontario, Canada.

† Professor of Neurology, Departments of Medicine and Neurology, McMaster University Medical Center, Hamilton, Ontario, Canada.

‡ Professor, Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada.

§ Professor and Chairman, Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada.

Accepted for publication June 15, 1977. Supported by grant no. MA-565 from the Medical Research Council of Canada.

Address reprint requests to Dr. Britt: Department of Anaesthesia, University of Toronto, Medical Sciences Building, Toronto, Canada M5S 1A8.

TABLE 1. Classification of Subjects Based on the Caffeine-induced Muscle Contracture Test

Halothane (1.0 vol per cent) Absent / Present	Caffeine Specific Concentration (mM)* <8.5 <1.30	<8.5 >1.30	>8.5 <1.30	>8.5 >1.30	Halothane Absent	Halothane Present
Normals	—	—	1†	13	14.3 (1.3)‡	2.46 (0.26)‡
Non-rigid relatives	—	—	—	7	26.3 (2.4)	2.52 (0.20)
Non-rigid patients	—	—	2	5	22.3 (2.2)	2.19 (0.33)
Rigid relatives	13	1	15	13	11.0 (0.6)	1.17 (0.08)
Rigid patients	15	1	1	—	4.86 (0.68)	0.63 (0.08)

* The concentration required to raise the resting skeletal muscle tension by 1 gram.
† Number of subjects.
‡ Average caffeine specific concentration (in mM), with standard error in parentheses.
Reprinted from Canadian Anaesthetists' Society Journal 23: 624, 1976.

ANESTHETIC TECHNIQUE

The patients were premedicated with Pantopon®, 1 mg/4 kg, and diazepam, 1 mg/4 kg. Anesthesia was induced with Innovar® (droperidol, 1.0 mg/8 kg, and fentanyl, 0.02 mg/8 kg) and a sleep dose of diazepam, and was maintained with nitrous oxide, 5 l/min, oxygen, 3 l/min, and fentanyl as required. We found that these agents did not interfere with our *in-vitro* studies. The patients' lungs were hyperventilated via an Air Shields ventilator.

SURGICAL TECHNIQUE

The muscles biopsied were the vastus lateralis, the rectus abdominis, the deltoid and the intercostales. Without employing cautery or excessive mechanical compression, all possible fat and connective tissues were gently removed from the surface of the muscle prior to severing its blood supply. The muscle fascicles to be excised were selected so that the fibers ran parallel to the lines of incision. Each fascicle was secured at each end with very fine black silk sutures and was then meticulously dissected to free it from the surrounding muscle. During the dissection constant longitudinal tension sufficient to prevent contractures or stretching of the muscle cells was maintained on the sutures.

CAFFEINE CONTRACTURE TEST

The fascicles were immediately transported to the laboratory in ice-cold Ringer's solution. The time elapsed between excision and further processing in the laboratory was about 10 minutes. Each specimen was trimmed free of irregularities or remaining fat and was divided into two pieces to permit duplicate measurements. The size of each muscle strip was approximately 3 × 5 × 20 mm, each weighing roughly 0.3 g with a range from 0.2 to 0.4 g. In trimming the muscle, care was taken to ensure that the direction of the long cut ran parallel to the fibers.

Each muscle strip, secured by a silk suture to an electrode housing, was immersed in 30 ml of a Krebs–Ringer solution¶ adapted for human tissues. The upper end of the muscle was connected via a second silk suture to a Grass force-displacement transducer (ST-10-DC). Isometric tension was recorded with a Grass polygraph. The initial tension was set at 0.5 or 1.0 g (the magnitude of the contracture was not altered by changing the baseline tension from 0.5 to 1.0 g). In order to assess viability, the muscle was stimulated every 5 seconds via platinum electrodes connected to a square-wave Grass stimulator, which was set to deliver 8-volt impulses 20 milliseconds in duration. Oxygen containing carbon dioxide, 5 per cent, was bubbled through the bath at 1 l/min. As desired, halothane, 1.0 volume per cent, was added to the gas mixture. Caffeine in concentrations ranging from 0.25 to 32.0 mM was added directly to the bath. Each caffeine dose was left in the bath for 5 minutes, then removed by washing. The modalities measured were the contractures expressed as grams of tension increases produced by graded concentrations of caffeine within 4 minutes, once in the presence and once in the absence of halothane in the gas phase.

From the concentration–response curves, we calculated the concentration of caffeine (in mM) required to increase the resting tension of the isometric skeletal muscle preparation by one gram (table 1). This value was defined as the "caffeine specific concentration."[13]

MOTOR UNIT COUNTING

Two or more of the following muscles or muscle groups were examined in each subject; the extensor digitorum brevis, the hypothenar muscle group, the thenar muscles supplied by the median nerve, and the soleus. In the latter part of the study it was customary to investigate all four muscles, but in the earlier part, because of technical limitations, only the extensor digitorum brevis and hypothenar

¶ 118.4 mM NaCl; 3.3 mM KCl; 0.9 mM $MgSO_4$; 1.1 mM KH_2PO_4; 11.1 mM glucose; 24.9 mM $NaHCO_3$; 2.5 mM $CaCl_2$. *p*H of medium adjusted to 7.4 at 25 C.

TABLE 2. Motor Unit Counts in Four Muscles of Control and MHS Subjects

Muscle Group	Control Subjects Mean* ± SD†	MHS Subjects Mean* ± SD†
Extensor digitorum brevis	192 ± 54	113 ± 62
Thenar	371 ± 81	210 ± 139
Hypothenar	375 ± 85	331 ± 162
Soleus	932 ± 225	531 ± 329

* Harmonic average.
† Standard deviation corresponding to the harmonic average.

muscles were employed. Care was taken to avoid examining a limb that had been injured in the past or was the seat of neurologic symptoms (for example, such as those suggestive of cervical spondylosis or a prolapsed intervertebral disc). In the few subjects who did not have an unaffected side, the limb associated with fewer symptoms was selected for study.

For each muscle or muscle group a stigmatic electrode was placed over the endplate zone of the muscle and a reference electrode positioned at a distance; these electrodes, and also the ground, consisted of strips of silver foil, 6 mm wide, which were coated with a conducting jelly and attached to the skin with adhesive tape. The stimulating electrodes were two silver discs, each 1 cm in diameter and separated from the other by 2 cm; they were mounted in a Plexiglass holder and placed on the skin over the appropriate motor nerve. The repetition rate for the stimuli was approximately 0.7 Hz. The muscle responses were passed through an amplifier with a passband of 5 Hz to 1 kHz and displayed on a variable persistence storage oscilloscope.** As the stimulus was gradually increased from a threshold value, the evoked muscle response enlarged in a quantal manner. Each new response could be distinguished from its predecessor by an increase in amplitude or by an alteration in configuration; the incremental change was assumed to reflect the excitation of an additional motor unit. The peak-to-peak amplitudes of the responses were made from the oscilloscope screen, using an initial sensitivity of 20 μV/cm. When the potentials of 10 or more motor units had been identified and measured in a subject muscle, their mean amplitude was calculated. A larger electric shock was then used to evoke the maximal response from the muscle under study. The approximate number of functioning motor units could then be found by dividing the mean motor unit potential amplitude into the amplitude of the maximum muscle response.

COAXIAL NEEDLE ELECTROMYOGRAPHY

Unless the subject declined, a coaxial type of recording electrode†† was used to investigate a proximal and a distal muscle in the arm and leg. Usually the brachial biceps, abductor pollicis brevis, medial vastus, and extensor digitorum brevis muscles were chosen. Muscle activity was examined at rest and during

** Hewlett-Packard model 141B.
†† Disa 9013L0501.

TABLE 3. Standardized Scores and Counts* in Control and MHS Subjects

Muscle Group	Control		MHS		
	Standard Counts or Scores†	N‡	Standard Counts or Scores†	N‡	t§
Extensor digitorum brevis	0 (1)	148	−2.53 (3.35)	44	8.09 ($P < 0.001$)
Thenar	0 (1)	94	−2.12 (4.02)	34	4.75 ($P < 0.001$)
Hypothenar	0 (1)	87	−0.58 (2.44)	25	1.77 ($P < 0.05$)
Soleus	0 (1)	30	−3.13 (4.51)	34	3.72 ($P < 0.001$)
Extensor digitorum brevis and thenar	−0.49 (0.90)	51	−4.07 (4.86)	34	5.58 ($P < 0.001$)
Extensor digitorum brevis and hypothenar	−0.51 (0.82)	41	−3.45 (3.55)	25	5.11 ($P < 0.001$)
Extensor digitorum brevis and soleus	−0.21 (0.85)	18	−4.48 (4.17)	34	4.28 ($P < 0.001$)
Thenar and hypothenar	−0.68 (0.88)	63	−3.70 (4.09)	20	5.54 ($P < 0.001$)
Thenar and soleus	−0.52 (0.91)	24	−4.80 (5.11)	29	4.04 ($P < 0.001$)
Hypothenar and soleus	−0.27 (1.01)	14	−4.69 (5.78)	16	2.82 ($P < 0.01$)
Extensor digitorum brevis, thenar and hypothenar	−0.96 (0.71)	30	−5.34 (4.68)	20	5.06 ($P < 0.001$)

* For one muscle: standardized count, $d = (\bar{x}_c - x)/s_c$, where x = reciprocal of observed motor unit count, $\bar{x}_c$ = its average among control subjects, s_c = its standard deviation among control subjects. For more than one muscle simultaneously assessed: standardized score = lowest of the standardized counts.
† Average standard count or score, with the corresponding standard deviation in parentheses.
‡ Number of subjects.
§ Student's t-value for the comparison of MHS and control standardized counts or scores. The probability levels correspond to one-sided tests.

TABLE 4. Criteria and Effectiveness of Muscle Motor Counts for Identifying MHS Subjects

Muscle Group	MHS Percentage Limits Below*		1 Per Cent Limit for Muscle†			0.1 Per Cent Limit for Muscle†		
	1 Per Cent	0.1 Per Cent	(1)	(2)	(3)	(1)	(2)	(3)
(1) Extensor digitorum brevis	47.7	31.8	116	—	—	102	—	—
(1) Thenar	32.4	23.5	201	—	—	178	—	—
(1) Hypothenar	28.0	20.0	243	—	—	217	—	—
(1) Soleus	50.0	35.3	584	—	—	512	—	—
(1) Extensor digitorum brevis and (2) Thenar	55.9	44.1	110	192		98	172	—
(1) Extensor digitorum brevis and (2) Hypothenar	60.0	44.0	113	239	—	101	216	—
(1) Extensor digitorum brevis and (2) Soleus	73.5	55.9	115	590	—	100	518	—
(1) Thenar and (2) Hypothenar	45.0	40.0	189	229	—	170	208	—
(1) Thenar and (2) Soleus	62.1	41.4	189	557	—	167	493	—
(1) Hypothenar and (2) Soleus	56.3	31.3	224	544	—	192	465	—
(1) Extensor digitorum brevis, (2) Thenar and (3) Hypothenar	65.0	50.0	109	191	231	99	173	212

* Percentage of MHS subjects whose standardized counts or scores fall below the cut-off corresponding to the given probability levels.
† Limiting cut-off values corresponding to the given probability levels. These indicate the percentages of normal subjects expected to have lower motor counts than the presented values in *any one* of the muscles.

graded effort in the conventional way. A visual analysis was made of the amplitudes, durations and complexities of the potentials using a freely running time base together with stored displays of the activity.

Results

CAFFEINE CONTRACTURE TEST (TABLE 1)

In many patients the MH episode was characterized by rigidity. These are referred to as "rigid patients." In studies of the contracture of their resting skeletal muscle fascicles the tension was increased by 1 g in the presence of less than 8.5 mM caffeine. With the addition of halothane, less than 1.30 mM caffeine was required to increase the tension by 1 g.

By contrast, in normal subjects it was usually necessary to exceed the quoted caffeine concentrations under both experimental conditions.

Some relatives of the rigid patients ("rigid-R relatives") manifested responses similar to those of the patients themselves. The reactions of other relatives ("rigid-N relatives") resembled those of the normal subjects. Still other relatives ("rigid-I relatives") showed intermediate responses: the specified (1.0 g) muscle tension was evoked by more than 8.5 mM caffeine in the absence of halothane but by less than 1.30 mM caffeine in the presence of halothane. This classification of MHS patients and their relatives corresponds to that described earlier.[13]

In statistically considering the motor unit counts (see below), the responses of the rigid patients are pooled with those of the rigid-R and rigid-I relatives. This pooled group is termed MHS subjects. Justification for this is given below.

In a few patients the MH episode was not characterized by rigidity. These are referred to as "non-rigid patients" and their relatives as "non-rigid relatives." Their muscles showed resistance to caffeine in the absence of halothane. Thus, more than 17.5 mM caffeine was required to increase the resting tension of their muscles by 1.0 g.

MOTOR UNIT COUNTING (TABLES 2–5)

The motor unit counts measured in the various muscle groups (table 2) did not follow a normal distribution, since the counts obtained with all four muscles showed highly significant positive skewness (a positively skewed distribution has a long tail at its upper end). This feature is, at least in part, an inevitable consequence of the type of calculation involved in the determination of motor unit numbers. It will be recalled that, for each subject, the mean amplitude of the motor unit potentials is calculated

TABLE 5. Distribution of Scaled Standardized Counts and Scores* in MHS Patients, Their Relatives, and Normal Subjects

Muscle Groups	Patient Classification	Number of Subjects in the Range of Standard Counts/Scores					
		to −3	−3 to −2	−2 to −1	−1 to 0	0 to 1	1 to 2
Extensor digitorum brevis	Normals	—	—	7	63	72	6
	Rigid-N relatives	2	1	1	5	4	—
	Rigid-I relatives	1	1	5	3	3	—
	Rigid-R relatives	5	1	1	3	3	1
	Rigid patients	4	2	5	3	2	1
Thenar	Normals	—	—	3	43	46	2
	Rigid-N relatives	—	—	2	2	4	1
	Rigid-I relatives	2	—	2	4	4	—
	Rigid-R relatives	2	1	—	3	5	1
	Rigid patients	2	1	2	3	2	—
Extensor digitorum brevis and thenar	Normals	—	—	1	28	20	2
	Rigid-N relatives	1	1	—	4	2	—
	Rigid-I relatives	3	—	3	3	2	1
	Rigid-R relatives	6	—	1	2	3	—
	Rigid patients	5	1	1	1	2	—

* Motor unit counts are standardized and scaled as described in the text and in the legend of figure 1.

from the oscilloscope traces, and it is this value that is then divided into the maximum muscle response to give the number of functioning motor units. When the mean motor unit potential amplitudes for normal subjects are pooled the values decrease, as expected, in a normal distribution about their own population mean. However, because of the division step in the calculation of motor unit numbers, this normal distribution of mean potential amplitudes gives rise to a positively skewed distribution of motor unit numbers. In previous studies the lower limit of the corresponding control range has been used for the detection of abnormality. In the present study reciprocals of the motor unit numbers were used; these showed, for each type of muscle studied, an almost symmetrical and nearly normal distribution, the skewness and kurtosis of which were statistically not significant. Consequently, assessment of the observations described below was based on their reciprocally transformed values.

The evaluation of motor unit counts obtained in a single kind of muscle involved their standardization. The standard counts (d) were differences between the reciprocals (x) of the observed values and their average among control subjects ($\bar{x}_C$) referenced to the standard deviation for controls (s_C):

$$d = (\bar{x}_C - x)/s_C$$

(The defining expression permits the values of the standard counts to increase in parallel with those of the observed motor unit counts.) Among control subjects these standard counts (d_C) had an average of zero and standard deviation of unity. In contrast, the lower counts in the MHS group (d_M) implied a negative average value (table 3).

For several subjects motor unit counts were obtained in more than one kind of muscle. In these instances, each standard count was evaluated and the smallest value was selected and accepted as the standard score for the subject. Naturally, even among the control subjects, this score was lower than the one based on assessing a single muscle. However, average scores for the MHS group showed even larger decreases in comparison with the single-muscle standard counts. As a result, evaluation of motor unit counts in more than one muscle was expected to provide better discrimination between the control and MHS subjects than that obtained from single-muscle counts. The superior discrimination by double or multiple motor unit counts may be suggested in spite of the comparable t-values (table 3) since these had to take into account the smaller sample size available for their evaluation.

The effect of multiple counts is illustrated further in table 4. First, the test procedures selected a probability level for the control subjects. For instance, motor unit counts corresponding to the 1 per cent level represented one set of cut-off values: only 1 per cent of the control subjects were expected to have lower counts. (This corresponded to one-sided probability levels. Indeed, MHS subjects were thought to have, on the whole, lower and not higher motor unit counts than normals.) Table 4 demonstrates that the cut-off values of the motor counts were, in a given muscle, almost independent of the number of muscle types simultaneously considered (table 4). Actual tests utilized these cut-off values for the detection of MH susceptibility.

Motor unit counts were lower than the cut-off values corresponding to the selected probability levels in a rather high proportion of MHS subjects (table 4). The proportion was seen in the tabulation to be larger

in tests utilizing pairs of muscles than in those involving the appropriate muscle types alone. A further increased proportion, and thereby more sensitive discrimination, was obtained by a triple combination of muscles (the only triplet for which the sample size was not too small for analysis) in comparison with the corresponding muscle pairs.

Control and MHS standard count and score distributions are shown in figure 1 for one of the muscle combinations. These illustrate the shifts of the MHS distributions, with respect to the controls, especially when scores involving the two muscles simultaneously were considered. The possible nonhomogeneity of the MHS distributions is noteworthy.

Standard count and score distributions for the Rigid-R and rigid-I relatives were indeed similar to those for the rigid patients, while distributions for the rigid-N relatives were, on the whole, closer to those for the normal subjects (table 5). The similarity in the MHS sensitivity and characteristics of the rigid-R and rigid-I relatives to those of the normal subjects paralleled the patterns described earlier with regard to the adenosine triphosphate (ATP)-depletion test.[13]

Concentric Needle Electromyography

Concentric needle myography (EMG) was not as accurate a prognosticator of the MH trait as was motor unit counting (table 6). Thus, while at the 1.0 per cent probability level all rigid patients showed decreases in motor unit counts for one or more muscle groups, only a third of the rigid patients had abnormal EMG values. A corresponding difference was observed when the pooled data for all MHS subjects were considered. The most commonly observed EMG abnormalities were frequent, small and brief volitional potentials and evidence of chronic denervation.

Discussion

Etiology of MH

The present observations suggest that the human MH gene is expressed in terms of a primary neural abnormality as well as a defect in skeletal muscle fibers. Thus, the finding of reduced motor unit counts, taken in conjunction with the normal or increased sizes of the potentials of the surviving units, is characteristic of a denervating disorder.[8] This conclusion is in agreement with histologic findings indicative of neuropathy in both MHS man and MHS swine. For example, silver,[14,15] methylene blue,[16] and trichrome–Gomori[12] stains reveal degeneration of intramuscular neurons. Increased variation of fiber diameter,[17,18] clumping of type I and type II fibers,[19,20] and abnormal type I/II fiber ratios (unpublished data, Britt) can be seen on ATPase stains. The brain band

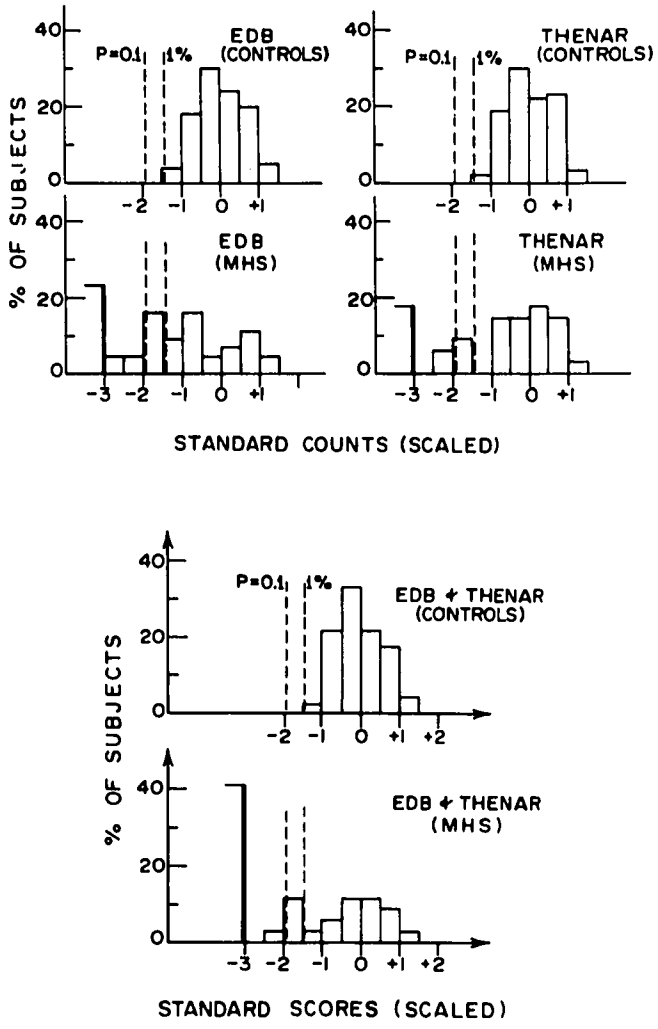

Fig. 1. Distribution of standardized motor unit counts in the extensor digitorum brevis (EDB) and in thenar muscles of MHS and control subjects, and distribution of standard scores obtained by considering the standard counts in both muscles.

The standardized counts and scores (d) are derived in the text and in the first footnote of table 4. They are scaled around the means of the control values ($\bar{d}_C$) to yield $d' = (d - \bar{d}_C)/ts_{d,C}$, where t is the tabulated value of Student's t-statistic at the 5 per cent one-sided probability level with (N − 1) degrees of freedom (N being the number of observations), and $s_{d,C}$ is the standard deviation of standardized counts or scores in the control subjects. The scaling permits direct comparison of the various diagrams: In each case, about 5 per cent of the control subjects are expected to show scaled counts or scores having values lower than −1.0, and another 5 per cent would have values exceeding 1.0. Scaled counts and scores of less than −3.0 are pooled.

In addition, the cut-off values corresponding to 0.1 and 1 per cent probability levels in the controls are illustrated with dashed lines. Their interpretation is analogous to that of the five per cent levels: 0.1 and 1 per cent, respectively, of the control subjects are expected to have values lower than the indicated scaled values.

The diagram illustrates the shifted distribution of responses among the MHS subjects and consequently, that many of these subjects have motor unit counts substantially and significantly lower than normal. This is particularly apparent when scores based on observations in two (or more) muscle groups are considered.

TABLE 6. Identification of MHS Subjects by Motor Unit Counts and by Concentric Needle Myography

Patient Classification	Number of Patients				
	Motor Unit Counts†			Electromyography	
	Abnormal* at P =				
	0.1 Per Cent	1 Per Cent	Total	Abnormal	Total
MHS subjects					
Rigid patients	13	17	17	4	12
Rigid-R relatives	10	11	14	7	12
Rigid-I relatives	6	8	13	1	14
Rigid-N relatives	3	4	13	1	12
Non-rigid patients	2	2	3	0	3
Non-rigid relatives	0	0	2	1	3
Normal subjects	0	1	206		

* Having lower than the critical motor unit counts at the 0.1 and 1 per cent probability levels established in this paper for any of the muscle groups observed in a given subject.

† Reduced number of motor unit counts in one or more muscle groups.

may be increased in the sera of many, but not all, MHS subjects.[21,22]

This study does not elucidate whether the myopathy of MH is secondary to the neuropathy or whether the myopathy and the neuropathy are parallel defects, each part of the membrane abnormality involving many types of cells throughout the body. The latter hypothesis is favored, since in MHS subjects biochemical disturbances seem to be present in cell types other than skeletal muscle or nerve. For example, some MHS patients have a cardiomyopathy typified by unusual arrhythmias and murmurs, a tendency to ventricular fibrillation during or after physical exercise or emotional stress, symmetrical myocardial hypertrophy, a greater than normal myocardial uptake of radioactive thallium, but a less than normal myocardial uptake of radioactive technetium (unpublished data, Britt). Other MHS subjects have a von Willebrand's disease-like disorder characterized not only by a deficiency of factor VIII, but also by platelets that do not adhere normally to glass beads (unpublished data, Britt). A deficiency of ouabain-sensitive ATPase activity has been observed in the erythrocyte membranes of some MHS subjects.[23] Denborough *et al.*[24] reported that MHS subjects have excessively elevated plasma levels of insulin after a glucose load.[24] These investigators postulated that a membrane defect exists in MHS beta islet cells such that glucose induces an abnormally high level of calcium in MHS cytoplasm. Secretion of insulin is correspondingly high since the level of calcium in the beta cell cytoplasm is the single mediating factor in the secretion of insulin.[25,26]

The most likely explanation for this multiplicity of findings is some very simple molecular disarrangement of a membrane structural component—one that is sufficiently uncomplicated to be common not only to the outer membranes of many different cell types but also possibly to the membranes of different sorts of intracellular organelles. Defects in the latter structures would explain the reported deviations from normal of calcium uptake into the sarcoplasmic reticulum[19,27–30] and the mitochondria.[31] The recent report of McIntosch and Berman[32] that the phospholipid moiety of MHS porcine sarcolemma is more unsaturated than normal is of great significance. It may be, as they have suggested, that this defect renders the sarcolemma unusually permeable to extracellular calcium. A similar defect might also be present in many other similarly constituted membranes.

Diagnosis of MH

As a test diagnostic of rigid MH, motor unit counting is considerably more accurate than concentric needle electromyography, but is slightly less accurate than the caffeine contracture test. Because motor unit counting, unlike the caffeine contracture test, is noninvasive and not too time-consuming, it is a useful screening method and adjunct in the investigation of individuals belonging to rigid MHS families. Motor unit counting is not of value in the diagnosis of nonrigid MH. The latter, relatively uncommon, variant of MH appears at least in some instances to be an etiologically distinct entity, the nature of which remains obscure. Non-rigid MH can, nevertheless, be diagnosed by the finding of a less than normal amplitude of contracture in the presence of caffeine (without halothane).

Among the four observed muscle groups, motor unit counts detected MH susceptibility in rigid patients and their rigid-R and rigid-I relatives most sensitively in the soleus or the extensor digitorum brevis. Tests utilizing two or more muscle groups moderately increase the sensitivity.

The following procedure is recommended for evaluating the test for MH susceptibility by motor unit counting. First, select a probability level of either 1 or 0.1 per cent, which corresponds to the percentage of healthy subjects who would be, falsely, declared to be susceptible. For the extensor digitorum brevis, thenar, hypothenar and soleus muscles, the following motor unit counts should be used: 115, 195, 240, and 580, respectively, at the 1 per cent level; 100, 175, 215, and 510, respectively, at 0.1 per cent level. Counts below these readings would support MH susceptibility.

A deficiency of motor neuron unit counts is a finding that is not specific for MH. As previously mentioned, abnormally low motor unit counts are also

observed in other myopathies.[1] The caffeine contracture test is, on the other hand, specific for MH, *i.e.*, patients with other myopathies have normal muscle contracture amplitudes in the presence of caffeine or caffeine plus halothane (unpublished data, Kalow). However, a loss of functioning motor units is a finding that is not specific for MH. As previously mentioned, abnormally low motor unit counts are also observed in any denervating process, as well as in disorders conventionally classified as myopathies.[2] Hence, a meticulously thorough history and physical examination of the nervous and muscle systems of all prospective patients are essential in order to differentiate and exclude any individual who might have some condition that could yield low motor unit counts similar to those of malignant-hyperthermia-susceptible patients.

The authors are grateful for the assistance of Mr. F. H. F. Kwong, computer programmer, and Miss Pearl Peters, technician.

References

1. McComas AJ, Fawcett PRW, Campbell MJ, et al: Electrophysiological estimation of the number of motor units within a human muscle. J Neurol Neurosurg Psychiat 34:121–131, 1971
2. Sica REP, McComas AJ, Upton ARM, et al: Estimation of motor units in small muscles of the hand. J Neurol Neurosurg Psychiat 37:55–67, 1974
3. Brown WF: A method for estimating the number of motor units in thenar muscles and the changes in motor unit counting with ageing. J Neurol Neurosurg Psychiat 35: 845–852, 1972
4. Ballantyne J, Hansen S: A new method for the estimation of the number of motor units in a muscle. 1. Control subjects and patients with myasthenia gravis. J Neurol Neurosurg Psychiat 37:907–915, 1974
5. Campbell MJ, Paty DW: Carcinomatous neuromyopathy. 1. Electrophysiological studies. An electrophysiological and immunological study of patients with carcinoma of the lung. J Neurol Neurosurg Psychiat 37:131–141, 1974
6. Serratrice G, Gastaut GL, Pellissier JF, et al: Amyotrophies et depopulations neuronales d'origine encephalique. Rev Neurol 131:185–192, 1975
7. Caccia MR, Ubiali E, Schieroni F: Axonal excitability and motor propagation velocity of peripheral nerves in patients with acute vascular lesions of the brain. J Neurol Neurosurg Psychiat 39:900–904, 1976
8. McComas AJ: Neuromuscular Function and Disorders. London, Butterworths, 1977
9. Eisen A, Karpati G, Carpenter S, et al: The motor unit profile of the rat soleus in experimental myopathy and reinnervation. Neurology (Minneap) 24:878–884, 1974
10. Peyronnard JM: An experimental evaluation of the motor unit counting technique. Can J Neurol Sci 2:332, 1975
11. Kalow W, Britt BA, Terreau ME, et al: Metabolic error of muscle metabolism after recovery from malignant hyperthermia. Lancet 2:895–898, 1970
12. Britt BA, Kalow W, Gordon A, et al: Malignant hyperthermia: An investigation of five patients. Can Anaesth Soc J 20:431–467, 1973
13. Britt BA, Endrenyi L, Kalow W, et al: The adenosine triphosphate (ATP) depletion test: Comparison with the caffeine contracture test as a method of diagnosing malignant hyperthermia susceptibility. Can Anaesth Soc J 23: 624–635, 1976
14. LaCour D, Juul-Jensen P, Reske-Nielsen E: Malignant hyperthermia during anaesthesia. Acta Anaesthesiol Scand 15: 299–317, 1971
15. Reske-Nielsen E, Harmsen A, Hauggard J: Modified technique of muscle biopsy. Acta Pathol Microbiol Scand 77:578–588, 1969
16. Harriman DGF, Sumner DW, Ellis FR: Malignant hyperpyrexia myopathy. Q J Med 42:639–664, 1973
17. Ellis FR, Harriman DGF: A new screening test for susceptibility of malignant hyperpyrexia. Br J Anaesth 45:638, 1973
18. Schmitt HP, Simmendinger HJ, Wagner H, et al: Severe morphological changes in skeletal muscles of a five-month old infant dying from an anesthetic complication with general muscle rigidity. Neuropaediatrie 6:102–111, 1975
19. Isaacs H, Heffron JJA: Morphological and biochemical defects in muscles of human carriers of the malignant hyperthermic syndrome. Br J Anaesth 47:475–481, 1975
20. Isaacs H, Barlow MB: Central core disease associated with elevated creatine phosphokinase levels. Two members of a family known to be susceptible to malignant hyperpyrexia. S Afr Med J 48:640–642, 1974
21. Zsigmond EK, Starkweather WH, Duboff GS, et al: CPK and malignant hyperthermia. Anesth Analg (Cleve) 51:220–225, 1972
22. Starkweather WH, Zsigmond EK, Duboff GS, et al: Creatine phosphokinase isoenzyme patterns in a malignant hyperthermic family, International Symposium on Malignant Hyperthermia. Edited by Gordon A, Britt BA, Kalow W. Springfield, Ill., Charles C Thomas, 1973, pp 339–349
23. Kelstrup J, Haase J, Jorni J, et al: Malignant hyperthermia in a family. Acta Anaesthesiol Scand 17:283–284, 1973
24. Denborough MA, Waine GL, Moulds RFW, et al: Insulin secretion in malignant hyperpyrexia. Br Med J 3:493–494, 1974
25. Malaisse WJ: Insulin secretion. Multifactorial regulation for a single process of release. Diabetologia 9:167–173, 1973
26. Malaisse WJ, Malaisse-Lagae F: A possible role for calcium in the stimulus–secretion coupling for glucose-induced insulin secretion. Acta Diabetol Lat 7:264, 1970
27. Britt BA, Endrenyi L, Cadman DL: Calcium uptake into muscle sarcoplasmic reticulum of pigs susceptible to malignant hyperthermia: In vitro and in vivo studies with and without halothane. Br J Anaesth 47:650–653, 1975
28. Ryan JF, Donlon JV, Malt RA, et al: Cardiopulmonary bypass in the treatment of malignant hyperthermia. N Engl J Med 290:1121–1122, 1974
29. Denborough MA, Hird FJR, King JO, et al: Mitochondrial and other studies in Australian Landrace pigs affected with malignant hyperthermia, International Symposium on Malignant Hyperthermia. Edited by Gordon A, Britt BA, Kalow W. Springfield, Ill., Charles C Thomas, 1973, pp 229–237
30. Isaacs H, Heffron JJA, Badenhorst M: Predictive tests for malignant hyperthermia. Br J Anaesth 47:1075–1080, 1975
31. Britt BA, Endrenyi L, Cadman DL, et al: Porcine malignant hyperthermia: Effects of halothane on mitochondrial respiration and calcium accumulation. ANESTHESIOLOGY 42:292–300, 1975
32. McIntosch D, Berman MC: Neutral lipid and phospholipid composition of normal and myopathic skeletal muscle of pigs. S Afr Med J 48:1221, 1974