

F Richard Ellis
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In 1966, at the University of Leeds, Richard Ellis was a MRC research fellow. He became Senior lecturer in 1971 and reader in 1976. In 1992 he was appointed to a developmental chair and became head of department at Leeds General Infirmary. More than 50% of

Ellis's work is associated with malignant hyperpyrexia and the content of this bibliography will reflect this, but brief comments on his other publications are included.

Studies unrelated to MH

Like many before and after him Ellis started publishing with a case report: "Postoperative Respiratory Inadequacy; an Instructive Case" [1] The postoperative respiratory problem was due to a dual neuro-muscular block following suxamethonium which was treated with anti-cholinesterases. Another respiratory paper appeared in 1971 which was a survey of respiratory problems in the post-operative period [2].

Assessment of premedicant drugs was also a favourite 'intro' to research; droperidol 1972 [3], lorazepam 1973 [4], and various forms of morphine later in 1988 and 1989 [5, 6].

There are always some titles that catch the eye: "The management of the cut-throat" (1966), "Cardiorespiratory response to dangling on a rope in simulated rock-climbing accident" (1973)[7], "A study of body temperatures of anaesthetized man in the tropics" (1977), and "Time of death of an organ donor" (1980).

ⁱ Picture courtesy of JG Jones

Cut-throat: A review of a series of 22 patients, tracheostomy was advised for patients where the airway has been entered (intubation under local analgesia) [8].

Dangling on a rope: [7] This is an interesting investigation of how different means of securing a climber to a rope can change the physiological status. A waist loop that was commonly used was very painful and was said to cause death within 20 minutes even without trauma due to the fall. This commonly used technique was compared with shoulder and pelvic harnesses. Blood pressure changes with the waist loop were great (both up and down) and the shoulder harness was too painful for measurements to be made. The pelvic harness was comfortable and the cardiovascular changes minimal. Analysing their results they concluded that the waist loop caused an oxygen debt, lactic acidosis and hyperkalaemia and could result in a cardiac arrest.

Twenty African patients undergoing surgery in hot and humid conditions still had a decrease in body temperature in a local temperature of 28.7°C and a relative humidity of 72%. A thermal equilibrium occurred at 30 minutes [9].

Brain death: Gained legal acceptance on 22 February 1978 when the Bradford and Calderdale Coroner, Mr Turnbull, accepted it as a diagnosis in an inquest. Seeing a 'pink and warm' relative diagnosed as dead is a problem for some and needed "considerate explanation" by the medical staff; the medical staff, too, has to accept "brain death" as death. This was just two years after Mr Turnbull's decision [10].

Propanidid: "The neuromuscular effects of propanidid" [11], "The neuromuscular interaction of propanidid with suxamethonium and tubocurarine" [12], "The site and mode of action of propanidid on the peripheral motor unit" [13] and "Effect of propanidid on peripheral motor function in myasthenics" [14].

Studies relating to blood gases and pH and their effect on nerve tissue: "The interaction of PCO₂, pH and halothane on nerve action potentials" (1968) [15], "Some effects of PCO₂ and pH on nerve tissue" (1969) [16] and the "Effect of hyperbaric oxygen on nerve tissue" (1970) [17].

In the late 80s and 1991 there was a set of papers on local anaesthetic blocks, femoral and "3 in 1" lumbar plexus block (used to facilitate muscle biopsy) [18-20]. And, of course there were odds and ends [21-31].

Malignant hyperpyrexiaⁱⁱ

Although Ellis's name is attached to a large body of work on the clarification of aetiology, diagnosis and management of patients susceptible to malignant hyperpyrexia there were many other workers associated with the Leeds Group. P. Jane Halsall (47 co-authored papers with Ellis), Philip M. Hopkins (25), D.G. Harriman (14), I.M. Clarke (8), A.D. Stewart (6), P.A. Cain (5), I.T. Campbell (5), A.S. Christian (5), D.E. Iles (5), Rachel L. Robinson (5) and not forgetting the European Malignant Hyperthermia Group.

To see a brief time-line of the research go to the end of the chapter.

1971

Ellis is renowned for his work on the investigation of the rare condition malignant hyperpyrexia (MH). The first time his name was associated with MH was in 1971 with NP Keaney, DGF Harriman, K Kyei-Mensah and JH Tyrrell [32], 'Halothane-induced muscle contracture as a cause of hyperpyrexia'. This was a presentation to the Anaesthetic Research Society (ARS) in March, in Belfast.

This was followed by a letter to the British Medical Journal in the following October [33]. It is an interesting detailed letter in that it points out a variety of problems with a 'leader' in a previous issue and sets out a definition of the condition.

MH is described as a "confused subject"; they highlight the relevance of the muscle contracture, (is it causative or secondary?), note that the writer of the leader was unaware of halothane and methoxyflurane causes irreversible contractures, etc, etc. They describe the use of procaine to reverse the effect. They, Keaney and Ellis, said that although the aetiology was unknown a working definition was required and they created one "... *malignant hyperpyrexia is a specific potentially fatal condition occurring during anaesthesia in which heat production exceeds physiological heat loss to an extent that causes a progressive rise of body temperature at a rate of at least 2oC per hour.*" However they do say that muscle contractures are probably secondary, together with acidosis, hypoxia etc.

ⁱⁱ A disclaimer; the author is not an expert on the subject of MH, its biochemistry or genetics. Every care has been taken but it is possible that some details in this bibliography may not be without error.

1972

Screening for MH is the subject of one paper in 1972 [34]. They present what they consider to be a more specific method than previously available using a motor-point muscle biopsy which undergoes histopathological examination and exposure to halothane and suxamethonium under near physiological conditions.

The second [35] is about the structural and neuro-pharmacological aspects of malignant hyperpyrexia. This was about the examination of motor-point muscle biopsy which all showed variable structural features of myopathy, differing from family to family. The in-vitro test, presumably the one described above, was described.

1973

This article in *Anaesthesia* contains a description of Ellis's first involvement with MH in 1971. He was asked to suggest a safe anaesthetic for a patient whose sister had an MH event and they did a muscle biopsy at the same time, found a myopathy and the muscle formed a contracture with halothane and methoxyflurane [36]. They studied another 18 patients and suggested the in vitro testing of muscle as the basis for diagnosis of MH

A new screening test for susceptibility to malignant hyper-pyrexia was presented at the ARS meeting at Imperial Chemical Industries Pharmaceutical Division in Macclesfield (April 1973) [37]. They described how muscle from patients susceptible to MH had histological abnormalities consistent with myopathy and, because of problems with the established screening methods; a new test had been devised. It can detect susceptibility to non-rigid MH and so by using both tests it is possible to differentiate between the two types of hyperpyrexia. The test stretches the muscle strip by about 30% and measures the resting tension; it is then allowed to relax. The resting tension in the hyperpyrexia group was significantly higher than normal muscle. They also said "... increased stress relaxation in hyperpyrexia muscle suggests that there could be a structural abnormality in the muscle proteins to account for MH."

"Histopathological and neuropharmacological aspects of malignant hyperpyrexia". [38]. This publication in the *Proceedings of the Royal Society of Medicine* describes the histology and analysis of a biopsy of the symptomless brother of a girl who died of MH. "These pharmacological results were so different from control responses that we thought our findings could represent a

more specific test of the susceptibility to malignant hyperpyrexia than serum enzyme estimations.” They found “... a perfect correlation was obtained between the neuropathological and the neuropharmacological results.” And this “... *encourages us to believe that positive identification of the patient susceptible to malignant hyperpyrexia is possible.*” Is this the key publication to the future of MH identification?

[39] This is a letter in the correspondence section of the BMJ referring to a report by Denborough et al.ⁱⁱⁱ on the description of core-like areas in type 1 fibres in MH myopathy. They (Ellis et al) preferred the term “moth-eaten fibres”. Their view was that ‘central core disease’ should be reserved for those appearances that “resemble the original descriptions”. Ellis et al were making the point that, in their view, central-core disease patients do not have susceptibility to MH. It was a strongly worded critique and went on to describe their experience in obtaining muscle biopsies that included the “motor point”.

Malignant hyperpyrexia myopathy [40]. The basic points of this was of five patients, three died (their families were investigated) and two survivors were examined along with their relatives. Those whose muscles reacted to stimulation with contracture were considered liable to develop malignant hyperpyrexia. All had structurally abnormal muscle, their histopathological and histochemical characteristics were described but the myopathy in reactors was asymptomatic. Serum creatine phosphokinase estimation was stated to be unreliable as an indicator of MH.

1974

At the ARS meeting in Kings College Hospital (March '74) Ellis and Clarke described the therapeutic value of procaine and lignocaine in malignant hyperpyrexia [41]. They showed how procaine could potentiate the muscle abnormality in the hyperpyrexic patient. They cautioned against its use.

A publication that probably stimulated many departments of anaesthesia to act was this with the title “A pack for the emergency treatment of malignant hyperpyrexia” [42]. The pack included a battery powered multi-site thermometer, instant ice bags (to be placed over axillae, groins and praecordium), dextrose 5%, sodium bicarbonate 8.4%, procaine 2%, dextrose

ⁱⁱⁱ Denborough MA, Dennett X, Anderson RM. British Medical Journal. 1(5848):272-3, 1973 Feb 3.

50%, dexamethasone, chlorpromazine (to prevent shivering), diazepam, practolol, isoprenaline, insulin, adrenaline. Sterile infusion sets with assorted intravenous needles, syringes, intravenous cannulae etc, record forms and lithium-heparin blood-sample bottles.

“Neuromuscular disease and anaesthesia” was a review article with 85 references [43].

Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone [44], a very interesting case report. A young girl, whose father had died of MH, needed dental extractions under anaesthesia, muscle biopsies were to be done at the same time. Diazepam, thiopentone and nitrous oxide resulted in a pyrexia; temperature had risen at a rate of 6°C per hour. Dexamethasone had dramatic results. A second anaesthetic was with nitrous oxide and oxygen, her body temperature increased again. A third anaesthetic was induced and maintained with thiopentone and was uneventful. She and her sister had normal serum creatine phosphokinase levels. The three main facts from this case report are that nitrous oxide can cause MH, dexamethasone is effective (and preferable to procaine) and creatine kinase is not always raised in MH susceptible patients.

They concluded that the first treatment should be a high dose dexamethasone 1-2 mg/kg.

1975

Procaine had been used to treat contractures (see 1971) and this study evaluated the effect of its effect (and that of lignocaine) in in-vitro experiments [45]. It was shown that procaine could cause or accentuate a contracture and that in some cases the dose required to abolish a halothane induced effect grossly in excess of clinically acceptable doses. There was no significant difference between procaine and lignocaine. They challenged the view that procaine was an appropriate treatment for MH.

[46] This was another ARS presentation, this time at the Research Department of Anaesthetics in the Royal College of Surgeons (obviously prior to the formation of the ‘independent’ college of anaesthetists. It was about nitrous oxide causing MH and being successfully treated with steroids. Was this not published in 1974 [44]?

Having disposed of procaine they now disposed of serum creatinine phosphokinase (CPK) as a screening blood test [47]. It did not correlate with

halothane-induced muscle contracture or the presence of myopathy, and CPK values were inconsistent in both normal and MH patients.

[48] “New causes of malignant hyperpyrexia”: This is an anonymous short article (normal in the BMJ at that time) about recent developments in the understanding of MH and describing the possible multiple agents that may cause MH and the use of high dose steroids in its management. One can speculate on the identity of the author.

1976

[49] This is another letter. It is critical of Denborough’s criticism of their findings that CPK was of no value in assessing MH susceptibility. They were of the opinion that if their contracture tests were positive all the other tests would also be positive.

1977

Calcium was known, from the very earliest physiological studies on muscle, to be involved in muscle contraction. It was therefore sensible to investigate the role of calcium in conditions involving abnormal muscle, and so they did [50]. Muscle from MH susceptible patients (diagnosed using the halothane contracture test) were analysed and there was no difference between normal patients and MH susceptible patients in either calcium or magnesium concentrations.

Another avenue for their research was to see what drugs depressed the halothane induced contractures, in this case pancuronium and methylprednisolone [51]. They were both effective and so were deemed safe to use in MH susceptible patients

1978

Acidosis occurs during MH and so the rate of acid production was investigated [52]. Halothane was shown to double the rate of acid production in MH susceptible muscle but had no effect on normal muscle. It was not lactic acid.

[53] “Plasma cholinesterase and malignant hyperpyrexia”: This is a comment about a report by Whittaker et al. ^{iv}. It would appear that MH patients

^{iv} Whittaker, M., Spencer, R., and Searle, J. (1977). *Br. J. Anaesth.*, 49, 393.

had an increased incidence of fluoride-resistant genes controlling plasma cholinesterase. Ellis et al. admitted finding a correlation and said that the inheritance of MH was likely to be of a polygenic nature.

1979

One of the confusing aspects of MH is that some patients, subsequently found to be MH susceptible, had anaesthesia involving triggering agents and did not develop the condition. They reviewed the patients' medical histories but could not find any common factor [54].

1980

[55] This was an article in a British Journal of Anaesthesia symposium devoted to muscle, its physiology and diseases.

The article on MH in the British Journal of Hospital Medicine [56] has not been sighted.

[57] Muscle: An editorial in the British Journal of Anaesthesia

1981

The metabolic processes in muscle are complex and in an attempt to determine the abnormality in MH susceptible patients (MHS) a laboratory controlled study of exercise in MHS patients and normal control subjects was performed [58]. There were nine patients in each group and they were exercised on a bicycle ergometer. Some experiments were carried out in fasting patients and some after a 600-kcal meal.

The results, in brief, showed that MHS patients had no increased heat production compared with controls and had no dietary-induced thermogenesis at all. They had higher insulin levels, and triglycerides rose over the course of the experiment. Pyruvate levels rose in the control subjects but not in the MHS patients.

One suggestion was that blood was shunted away from thermogenic tissue and another was that there was an underlying abnormality of sympathetic control mechanisms in the MHS subjects.

A "Collaborative study of the frequency of the fluoride-resistant cholinesterase variant in patients with malignant hyperpyrexia" [59] was the first genetic investigation into MH by the Leeds group. Previously reported work had shown an increase in the frequency of the E1u E1f genotype for cholinesterase. The Leeds work could not reproduce these results.

1982

It was now 20 years since MH was first described by the Australian anaesthetists Denborough, Forster, Lovell, Maplestone and Villiers^v, and the condition was still relatively unknown territory.

Some muscle diseases are associated with enlarged muscles and MHS patients were studied to examine the possibility that MHS patients also had enlarged muscles. They assessed body fat at the same time [60]. The amount of body fat was calculated from skinfold measurement and using antero-posterior photographs the diameters of the left thigh were assessed.

Male MHS subjects had significantly less body fat than the controls and upper thigh diameters in the MHS females were significantly greater than controls. However, they suggested that these differences were subtle and appeared to vary with sex.

1983

Another physiological study was carried out using exercise as the stimulant for abnormal responses [61]. Body temperature and blood chemistry were measured in five MHS subjects and five normal subjects during progressively severe exercise. As the exercise increased central temperature increased more in the MHS subjects. The temperature in the MHS subjects was significantly delayed and this was thought to be due to a delay in the onset of vasodilatation. It was concluded that this was evidence of abnormal heat dissipation mechanisms. Free fatty acids, cortisol levels and blood lactate concentrations were also higher in the MHS subjects than in the controls.

The thermal results from this study do not seem to be totally aligned with the 1981 paper [58] but they were measuring thermo-genesis then rather than measuring temperature.

Dantrolene was initially used for treating muscle spasticity but in 1975 a paper by GG Harrison^{vi} showed its usefulness in MH. This paper [62] investigated the action of dantrolene on the sarcolemma. It was shown to have

^v Denborough MA, Forster JF, Lovell RR, Maplestone PA, Villiers JD. *British Journal of Anaesthesia* 1962; 34 (6): 395-6.

^{vi} Harrison GG. *Br J Anaesth* 1975;47 (1): 62-5

no effect on contractures induced by 2:4 dinitrophenol, a small effect on caffeine contractions, but a marked effect on the contractures produced by K⁺. They suggested that the site of the MH abnormality could be on the sarcolemma which was now where dantrolene was thought to work.

1984

A busy year with six publications.

The topic of MH was addressed to the paediatric speciality in the journal *Archives of Disease in Childhood* [63]. It is a general overview of the topic as it was known at that time.

[64] This is an editorial about the formation of the European Malignant Hyperpyrexia Group; a collaboration of eight countries. "...from now on work from members will conform to the agreed format." The goal was to define MH more accurately and to differentiate it from other conditions.

Suxamethonium is the major armament in the anaesthetists' arsenal when control of the airway with rapid intubation is required but it sometimes causes muscle spasm (as distinct from fasciculation, which is normal). The muscle spasm was considered an early indicator of the condition and was used as the trigger for further investigation of the patient's MH susceptibility. This paper [65] involved the analysis of 277 case histories and reinforced the view that muscle spasm induced by suxamethonium means that MH should be considered a likely diagnosis.

[66] This was a report by the Neurochemical Group to the 606th meeting of Biochemical Transactions held at University of Cork, 27-30 September 1983. The colloquium was on Molecular Aspects of Malignant Hyperpyrexia and Muscular Dystrophy. Ellis's team presented '*A biochemical abnormality found in muscle from unstressed malignant-hyperpyrexia-susceptible humans*'. After much biochemical description the bottom line was "*The human results lend further support to the suggestion that MHS subjects have an increased sympathetic activity, even in the unstressed state.*"

[67] "Malignant hyperpyrexia: A role for the community physician in Community Medicine". This article was not viewed.

"Dantrolene sodium and dystrophia myotonica" [68]: This paper described the use of dantrolene as a possible muscle relaxant during surgery in this condition associated with myotonica; it was not sufficiently effective for intubation or surgery.

1985

This paper [69] approached the abnormal thermoregulation and thermogenesis process of MHS patients from a different angle. They cooled the MHS and control subjects. Skin cooling was similar in both groups but there was slightly increased heat production in the MHS group with a more significant increase in core temperature. The MHS subjects developed higher glucose levels and plasma noradrenaline was greater than some of the control subjects.

1986

[70] "Susceptibility to malignant hyperpyrexia": A letter – in response to an article by Dr Moxon^{vii}. It was critical of her "... narrow view of the importance of the diagnosis of malignant hyperpyrexia susceptibility...". Her response was that "The purpose of the article was not to take a narrow view of the diagnosis of malignant hyperpyrexia, but rather to discuss some of the problems [*social, logistic, financial*] which continue to arise in a District General Hospital ... The advantages of a precise diagnosis are not disputed."

"The work of the Leeds Malignant Hyperpyrexia Unit" [71]: This was the first report from the unit and covered the years 1971-1984. It included a review of the results obtained from 1127 patients. To say this was a substantial body of work is an understatement.

This next study was an investigation into the effects of glycopyrrolate and atropine on heat production and loss during exercise in normal volunteers [72]. There were no significant differences in resting and peak heat production and, as might be expected, sweat evaporation was greater after saline placebo compared with atropine, but not after glycopyrrolate. Their conclusion after considering all of the results was that non-evaporative heat loss compensated for the reduction in sweating due to anticholinergic drugs.

1987

This was another exercise study, this time on a treadmill, walking at 40% of maximum oxygen consumption. This showed that "non-competitive, low-intensity, steady-state exercise" was not contraindicated in MHS patients [73].

^{vii} Anaesthesia 1985; 40:693-5

1988

[74] "Ambulatory laboratory investigations for malignant hyperthermia susceptible patients". *Acta Anaesthesiologica Belgica* . This article has not been sighted.

[75] "The diagnosis of MH: its social implications": This is an opening editorial for a symposium on MH. It was not sighted – the BJA website strangely comes up with an Erratum notification – it is the next item in the table of contents.

Sudden infant death syndrome (SIDS) has been looking for a cause ever since it was described. This paper [76] considered its relationship to malignant hyperpyrexia (MH). There were two studies: 151 MH-susceptible families and 106 SIDS families; they completed questionnaires designed to identify the incidence of either MH or SIDS events. In a third study 14 SIDS parents had muscle biopsies and in-contracture screening for susceptibility to MH. The results suggested no association.

1989

Following the 1984 study about muscle spasm the occurrence of masseteric muscle spasm (MMS) in children was studied [77]. Fifty percent of the children had no muscle abnormality. Although both adults and children can get muscle spasm in response to suxamethonium, an exaggerated response should still be considered as a possible sign of MH.

[78] "Implications of the inheritance of MHS". *Annales Francaises d Anesthesie et de Reanimation*. This is an interesting short article in that it expresses points that have not been made so clearly elsewhere. One comment is the "... disturbing tendency for doctors to fabricate association between rare diseases [and MH] which prove to be unfounded." It is also pointed out that in their database of almost 2,000 patients there is not a higher incidence of kyphoscoliosis, hernia, strabismus, orthopaedic abnormalities, greater muscle mass, or greater athletic performance. A positive genetic test for MH may also lead to discrimination for certain types of occupation, or even marriage (particularly in Japan).

[79] This was a letter to *Anaesthesia* about Malignant hyperthermia in the Wolf-Hirschhorn syndrome ^{viii}. To quote “We read with interest and disquiet of the suggested relationship between malignant hyperthermia (MH) and the Wolf-Hirschhorn syndrome (Anaesthesia 1988; 43:386-8).” ... “We believe the authors are responsible for reporting a far-from-proved relationship between two rare diseases. Unfortunately all the bibliographic computers will regurgitate this unproved relationship quite uncritically and generations of anaesthetists will be misled.” This is a very strongly worded critical response. The original authors, R Ginsburg and G Purcell-Jones replied equally strongly defending their position.

[80] Stress as a factor in the triggering of MH and was assessed by measuring adrenal cortical reserve in patients undergoing muscle biopsy and a control group. They used the Short Synacthen Test and there was no significant difference between the groups.

1990

A review of the last 30 years of MH was published in 1990 [81] and highlighted the changes in its apparent incidence and future genetic screening.

[82] This was an editorial commenting on a paper in the journal on prediction of MHS by a statistical evaluation of clinical signs^{ix}.

The clinical picture of the presentation of MH, high levels of creatine kinase and myoglobinuria were used to classify allowed the probability of MH to be determined [83]. As expected some predictors were found to be more important than others – a high creative kinase, myoglobinuria and a clear contemporaneous description of the clinical events.

Using a myotonometer [84], the myotonic response of masseter muscles to suxamethonium was measured in 50 “*apparently healthy patients*”. The majority showed a short-lived myotonic response, the maximum increase

^{viii} A syndrome caused by deletion of part of the short arm of chromosome 4. The patients have delayed growth and development, intellectual disability, seizures and a characteristic facial appearance.

^{ix} W. Hackl, W. Mauritz, M. Schemper, M. Winkler, P. Sporn and K. Steinbereithner Br. J. Anaesth. (1990) 64 (4): 425-429 [the prediction of MH had a maximum sensitivity and specificity of 78% and were therefore unacceptable for clinical use]

(>1kg) was found in five patients and >500g in 12 patients. This might be classed as masseteric muscle spasm so the value of this myotonia as an early sign of malignant hyperthermia was questioned.

A study of muscle relaxation rates following a tetanic stimulus of adductor pollicis muscle was measured in 26 patients, 11 were MHS, 15 MHS negative [85]. The results suggested that relaxation rates could not be used for MH screening.

1991

[86] An editorial: This was commenting on a paper in the journal^x and reflected on the previous lack of consistent differences between the effect of exercise in MHS and MHN subjects. The study referred to used an in-vivo probe and did demonstrate a difference after short-duration violent exercise. They thought it was important because if there was a difference non-invasive NMR screening for MH might be possible and a 'physiological' abnormality in the muscle might be consistent with the associated defect in the ryanodine calcium receptor in the sarcoplasmic reticulum.

Heat stress due to exertion was studied in two military personnel [87]. Muscle testing revealed an abnormal response to halothane. One of the fathers had an abnormal response to halothane, and the father of the other patient had an abnormal response to ryanodine. The results suggested that heat stroke may be associated with an "abnormality of skeletal muscle that is similar, but not identical, to that of malignant hyperthermia."

Two patients who were suffering from arthrogryposis multiplex congenita developed hypermetabolic reactions during anaesthesia [88]. It was suggested that the reaction was not malignant hyperthermia and was independent of the anaesthetic drugs used.

This paper is the paper that hypothesises that the ryanodine contracture test is a specific in vitro test for MH [89]. The sarcoplasmic reticulum has a calcium release channel and ryanodine binds avidly to it. It was shown to differentiate between MH susceptible and normal patients when tested with a contracture response.

^x Allsop P, Jorfeldt L, Rutberg H, Lennmarken C, Hall GM. British Journal of Anaesthesia 1991; 66:541-545.

1992

[90] A letter to Anaesthesia: This was in response to a case report of a patient who may have had an MH episode. The diagnosis was questioned and a member of the Department of Anaesthesiology, A A Broekema, of the University Hospital Groningen who responded, was not one of the original authors. The diagnosis was defended.

[91] This was a short communication in the British Medical Journal about the detection of susceptibility to malignant hyperthermia and communication in susceptible families – “New genetic tests and better communication among affected families could help.” Detection of clinical MH remains the responsibility of the anaesthetist in the operating theatre, but detecting susceptibility to MH in members of known MH families is dependent on communication between family members. A member of two families died due to MH because of this and so better communication was “essential to avoid further anaesthetic tragedies”.

[92] “Malignant hyperthermia”, in *Minerva Anestesiologica*, the Journal of the Italian Society of Anesthesiology, Analgesia, Resuscitation and Intensive Care

[93]. Testing for MH with caffeine and halothane gave conflicting results if they were tested separately or together. When used concurrently a contracture occurred, but when used separately there was a normal response; these patients were termed “K-type”. In this study the K-type was not correlated with the MH susceptibility as accepted by the European MH group

[94] This is a letter to ‘*Anesthesia and Analgesia*’ about masseter muscle spasm in response to letters in response to a paper^{xi}. They were unhappy about the suggestions by other workers about the response to masseter muscle spasm and stated that “...any patient with *abnormally severe* MMS must be considered MH susceptible until proven otherwise”.

Postoperative pyrexia; in this study of 30 such patients postoperative pyrexia was shown to have no relationship to MH [95]. Another negative outcome was an attempt to show the existence of a generalised membrane abnormality by using a spin labelled electron spin resonance technique; there was no difference between MHS and normal patients [96].

^{xi} Littleford JA, Patel LR, Bose D, Cameron CB and McKillop C. *Anesth. Analg.* 1991;72:151-60

[97] "Inconsistency of data linking the ryanodine receptor and malignant hyperthermia genes". "This is a comparison of the caffeine halothane muscle contracture test with the molecular genetic diagnosis of malignant hyperthermia."

1993

"Genetic linkage analysis of chromosome 19 markers in malignant hyperthermia" [98]:

MHS in some families may be caused by a variation in a gene located on chromosome 19 in close proximity or identical to the ryanodine receptor gene (RYR1), expressed as a calcium release channel of the sarcoplasmic reticulum. The analysis of DNA samples from three large MHS British families strongly suggested that the MHS gene was located in the same region of chromosome 19q. Because genetic heterogeneity could not be excluded they could not recommend DNA markers as a replacement for in vitro contracture tests.

[99] This is a letter about a report by authors who worked in the New Zealand MH referral centre at Palmerston North. They suggested that the MH event was triggered by stress rather than drugs used for the anaesthetic. Ellis et al disputed the diagnosis but the response from the NZ authors was strong and insisted that the clinical and biochemical information suggested an increased metabolic rate.

[100] This is a letter to the editor of the journal *Human Mutation*. In the letter the authors describe how a suggested mutation (described by other workers) could be used as a pre-symptomatic test for MH. They refuted this idea with their analysis of 100 British families. They did not find this mutation and therefore the idea of its usefulness was rejected.

A comparison of ryanodine, halothane and caffeine for contracture testing was reported in MH and other neuromuscular disorders [101]. The ryanodine contracture test was not specific for MH but, in conjunction with halothane and caffeine, might help accurate phenotyping of individuals for further genetic analysis.

This paper describes the genetic mapping of the beta 1 and gamma-subunits of the human skeletal muscle L-type voltage-dependent calcium channel on chromosome 17q. However, it also excludes the genes as causative of MH [102]; an achievement but another negative outcome for a screening test.

1994

[103]; this paper describes the effects of benzamil on the sodium-calcium exchange in muscle. It caused contracture of skeletal muscle samples from MHS patients but not from normal muscle. It also increased the contracture response of both types of muscle to halothane. At low concentrations it reduced the contracture response to halothane in MHS patients.

An editorial in *Anaesthesia* in 1994 [104] restated the belief that genetic testing alone was insufficient for the diagnosis of MH, IVCT was still necessary.

Localization of the gene encoding the alpha 2/delta-subunits of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families [105]:

The genetic heterogeneity of MH suggests other sites of calcium regulation than the ryanodine receptor (RYR1). RYR1 is linked to less than 50% of MHS European families. They describe the cloning and partial DNA sequence analysis of the gene CACNL2A on chromosome 7q. D7S849 and flanking genetic markers were found to co-segregate with the MHS locus. These results suggested that mutations in or near CACNL2A might be involved in some forms of MH.

It is always good to have some scoring system to provide an indication of the likelihood of an uncommon disease entity. This paper, "A clinical grading scale to predict malignant hyperthermia susceptibility" [106] tried to do this for MH. They used the Delphi ^{xii} method with 11 experts. The scale ranks the likelihood that an anaesthetic event is indicative of MH and that further investigation of family history will confirm MH susceptibility. They felt that the clinical grading system provided a comprehensive clinical case definition for the malignant hyperthermia syndrome and would aid research into the condition. This was an improvement on the 1971 definition.

1995 was a quiet year.

^{xii} The Delphi method is an iterative technique, using experts, to get a consensus of opinion. http://en.wikipedia.org/wiki/Delphi_method

1996

“Should patients with central core disease be screened for malignant hyperthermia” [107]? This was in the section devoted to ‘Letters to the Editor’; a very long letter. This described a study of six families in an attempt to address the assumption that all patients with central core disease (CCD) are susceptible to malignant hyperthermia and therefore do not require screening. They showed this assumption was wrong. The data indicated CCD and MH are not the same even though a similar genetic locus was implicated in both.

This raised the issue of defining (diagnosing) CCD and MH myopathy. Although histology may be similar the authors thought that clinical information should be included in the final decision. “If the patient is symptomatic [of CCD] and susceptible to malignant hyperthermia a diagnosis of central core disease is appropriate. However, if symptomatic and susceptible to malignant hyperthermia, malignant hyperthermia myopathy is probably better.”

Not all MHS families are represented by ryanodine receptor mutations or linkage to the region of 19q on chromosome 19. Some families have a linkage to chromosome 17, but some families are not linked to either. The view was that the muscle contracture test still remained the only reliable test of MHS. This paper [108] describes a linkage analysis in a large family group with malignant hyperthermia. They had none of the ryanodine receptor gene mutations but had linkage to intragenic ryanodine receptor markers. This resulted in accurate prediction of MHS in 11 untested subjects who were at 50% risk^{xiii}.

^{xiii}The author himself was involved in this study. I was working in New Zealand and received a letter from Pat Ford asking if I could find a relation of one of the MHS families in New Zealand. Being an expat UK national, I knew there was a general impression in the UK that NZ was so small everybody knew someone who knew the person they were looking for! Auckland, the biggest city in NZ (25% of the population), was a good start. The family name was relatively unusual and so, in fact, it only took two phone calls to find the correct family. The direct descendant had died but he had an extended family throughout the country and they were able to be tracked down. Two problems ensued – one was that one branch of the family was doctor-phobic and the second was that arranging for blood to be sent via the USA back to the UK was bureaucratically insurmountable. In the end the DNA was extracted in Auckland and sent via normal postage to the UK.

1997

“The G1021A substitution in the RYR1 gene...” [109]: A single base change in the RYR1 gene has been proposed to underlie MHS in up to 10% of cases. They investigated this substitution in 151 subjects and detected G1021A heterozygotes in seven families. This mutation was not found in MH-negative subjects, nor was it found in families with central core disease. This, together with other findings, reinforced the view that DNA testing for MH status was still unreliable.

The aim of this study [110] was to evaluate statistical models that might predict MHS from the results of their in vitro contracture tests (IVCTs), again with a view to improving the assessment of genetic linkages. Logistic regression was used and of the individual contracture tests the ryanodine test was most closely correlated with MH status. Models were also made with combinations of tests and data from individual contracture tests and receiver operating characteristic curves were used to enhance the discrimination of the assessment model. The reproducibility and generalizability of the model was also assessed. The study required the testing of a total of 250 subjects

The purpose of this next study was to determine the sensitivity and specificity of IVCT test results [111]. The patients studied were those who had had fulminant MH and a set of low risk control subjects. After strict exclusion of potential confounding subjects they found a diagnostic sensitivity of 99.0%, a specificity of 93.6% (95% confidence interval 89.2-96.5%).

1998

“Genetic heterogeneity and HOMOG analysis in British malignant hyperthermia families” [112]: This a review of the status quo re MH genetics. It confirmed genetic heterogeneity in the “...UK MH population together with the possibility of the presence of two MH genes in some pedigrees ...”; the danger of just using DNA to diagnose MHS was restated.

1999

Patients with central core disease (CCD), a myopathy, were thought to be susceptible to MH. Eight CCD families were screened for 13 mutations of the ryanodine receptor gene; none were detected. They produced “unequivocal evidence” that CCD was genetically heterogeneous and not all individuals with CCD were susceptible to MH [113].

2000

“Multiple interacting gene products may influence susceptibility to malignant hyperthermia” [114]: It had been assumed that abnormal single genes were responsible for MHS. This was not seen in some families so a new genetic model was proposed, that susceptibility is due to the effects of more than one gene. They used the ‘transmission disequilibrium test’ on the data from 130 MH families and the results supported the new model.

2002

“RYR1 mutations causing central core disease are associated with more severe malignant hyperthermia in vitro contracture test phenotypes”. [115]: CCD patients are at risk of MH and mutations in RYR1 (19q13.1) account for the majority of MH and CCD cases. Five of the fifteen RYR1 considered causative of MH are associated with CCD. Mutation type was shown to affect IVCT response to caffeine, halothane, and ryanodine. The RYR1 mutations associated with both CCD and MH had greater caffeine and halothane responses than those associated with MH alone. They made the point that this “was the most extensive study of MH patient clinical and genetic data to date.”

2004

Hypokalaemic periodic paralysis (HypoPP, another rare muscle condition) had been associated with MH and therefore there was a potential link between these disorders. This investigation [116] of two independent HypoPP patients, one diagnosed as MHS, suggested that the two conditions occurred independently.

2010

“Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group” [117]. These guidelines, in two sections, relate to the recognition of MH and the management of the crisis. The early and late signs were listed together with possible differential diagnoses - insufficient anaesthesia, infection, insufficient ventilation, anaesthetic machine malfunction, anaphylactic reaction, phaeochromocytoma, thyroid crisis, cerebral ischaemia, neuromuscular disorders, laparoscopic surgery, Ecstasy or other recreational drugs and malignant neuroleptic syndrome.

It is now time to produce a brief time-line of the MH story.

The 1972 publication [34] highlighted a possible more specific method for screening for MH; this work was taken further in [35, 37] and in [38] it becomes clear this is a 'breakthrough'. From this 'specific test' for MH evolves the investigation of the genetic basis of the condition. In 1974 it was refuted that procaine and lignocaine were good for the management of MH [41, 45] and in 1975 CPK [47] was demoted as a useful screening test. Dexamethasone became the favoured treatment [44, 48]. In 1977 the influence of Ca⁺⁺ was investigated but there was no difference between MHS and MHN [50]. In 1978 it was found that halothane doubled the rate of heat production and there may have been some relationship with plasma cholinesterase - it was then suggested that MH was polygenic [53]. The first genetic study in 1981 [59] could not reproduce the CHE results. Between 1981 and 1983 the hypothesis was that it was a sympathetic/heat distribution disorder. In 1983 there was also the first mention of dantrolene by the Leeds group and this was thought to act on the sarcolemma [62]. In 1984 the European Malignant Hyperpyrexia Group came into being; muscle spasm was investigated [65], and it was still thought to be a sympathetic disorder [66]; this continued in 1985 [69]. In 1989 they refuted the idea of MH being related to many other disorders [78].

1991 was a significant year with the advent of the ryanodine contracture test [89]. In 1993 it was stated that genetic testing was not totally indicative and that the genetic testing should be combined with contracture tests [101, 105, 108, 109, and 114]. In 1997 they created a model to predict MHS and the model had high sensitivity/specificity [110, 111].

A job well done by the whole team.

^{xiv} Swiss cheese and MH: The author has the infamy of perhaps being the only anaesthetist to give suxamethonium and halothane to a known MHS patient. To those unfamiliar with the Swiss cheese metaphor, the patient and anaesthetist progressed through all the holes in the checks and balances associated with a patient going for surgery. A terrifying MH episode ensued which was managed by colleagues who came to the rescue with an MH pack; the patient survived as did the anaesthetist.

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