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ARE MYOTONIAS AND PERIODIC PARALYSES ASSOCIATED WITH SUSCEPTIBILITY TO MALIGNANT HYPERTHERMIA?

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SUMMARY

Excised muscles from patients with myotonia or periodic paralysis were subjected to the in vitro *contracture test for susceptibility to malignant hyperthermia (MH). In a group of 44 patients, this standard test gave four positive, 10 equivocal and 30 negative results. The results for 27 control muscles from normal subjects were negative. When the test was performed with less than normal concentrations of contracture-triggering substances (caffeine $\leqslant$ 2 mmol litre^{-1}, $\leqslant$ 2% halothane), 70% of the muscles from the patients and only 15% of the controls responded with small contractures ($<$ 0.2 g). These results should not be taken to indicate that the patients have the genetic trait for MH. The positive and equivocal test results, in addition to the slight contractures, may be accounted for by the electrical after-activity in the cases of pure myotonia, and by increased resting myoplasmic [Ca^{2+}] in myotonic dystrophy. This shows that the* in vitro *contracture test lacks specificity.*

KEY WORDS

Complications: myotonia, periodic paralysis. Hyperthermia, malignant: in vitro *contracture test.*

Events similar to malignant hyperthermia (MH) may occur in patients with myotonia when they are exposed to volatile anaesthetics [1–11]. Moreover, depolarizing neuromuscular blocking drugs may cause masseter spasm or generalized muscle spasms in these patients and thus affect tracheal intubation or ventilation [1, 12–22]. When such incidents occur, it is important to ascertain if the patient is a genetic carrier of the trait of MH. The only generally accepted test for this is the *in vitro* contracture test. This standard test determines the sensitivity of excised muscle bundles to separately administered caffeine and halothane; muscles from persons susceptible to MH have lower contracture thresholds for these agents than normal muscle.

Although a clearly positive result (contractures during *in vitro* exposure of muscle bundles to caffeine $\leqslant$ 2 mmol litre^{-1} and $\leqslant$ 2% halothane) has never been reported for patients with any form of myotonia, an association between myotonia and MH seems possible, as the threshold concentrations of caffeine [3] or halothane [14, 15] for induction of muscle contractures have been reported to be reduced. To study this possibility, we have compared the caffeine and halothane thresholds of muscles from myotonic patients with those of normal muscle. A few patients with periodic paralysis were available also for this study. In selected subjects, we tested also the effect of a depolarizing agent, suxamethonium, on the excised muscles or measured the myoplasmic Ca^{2+} concentration during muscle rest, in order to obtain more insight into the mechanisms underlying abnormal results.

PATIENTS AND METHODS

Bundles of intact fibres or fibre segments were dissected from muscle biopsies obtained from normal control patients and from patients with one of the following disorders with symptoms of myotonia or periodic paralysis: recessive generalized myotonia [23]; myotonia congenita;

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Schwartz–Jampel syndrome; myotonic dystrophy [23]; hyperkalaemic periodic paralysis [24]; hypokalaemic periodic paralysis; and thyrotoxic periodic paralysis. The stage, distribution and specific characteristics of the disease were evaluated in each patient by electromyography and quantitative force measurements on several muscle groups. The diagnoses were verified by assessing the effects of exercise, K^+ load, glucose and insulin load, or peripheral cooling. As the patients and their diagnoses have been described previously in detail [23, 24], we have given them the same numbers as before to facilitate cross-reference.

Fibre segments $\geqslant 3$ cm long were dissected under local anaesthesia from the motor point region of muscles showing myotonia or episodes of weakness (vastus lateralis, vastus medialis, biceps brachii, deltoid or tibialis anterior muscles). One patient with Schwartz–Jampel syndrome and 21 control patients who had to undergo thoracic surgery consented to biopsy of intact intercostal fibres (approximately 1.5 cm long) or specimens of fibre segments (about 3 cm long) from their latissimus dorsi. Fibre segments were taken also from the vastus lateralis muscle of six healthy volunteers. All procedures were performed in accordance with the Helsinki convention and approved by the Ethics Committee of the Technical University of Munich.

The excised muscle specimens were transported to the laboratory in a standard solution (composition given below). The solution was at room temperature and was gassed continuously with carbogen (5 % carbon dioxide in oxygen). Bundles of muscle fibres were dissected with a diameter of approximately 2 mm. Up to four bundles were mounted in parallel experimental chambers and stimulated at 0.1 Hz with supramaximal pulses of 1 ms duration. Each bundle was stretched until the twitch amplitude was maximal. At this length, slight shortening or lengthening did not alter the force amplitude. The static version of the test protocol supported by the European Malignant Hyperpyrexia Group (EMHG) [25] was followed strictly, with the exception that muscles other than the vastus were used also. The force records were evaluated according to the criteria of this protocol. The baseline for contractures was defined as the force level just before addition of the smallest concentration of a drug. Twitch relaxation was defined as "slowed" when a noticeable fraction of force remained between twitches stimulated at the rate of 0.1 Hz. All tests were completed within 5 h after biopsy.

The standard solution contained (mmol $litre^{-1}$): NaCl 118.2, KCl 3.4, $MgSO_4$ 0.8, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25.0, and glucose 5.5 (315 mosmol $litre^{-1}$). The pH of the carbogen-gassed solution was 7.4, the temperature 37 °C. Halothane was bubbled through the bath via a halothane vaporizer (Vapor, Dräger, Lübeck, FRG). The concentration of halothane was monitored with a digital sensor (Iris, Dräger, Lübeck, FRG). The rate of bubbling was controlled by two Teflon flow meters (ROTA Apparate, FRG). The concentration of halothane in the bath was determined by gas chromatography [26]. Caffeine (dehydrated; Carl Roth, Karlsruhe, FRG) was added cumulatively to the bath to produce final concentrations of 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0 and 32 mmol $litre^{-1}$. As any slight mechanical stimulation (e.g. movements caused by gassing of the solution) may induce electrical activity in myotonic muscle, tetrodotoxin 1 μmol $litre^{-1}$ was added to the bath for suppression of action potentials when required. In some cases, the bundles were exposed also to suxamethonium (Lysthenon 2%, Hormon-Chemie, Munich, FRG). The agent was dissolved in water and was added directly to the bath so that the final concentration was 1.1 mmol $litre^{-1}$.

Myoplasmic $[Ca^{2+}]$ was estimated in thin sheets of resealed fibre segments by means of fura-2 while isometric force was monitored simultaneously with a strain gauge (Akers, Horton, Norway). The methodology was exactly as described elsewhere [27].

RESULTS

The *in vitro* contracture test is considered positive when the bundles produce sustained contractures with amplitudes $\geqslant 0.2$ g during both application of caffeine $\leqslant 2.0$ mmol $litre^{-1}$ and application of $\leqslant 2.0$ % halothane. The result is equivocal when a contracture is elicited by only one test substance.

Within the patient group, 30 of the tests were negative, 10 equivocal and four positive; all muscles from the normal subjects gave negative results (fig. 1, table I). The four positive results were obtained for patients with myotonic dystrophy. In two of these muscles we determined also the resting myoplasmic $[Ca^{2+}]$, which was increased (fig. 2, table II) [27]. In contrast, we found the resting $[Ca^{2+}]$ normal in muscles from

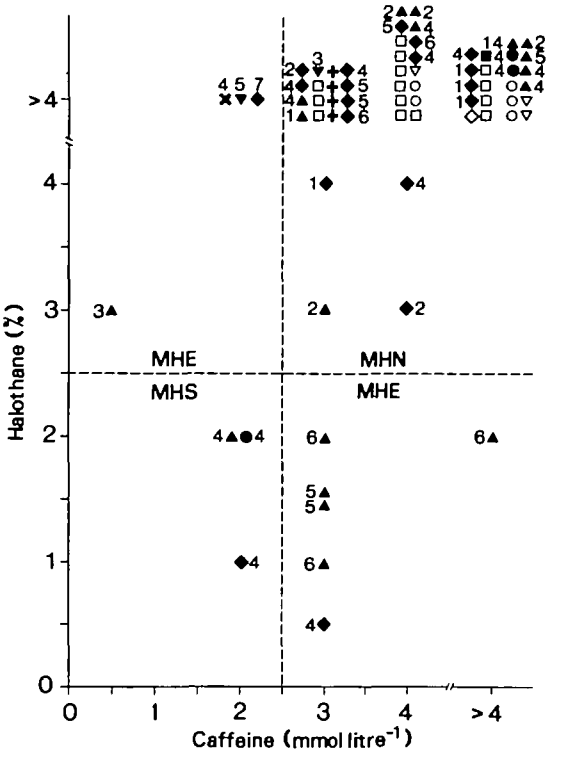

FIG. 1. Results obtained with the *in vitro* contracture test. Ordinate: concentration of halothane required for the induction of a contracture of $\geqslant 0.2$ g; abscissa: concentration of caffeine required for the same contracture amplitude. The dashed lines divide the plot into four regions designated [25]: malignant hyperthermia normal (MHN), malignant hyperthermia susceptible (MHS) and (two) malignant hyperthermia equivocal (MHE). The bundles used for the test were prepared from: cut intercostal (+), intact intercostal (□), biceps brachii (◇), latissimus dorsi (▽), tibialis anterior (×), vastus lateralis (○) and vastus medialis (△) muscles. Open symbols = controls: closed symbols = patients. Numbers next to symbols represent the various diseases: 1 = recessive generalized myotonia; 2 = myotonia congenita; 3 = Schwartz–Jampel syndrome; 4 = myotonic dystrophy; 5 = hyperkalaemic-, 6 = hypokalaemic- and 7 = thyrotoxic periodic paralysis.

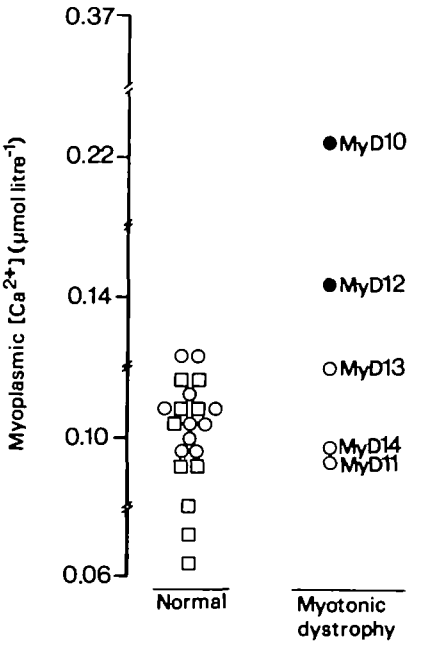

FIG. 2. Comparison of the myoplasmic Ca^{2+} concentration measured at rest in muscle fibres from normal subjects (left) and from five patients with myotonic dystrophy (right). Intact fibres (□) and long fibre segments (○) were studied. ● = Muscle fibres for which the contracture test had given a positive result.

TABLE I. *Summary of the* in vitro *contracture test results. RGMy = Recessive generalized myotonia; MyC = myotonia congenita; SJS = Schwartz–Jampel syndrome; MyD = myotonic dystrophy; HyperPP = hyperkalaemic periodic paralysis; HypoPP = hypokalaemic periodic paralysis; ThyrPP = thyrotoxic periodic paralysis. Hal. = ⩽ 2% Halothane; Caff. = caffeine ⩽ 2 mmol litre^{-1}*

Disease	*n* (−)	Positive	Equivocal	Negative	Small response		Slowed relaxation	
					Hal.	Caff.	Hal.	Caff.
RGMy	6	—	—	6	5	6	5	6
MyC	6	—	—	6	6	5	5	5
SJS	2	—	1	1	2	2	2	2
MyD	17	4	1	12	10	11	5	5
HyperPP	7	—	4	3	2	5	0	1
HypoPP	5	—	3	2	2	1	0	0
ThyrPP	1	—	1	—	0	1	0	0
Totals	44	4	10	30	27	31	17	19
Normal	27	—	—	27	4	4	0	0

TABLE II. *Additional findings for the patients who had positive or equivocal test results. SJS = Schwartz–Jampel syndrome; MyD = myotonic dystrophy; HyperPP = hyperkalaemic periodic paralysis; HypoPP = hypokalaemic periodic paralysis; ThyrPP = thyrotoxic periodic paralysis. †Severity of disease rated 1–5, with a score of 5 indicating severe affliction (e.g. wheelchair bound). §No permanent weakness, but periodic attacks (approximately 1/month). *Positive* in vitro *reactions to suxamethonium. ‡Increased* $[Ca^{2+}]$

Patient	Severity†	Test	Muscle	Morphology
SJS2	4	Equivocal	Vastus	Hypertrophic fibres, central nuclei
MyD2	3	Equivocal	Tibialis anterior	Moderate myopathy, sarcoplasmic masses
MyD5	3	Positive	Vastus	Slight myopathy, increased nuclei, slight interstitial changes
MyD10	3	Positive‡	Vastus	Moderate myopathy, slight neuropathy, increased nuclei, slight type grouping
MyD12	3	Positive‡	Biceps	Slight myopathy, slight neuropathy, increased nuclei, sarcoplasmic masses
MyD20	2	Positive	Biceps	Advanced myopathy
HyperPP5	2	Equivocal	Latissimus dorsi	Slight myopathy, vacuoles
HyperPP7*	2	Equivocal	Vastus	Slight myopathy, numerous vacuoles
HyperPP8*	2	Equivocal	Vastus	Slight myopathy, tubular aggregates
HyperPP9	2	Equivocal	Biceps	Moderate myopathy, tubular aggregates
HypoPP8	1§	Equivocal	Vastus	Normal
HypoPP10	2	Equivocal	Vastus	Vacuoles
HypoPP11	4	Equivocal	Vastus	Severe neuropathy, moderate secondary myopathy
ThyrPP1	2	Equivocal	Biceps	Slight calibre changes, type II atrophy

three patients with myotonic dystrophy (fig. 2) and two patients with recessive generalized myotonia who had negative results with the contracture test.

Small contractures (< 0.2 g) in response to low concentrations of halothane ($\leqslant 2.0\%$) or caffeine ($\leqslant 2.0$ mmol litre^{-1}) were provoked in up to 70% of the muscles from the patient group (table I). This type of response, which is not considered relevant by the EMHG, appeared in only 15% of the records from normal subjects. In MH negative subjects having a family member known to be susceptible to MH, this percentage is 23% ($n = 35$) [own unpublished observations].

Slowed twitch relaxation (see Methods) was observed in most bundles obtained from patients with myotonia [23]. In the presence of caffeine or halothane, the remaining force increased. The remaining force was the greatest in muscles from those patients in whom myotonia was detected most readily *in vivo* (in EMG); these were the patients with recessive generalized myotonia, myotonia congenita, or Schwartz–Jampel syndrome (table I). Slowed twitch relaxation in the presence of caffeine or halothane was observed also in muscles from five of 17 myotonic dystrophy patients. In muscles from the 13 patients with periodic paralysis, only three with slowed relaxation were noted when the fibres were exposed to very high concentrations of halothane ($\geqslant 4\%$) or caffeine ($\geqslant 4$ mmol litre^{-1}).

Suxamethonium 1.1 mmol litre^{-1} readily induced contractures $\geqslant 0.1$ g in the fibre segments from patients with myotonia (fig. 3c). In contrast, on fibre bundles from normal muscle ($n = 12$) and from patients with hypokalaemic periodic paralysis ($n = 2$), the agent did not cause contractures, in spite of the fact that they contained endplates as verified visually [15]. The following is a summary of the positive responses to administration of suxamethonium: recessive generalized myotonia, 100% ($n = 3$); myotonia congenita, 50% ($n = 6$); Schwartz–Jampel syndrome, 100% ($n = 1$); myotonic dystrophy, 70% ($n = 7$); hyperkalaemic periodic paralysis with myotonia, 100% ($n = 2$). The largest amplitudes (0.8 g) and the longest durations (120 s) were observed in contractures of fibres from patients in whom intense myotonic activity had been recorded both *in vivo* and *in vitro* (recessive generalized myotonia Nos 5, 6, 7 and Schwartz–Jampel syndrome No. 1) [23].

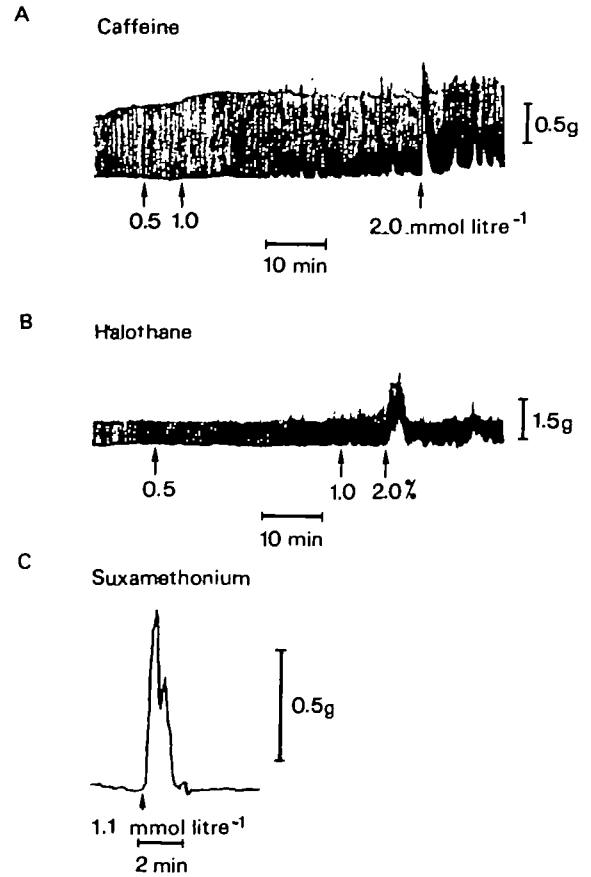

FIG. 3. Force records from muscles from patients with recessive generalized myotonia stimulated at 0.1 Hz with supramaximal pulses. A: Increasing concentrations of caffeine were added to the muscle bath, which led to abnormally slow relaxation of the twitches (recessive generalized myotonia patient No. 4). B: Similar results with halothane in the same patient. C: A contracture induced by suxamethonium (recessive generalized myotonia patient No. 7).

DISCUSSION

We did not obtain a positive or equivocal contracture test from any patient with pure (recessive generalized or congenital) myotonia. This supports results of similar studies on goats with congenital myotonia [28], but is in conflict with reports on patients with congenital myotonia with positive caffeine or halothane test results [3, 14, 15]. We did observe in the muscles of these patients, abnormally slowed relaxation which led to a type of contracture when the effect was increased by caffeine or halothane. This finding might explain the positive results mentioned above, but it does not seem related to pathologically increased reticular [Ca^{2+}] release, as are the contractures in MH. These pseudo-contractures are caused by the known myotonic abnormality of the sarcolemma—that is, the disturbed excitability. Contractions produced by electrical "after-activity" could, in severe cases, interfere with the contracture test. Thus it might be best to omit electrical stimulation when performing the *in vitro* contracture test with muscles from patients with pure myotonia.

The high incidence of positive or equivocal test results in muscles from patients with myotonic dystrophy may suggest that these patients possess the genetic trait for MH. The MH gene has been mapped recently on chromosome 19—the chromosome that codes also for the myotonic dystrophy (DM) gene [29], but the distance between the two genes is of the order of 25 cM, which makes it very unlikely that the two conditions are genetically linked.

Both MH episodes and progressive dystrophy are connected with an increased myoplasmic [Ca^{2+}] of the muscle, but via different patho-mechanisms. In MH, the intracellular Ca^{2+} release is disturbed by the triggering agents [27], while in dystrophy the Ca^{2+} influx from the extracellular space is abnormally great [30]. Both mechanisms seem to generate a similar condition for the test. Our findings show that the test result may depend on the stage of the disease, that is, on how many fibres are affected and to what degree. The difference in mechanisms in MH and myotonic dystrophy is reflected also in the finding that muscles from patients susceptible to MH are rarely dystrophic [31]. We conclude from our results that the standard MH testing procedure lacks specificity.

A positive test result does not imply that anaesthetic complications must occur—not even in patients who are susceptible to MH [32]. In fact, neither our patients described here nor their family members are known to have had an event during anaesthesia which could be classified clearly as MH.

A muscle may have a normal sensitivity to halothane (or caffeine, or both), and may react abnormally to other agents. The myotonic reaction is known to be exaggerated by depolarizing neuromuscular blocking drugs [1, 12–22]. An increase in involuntary electrical after-activity is the most likely cause of this stiffness. This is consistent with our *in vitro* finding that suxamethonium-induced contractions occur in

muscles from patients with myotonia, whereas no responses to suxamethonium were found in bundles from normal patients [33].

Although we conclude that the myotonias and periodic paralyses are not associated with susceptibility to MH, we should stress that the anaesthetist should be prepared for an anaesthetic-induced reaction in any of these patients and that non-triggering anaesthesia is indicated.

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REFERENCES

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61**: 173–187.
2. Brownell AKW. Malignant hyperthermia: relationship to other diseases. *British Journal of Anaesthesia* 1988; **60**: 303–308.
3. Gordon AS, Britt BA, Pritzker KPH. Myotonia and malignant hyperpyrexia. *Muscle and Nerve* 1986; **9**: 221.
4. Haberer J-P, Fabre F, Rose E. Malignant hyperthermia and myotonia congenita (Thomsen's disease). *Anaesthesia* 1989; **44**: 166.
5. Houk R, Anderson EF, Noto P. Anesthetic management of a patient with myotonia atrophica. *Anesthesiology* 1975; **43**: 689–692.
6. Houvenaeghel M, Achilli-Cornesse E, Jullian-Papouin H, Martin-Meyssonier A, Manelli JC. Dantrolène oral chez une parturiente atteinte de myotonie de Steinert et sensible à l'hyperthermie maligne. *Annales Françaises d'Anesthesie et de Réanimation* 1988; **7**: 408–411.
7. Jacquot C, Stieglitz P, Kozak-Reiss G, Krivosic-Horber R, Laxenaire MC, Lienhart A, Nivoche Y. Recensement des cas français d'hyperthermie maligne peranesthésique. Mise à jour. *Annales Françaises d'Anesthésie et de Réanimation* 1988; **7**: 524–534.
8. King JD, Denborough MA, Zapf PW. Inheritance of malignant hyperpyrexia. *Lancet* 1972; **1**: 365–370.
9. Morley JB, Lambert TF, Kakulas BA. A case of hyperthermia with myotonia congenita. *Excerpta Medica International Congress Series* 1973; **295**: 543–546.
10. Moulds RFW, Denborough MA. Myopathies and malignant hyperpyrexia. *British Medical Journal* 1974; **3**: 520.
11. Seay AR, Ziter FA. Malignant hyperpyrexia in a patient with Schwartz–Jampel syndrome. *Journal of Pediatrics* 1978; **93**: 83–84.
12. Cody JR. Muscle rigidity following administration of succinylcholine. *Anesthesiology* 1968; **29**: 159–162.
13. Haley FC. Anaesthesia in dystrophia myotonica. *Canadian Anaesthetists Society Journal* 1962; **9**: 270.
14. Heiman-Patterson T, Martino C, Rosenberg H, Fletcher J, Tahmoush A. Malignant hyperthermia in myotonia congenita. *Neurology* 1988; **38**: 810–812.
15. Heiman-Patterson T, Rosenberg H, Fletcher JE, Tahmoush AJ. Halothane–caffeine contracture testing in neuromuscular diseases. *Muscle and Nerve* 1988; **11**: 453–457.
16. Kaufman L. Anaesthesia in dystrophia myotonica. *Proceedings of the Royal Society of Medicine* 1960; **53**: 183–188.
17. Mitchell MM, Ali HH, Savarese JJ. Myotonia and neuromuscular blocking agents. *Anesthesiology* 1978; **49**: 44–48.
18. Örndahl G. Myotonic human musculature: Stimulation with depolarizing agents. II. A Clinico-pharmacological study. *Acta Medica Scandinavica* 1962; **172**: 753–765.
19. Paterson IS. General myotonia following suxamethonium. *British Journal of Anaesthesia* 1962; **34**: 340–342.
20. Talmadge EA, McKechnie FB. Anesthetic management of patients with myotonia dystrophica. *Anesthesiology* 1959; **20**: 717–719.
21. Thiel RE. The myotonic response to suxamethonium. *British Journal of Anaesthesia* 1967; **39**: 815–821.
22. Thomas A, Leopold U, Winkler H. Maligne Hyperthermie bei Paramyotonia congenita. *Anaesthesiologie und Reanimation* 1988; **13**: 295–300.
23. Iaizzo PA, Lehmann-Horn F. The correlation between electrical after-activity and slowed relaxation in myotonia. *Muscle and Nerve* 1990; **13**: 240–246.
24. Ricker K, Camacho LM, Grafe P, Lehmann-Horn F, Rüdel R. Adynamia episodica hereditaria: What causes the weakness? *Muscle and Nerve* 1989; **12**: 883–891.
25. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *British Journal of Anaesthesia* 1984; **56**: 1267–1269.
26. Van Dyke RA, Wood CL. Binding of radioactivity from ^{14}C-labelled halothane in isolated perfused rat livers. *Anesthesiology* 1973; **38**: 328–332.
27. Iaizzo PA, Klein W, Lehmann-Horn F. Fura-2 detected myoplasmic calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. *Pflügers Archiv* 1988; **411**: 648–653.
28. Newberg LA, Lambert EH, Gronert GA. Failure to induce malignant hyperthermia in myotonic goats. *British Journal of Anaesthesia* 1983; **55**: 57–62.
29. McCarthy TV, Healy SJM, Heffron JJA, Lehane M, Deufel T, Lehmann-Horn F, Farrall M, Johnson KJ. Localisation of the malignant hyperthermia susceptibility locus to human chromosome 19q12-q13.2. *Nature (London)* 1990; **343**: 562–563.
30. Bodensteiner JB, Engel AG. Intracellular calcium accumulation in Duchenne dystrophy and other myopathies: A study of 567,000 fibers in 114 biopsies. *Neurology* 1978; **28**: 439–446.
31. Ellis FR, Halsall PJ, Harriman DGF. The work of the Leeds Malignant Hyperpyrexia Unit (1971–1984). *Anaesthesia* 1987; **41**: 809–815.
32. Gronert GA. Malignant hyperthermia. In: Engel AG, Banker BQ, eds. *Myology*. New York: McGraw-Hill, 1986; 1763–1784.
33. Ørding H, Skovgaard LT. *In vitro* diagnosis of susceptibility to malignant hyperthermia: evaluation of tests with halothane–caffeine, potassium chloride, suxamethonium and caffeine–suxamethonium. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 462–465.