

## About MH

### Background

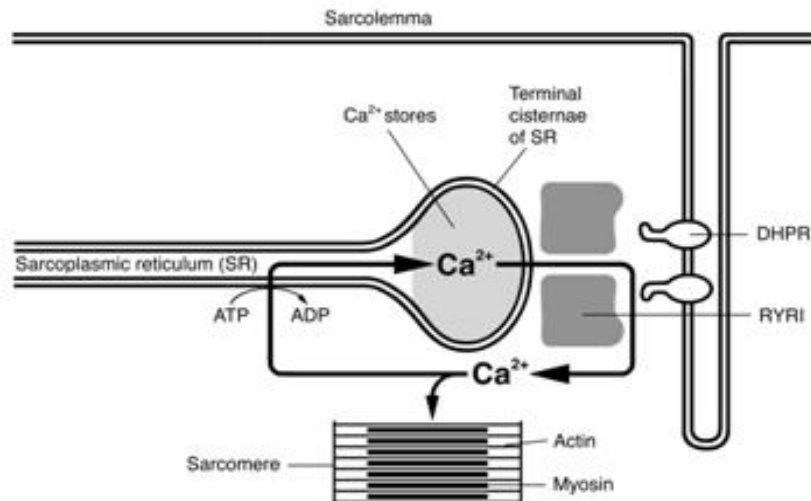
Malignant hyperthermia (MH) was first described in 1960 in Australia when a young, otherwise fit healthy man with a badly broken leg refused to have a general anaesthetic because 11 of his relatives had died during anaesthesia. He was anaesthetised with a relatively new drug called halothane instead of ether, which had been given to his relatives. However, he developed a reaction to the anaesthetic, which the anaesthetist could document very clearly having been alerted to a possible problem. The young man survived and investigation of the family showed that all his relatives had experienced a similar reaction. The most notable feature, in the days when monitoring facilities were not available, being a "raging temperature". Hence the name MH from malignant, meaning causing death (not cancer) and hyperthermia (or hyperpyrexia) meaning very hot. Drawing out the large family tree with the 11 deaths indicated that the condition was inherited in an autosomal dominant way. (see later). This serendipitous event was the start of the MH story. Following this many more cases were described around the world, affecting all age groups and all races.

It became apparent that a reaction was "triggered" by 2 types of anaesthetic agents, the muscle relaxant suxamethonium and all the inhaled agents (the modern versions of ether). It occurs in about 1 in 10,000 cases so is quite uncommon and occurs more frequently in males, although this may just reflect the type of surgery and therefore anaesthesia males more commonly get, rather than a true sex difference. Originally the mortality during a reaction was about 70-80% and was the commonest cause of unexpected mortality in fit young adults. Nowadays the mortality is much less about 2-3%, due to the huge improvement in monitoring standards during anaesthesia, the increased awareness of MH by anaesthetists and the availability of a specific treatment called dantrolene. It is impossible to identify an MH susceptible individual pre-operatively unless there is a personal or family history of MH or a previous suspicious reaction to anaesthesia. An MH individual is entirely normal and may well have had a previous anaesthetic without any obvious problems, indeed around 75% of probands (the person who has had a reaction) have had at least one uneventful anaesthetic prior to the one that caused the reaction, the record is 13! The reason for this remains a mystery but it is important that relatives of an MH person don't assume they haven't got MH just because they have had no problems with previous anaesthetics.

### Cause (aetiology) of MH

MH is a disorder of skeletal muscles, the ones found in arms and legs not the muscles in internal organs which have a different structure. Muscle is a very complex, highly sophisticated structure which contracts and relaxes in a controlled manner in response to an impulse from a nerve in a process called excitation-contraction (E-C) coupling. This is a well regulated process involving the movement of calcium ions across several different membranes. In MH patients this control is maintained in normal circumstances but is lost when certain anaesthetics known as "triggering" agents are used. The precise site of the defect along the E-C process which results in the loss of control of calcium movements in MH is unclear - it may involve more than one site or may be different sites in different families, all of which result in the same clinical MH reaction. Possible sites include the outer muscle membrane (sarcolemma), on the membrane that goes into the muscle tissue called the T tubule (dihydropyridine receptor) or on an internal membrane called the sarcoplasmic reticulum (SR) that stores calcium for release in response to a nervous impulse. The latter is called the ryanodine receptor and is a channel that opens and closes in response to stimulation so letting calcium out from the SR into the muscle tissue (see diagram).

**Diagram of structures involved in excitation-contraction coupling in skeletal muscles**



The released calcium then reacts with the muscle proteins to cause a contraction and then the calcium is taken back up into the SR making the proteins relax. Other chemicals are also involved in the process and could have an influence on the regulation of calcium movements during an MH reaction.

### **The inheritance of MH**

All the characteristics of humans are determined by their genetic makeup. This is carried by DNA that makes up the chromosomes. There are 23 pairs of chromosomes, 22 of which are autosomes and one pair of sex chromosomes (XX in females and XY in males). One of the pair comes from the mother and the other from the father of the individual. The order of the DNA sequences of 4 bases form the individual genes which in turn are responsible for making the 20 amino acids which make up proteins, the building blocks for all tissues. The position of a gene on a chromosome is called the locus. Over millions of years genes can change by a process called mutation so that the gene exists in one or more forms called alleles. In most cases the alleles will make the same protein so have no effect on the individual but sometimes the allele makes a different or faulty protein which results in disease.

Diseases that are caused by genes carried on the 22 pairs of autosomes are called autosomal. Diseases that need both of the pair to be affected are called recessive and those that need only one of the pair to be affected are called dominant. From descriptions of the family trees of MH patients, particularly the first Australian family described, it is clear that MH is inherited as an autosomal dominant condition.

In practice this means that in MH both sexes are affected, only one of the pair of genes needs to be present for the condition to be seen in an individual so the condition does not skip a generation as can occur in recessive conditions. It means that first degree relatives (parents, siblings and children) of an MH susceptible individual all have a 50 % chance of inheriting MH. Family screening is organised on the basis of this inheritance pattern.

In 1991 it was shown that the gene that controls the ryanodine receptor (see cause of MH section) was linked to MH. This is known as the ryanodine receptor gene (RYR1). Since then it has been shown that around 60% of MH families worldwide are linked to RYR1. Unfortunately this is a huge gene and many mutations have been identified but only a small proportion of these have been shown to cause an effect. Only causative mutations can be used for diagnosis, currently there are 27. There is a great deal of active research going on, looking for new mutations and to see if they have any causative effect, so increasing the number of families who could be offered a genetic DNA blood test. In some families other genes on other chromosomes may be linked to MH but these tend to be restricted to individual families. MH is referred to as heterogeneous because so many different mutations and possibly other genes are involved making it difficult to develop a DNA blood test that is safe (ie does not give false negative results) and so completely replace the muscle biopsy test.

### **The clinical reaction during anaesthesia**

The clinical reaction does vary and can sometimes be a very severe fulminant reaction or a mild reaction. Sometimes it can be very difficult to distinguish the signs of MH from other causes eg appendicitis causes a rapid heart rate and high temperature. It is therefore important to confirm that the reaction was a true MH reaction by testing (see later).

If the drug suxamethonium has been used then the first sign of MH is often rigidity of the jaw muscles making it difficult or impossible to insert the anaesthetic tubes into the mouth used to help with breathing. Otherwise the two most important signs are an unexplained, unexpected, increasing heart rate and breathing. The latter is measured by the amount of waste gas expired by the lungs and known as the "end-tidal carbon dioxide level" (ETCO<sub>2</sub>). These occur because the muscle is being stimulated to work excessively by the triggering anaesthetics – it can be likened to doing a large amount of physical activity – which results in an increase in the amount of oxygen used and the production of waste material, such as CO<sub>2</sub> and acid. Waste material is being produced so quickly during an MH reaction that it can't be processed and results in the signs of MH. Muscle activity is the main source of heat production so excess activity causes an increase in the internal body temperature. Because muscle can be damaged during a reaction, chemicals that normally occur in the muscle tissue, potassium (K<sup>+</sup>), creatine kinase (CK) and myoglobin, leak out into blood. Myoglobin, a protein similar to haemoglobin in blood, is excreted by the kidneys resulting in pink/red/black urine depending on how much there is. Sometimes there is so much the kidneys can become blocked and renal dialysis is needed while they recover. Many of these abnormalities can cause the heart to beat abnormally or stop.

### **Treatment of an MH reaction**

Once an MH reaction is suspected treatment should be rapidly begun, treatment begun too late is ineffective. The current standard monitoring facilities allow for early detection of a reaction and is the main reason for the improvement in survival. The only specific treatment is a drug called dantrolene, a different type of muscle relaxant to the ones normally used in anaesthesia. A supply of sufficient drug for initial treatment should be kept in all theatre suites. There are other important steps to take such as removal of the triggering agents and changing to an MH safe technique if the surgical procedure cannot be abandoned, as well as taking samples to measure all the parameters mentioned in the section on the clinical reaction so that they can be corrected. As an MH reaction can vary from person to person, treatment has to be tailored to each individual.