Malignant hyperpyrexia
Further muscle studies in asymptomatic carriers identified by creatinine phosphokinase screening

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SUMMARY The history, clinical presentation, and management of malignant hyperpyrexia are presented. The aetiology seems to be associated with some inherited abnormality which affects the movement and binding of calcium ions in the sarcoplasmic reticulum, sarcoplasm, and mitochondria. Whether this is a primary muscular defect or secondary to some trophic neural influence is yet to be established. The subjects carrying the abnormal trait show evidence of a myopathy which is subclinical in most instances and revealed only by estimation of serum CPK or biopsy. In some families where the myopathy is clinically obvious there may be, in addition, a variety of musculoskeletal abnormalities. A plea is made for routine monitoring of temperature during anaesthesia and for procainamide or procaine to be readily available in all operating theatres. A history of anaesthesia deaths in a family calls for special care, and, if the serum CPK is elevated, suxamethonium and halothane are to be avoided. Families with orthopaedic and muscular abnormalities are at increased risk, and should have estimation of serum CPK before surgery. As a bonus of this study it is suggested that serum CPK estimations be used to screen pigs for selective breeding and so eliminate this disease, which causes soft exudative pork.

Malignant hyperpyrexia may be defined as a specific potentially fatal condition which occurs in susceptible individuals in response to various triggering mechanisms, of which anaesthetic agents have been found to be the most common offenders. Once initiated, the heat generation which is characteristic of this condition so exceeds the capacity of the heat-losing mechanisms that a continuous rise in body temperature occurs and, unless the offending agent is withdrawn at an early stage and treatment started, death will occur in most cases.

The syndrome of malignant hyperpyrexia has been recognized only in the past decade and only since the publication by Denborough and Lovell (1960) who reported on the death of 10 members of a particular family who died during anaesthesia has this condition become widely reported. Britt, Locher, and Kalow (1970) gathered cases from the literature and added these to their own series, thereby accumulating no less than 170 cases. Since this time, as the syndrome has become more widely appreciated, many additional cases have appeared in the literature.

One of the earliest reported cases which can be identified as malignant hyperpyrexia was reported by Guedel (1951) in his monograph on inhalation anaesthesia. It is certain that this syndrome is not new and must have accounted for deaths occurring during anaesthesia for as long as inhalation anaesthetics have been in use. It is also difficult to speculate retrospectively about many of the deaths recorded as being due either to ether convulsions or to high fever attributed to overheating in the operating theatres of that time, but it is likely that some of these were examples of malignant hyperpyrexia. To support this contention, a typical case history, dating back to 1948 before this syndrome was recog-
nized, has been made available to us by Dr. J. F. Riccards of the South Staffordshire Medical Centre.

‘The anaesthetic was given to a 10 year old male and the operation was for the suture of a left olecranon process. Premedication was with atropine 0·01 gr and Nembutal 0·7 gr. Anaesthesia was maintained with gas, oxygen, and ether after induction with trilene administered through a semi-closed Boyle circuit. Death occurred one hour and 45 minutes after commencing the anaesthetic and the nature of the symptoms preceding death are recorded as follows:

“Induction complicated by slight amount of mucus in respiratory tract. Tensed jaws and pursed lips. Maintenance on 50% gas and oxygen with 5% ether, total flow 6 litres. Esmarach on limb, and face covered with towels. Maintenance difficult owing to mucus in trachea. Anaesthesia had proceeded for about 10 minutes when face was uncovered to display a moderate degree of cyanosis despite hyperpnoea and rich oxygen intake. Cyanosis cleared on full oxygen but returned when gas was added to the mixture. General rigidity was commencing at this stage, with legs and arms in slight flexion and eyeballs deviated upwards and to the right. The operation was hurriedly concluded and 100% oxygen continued. The colour was now flushed and pink but rigidity was increasing. The patient felt hot, the rectal temperature of 108° mounted to over 110° within a few minutes. Over the course of the next hour respiratory function was well maintained but cardiac action became embarrassed with slowing and softening of the pulse. Colour remained pink until about 10 minutes before death. Respiratory function failed quickly and suddenly about five minutes before death.”

The progressive rigidity of the limbs preceded by the early rigidity of the jaw muscles and subsequent hyperpyrexia make this a classical example of malignant hyperpyrexia. This patient died in the Casualty Theatre on 8 July 1948. So striking was this mode of death that Dr. J. F. Riccards was able to recall this case dating back 24 years.

There are many reasons why people die during anaesthesia and malignant hyperpyrexia is but one of these. This complication of anaesthesia is of particular interest and has stimulated a great deal of work into the pathogenesis of muscle disease and muscle physiology. Research workers in this field have been most fortunate in that certain strains of pigs have been found to develop malignant hyperpyrexia after exposure to suxamethonium and halothane (Hall, Woolf, Bradley, and Jolley, 1966). The work of Harrison, Biebuyck, Terblance, Dent, Hickman, and Saunders (1968); Harrison, Saunders, Biebuyck, Hickman, Dent, Weaver, and Terblance (1969) on susceptible pigs has made a notable contribution to our understanding of this disease. The onset of malignant hyperpyrexia in pigs may be triggered off by exertion or by fear, as before slaughter, and is known as the porcine stress syndrome (PSS). This condition is proving a problem in some countries as malignant hyperpyrexia produces a high lactic acid content which causes the meat of involved animals to become pale, soft, and exudative (PSEP) and generally unsatisfactory for consumption. The Scandinavian countries are particularly involved, as the Landrace breed of pig is prevalent there.

It is expedient at this stage to make the assumption that the disease in pigs and man is the same, though further study may prove that there are significant differences in these two species. It is unlikely, however, that such differences would be of prohibitive consequence in the overall understanding of this reaction.

CLINICAL ASPECTS

In many patients the first indication of impending trouble is a failure of relaxation of the jaw muscles after the administration of suxamethonium. Such rigidity is often mistaken as being due to inadequate suxamethonium dosage and consequently the relaxant is unfortunately repeated. The rigidity of the jaw muscles may be so profound as to make intubation impossible. More frequently the rigidity is mild or absent. The onset of malignant hyperpyrexia may be insidious on the one hand and apparently fulminating on the other. The early rise in temperature, however, has been frequently overlooked in the latter. It must also be realized that not all patients develop muscular rigidity, so that malignant hyperpyrexia occurs in two forms, the rigid and the non-rigid, the latter accounting for about 20% of cases. In the former, the rigidity of the muscles is indistinguishable from the rigidity of rigor mortis and in 70% of such cases the rigidity merges with and becomes rigor mortis.

The body temperature is perhaps the most
important clinical aspect of this condition and may rise within minutes after induction or be delayed for as long as four hours after commencement of anaesthesia and may even occur in the recovery phase after the anaesthetic has ended. The rise in temperature varies from case to case but may reach 44° C (112°F) and perhaps even higher. The mortality rate correlates very closely with the level of the pyrexia and where the pyrexia has not been allowed to develop beyond 39° C (102°F) the survival has been 100%, whereas at 44° C (112°F) there have been no survivors. As the temperature begins to rise, so tachypnoea occurs and this is noted long before the onset of rigidity. Once rigidity occurs the involvement of respiratory muscles further embarrasses respiration. Tachycardia is an early manifestation and pulse rates have been recorded up to 200 per minute. The blood pressure falls, bradycardia and arrhythmias may supervene usually associated with hyperkalaemia, reflecting the characteristic electrocardiographic changes.

Heart failure occurs at this stage and on cessation of cardiac activity the heart is found in a state of contraction.

As far as the skin is concerned, there is no constant pattern and cases have been described as sweating, flushed, pale, vasoconstricted, and mottled.

In the advanced stage of malignant hyperpyrexia, the nervous system becomes involved and the pupils may be found to be widely dilated or unequal and in most cases the patients remain in coma until death.

The laboratory findings during the phase of malignant hyperpyrexia reveal a reduced arterial oxygen tension despite enriched oxygen administration. The arterial CO₂ tension is elevated, the arterial blood pH is low, varying between 6.6 and 7.4 and the base deficit has varied from -6 to -30 m-equiv/l. The serum potassium rises and very high levels are recorded before death. The serum phosphorus is usually elevated, while the serum calcium generally falls, paradoxically.
Malignant hyperpyrexia

particularly in the rigid variety of malignant hyperpyrexia in humans. Because of the massive breakdown during this phase, the serum enzymes such as serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), aldolase and creatine phosphokinase (CPK) are found to be elevated. Myoglobinuria is present in varying amounts and adds to the likelihood of surviving patients developing renal failure. Haemoglobinuria occurs and defects in blood coagulability have also been noted presenting a picture of consumptive coagulopathy.

GENETIC ASPECT

The first clear-cut family history relating to this disease was reported by Denborough, Forster, Lovell, Maplestone, and Villiers (1962). Britt, et al. (1969) in an extensive study described the mode of inheritance of malignant hyperpyrexia, the pattern of inheritance being clearly that of an autosomal dominant abnormality. Direct transmission was demonstrated over several generations and affected the sexes to an equal degree. Most of the reported cases have occurred in young adults.

As we believed that all cases developing malignant hyperpyrexia did so because of a genetically-determined predisposition, manifesting when the muscles and possibly the liver were challenged by noxious agents, it was decided to reinvestigate a family in whom three hyperpyrexial deaths had occurred within the space of two years at the Coronation Hospital, Johannesburg.

CASE STUDIES

The clinical examination of these patients was entirely normal, there being no evidence of muscular weakness or of complaints referable to muscle. An electrophysiological study of these patients was unrewarding, though the motor-unit voltages and durations were at the lower limits of normal. There was no evidence of myotonia or of increased muscular irritability. There was no denervation activity and no increase in polyphasic activity. The motor units showed normal recruitment activity on volition. Nerve conduction studies, both motor and sensory, were carried out on median, ulnar, and medial popliteal nerves and the results again were within normal limits. The myoneural junctions examined by assessing the response to repetitive stimulation were normal. The number of cases subjected to electro-diagnostic testing was 14, of whom six were males and eight females. Ages varied from 7 to 50 years and all were close relatives of the three cases that died of malignant hyperpyrexia.

FIG. 2. Trichaardt generation II2.
It was next decided to examine various serum enzymes of the members of this family in the hope of finding some evidence of muscle abnormality. This investigation produced startling evidence of disease in many of the asymptomatic members of this family. At the onset the enzymes estimated included SGOT, lactic dehydrogenase, aldolase, and creatine phosphokinase. The most reliable index proved to be creatine phosphokinase (CPK), so that after a pilot survey the serum estimations were confined to this one enzyme. Over 100 cases (Isaacs and Barlow, 1970a, b; Barlow and Isaacs, 1971; Isaacs and Barlow, 1971) were examined and the study extended over four generations. The CPK abnormality was found to be inherited as a Mendelian dominant and was considerably elevated in many members and it was postulated that the elevated CPK reflected a subclinical myopathy. Figures 1 and 2 illustrate examples of such inheritance. Occasional examples of failure of expression were noted, which is not an unusual finding for an autosomal dominant abnormality.

Metabolic studies were carried out on 10 of the patients with the highest levels of CPK. The serum electrolytes and urea were normal, full blood count, and erythrocyte sedimentation rates were normal. Serum calcium, phosphorus, blood sugar, cholesterol, uric acid, alkaline phosphatase, and protein-bound iodine estimations were normal. Protein electrophoretic patterns were normal. Urine analysis revealed no evidence of sugar or albumin, nor was there any indication of aminoaciduria. Porphyrins were not present in excess.

After this study, the value of CPK estimations in members of susceptible families was confirmed by Denborough, Ebeling, King, and Zapf (1970), who also found clinical evidence of myopathy. Kyei-Mensah, Lockwood, Tyrrell, and Willett (1970) published details of a family in whom deaths from malignant hyperpyrexia had occurred and further confirmed the value of CPK.
**FIG. 5.** Degenerating fibre with marked lymphocytic infiltration. × 750.

**FIG. 8.** NAD diaphorase stain. Dark staining of type I fibres. × 75.

**FIG. 6.** Group of atrophic fibres. × 250.

**FIG. 7.** Group of atrophic fibres. × 250.
pigs could be selected for breeding purposes with the object of ultimately breeding out the susceptible strain, with enormous saving to the meat industry.

MUSCLE HISTOLOGY AND HISTOCHEMISTRY Asymptomatic members of the Coronation (Isaacs and Barlow, 1971) family with and without high enzyme activity have been subjected to muscle biopsy for histological and histochemical study. The muscle was removed under local anaesthesia and in all cases the posterior fibres of the deltoid on the non-dominant side were studied. After removal, the muscle was maintained at its resting length by means of ties at each end being stretched over wooden spatulas. The tissue was then covered with gauze soaked in saline for 20 minutes. The muscle was subsequently orientated on pieces of cork and secured with gum tragacanth for both transverse and longitudinal sectioning. The specimen was then frozen in isobutane which was in turn cooled by

estimations. Steers, Tallack, and Thompson (1970) described a susceptible family who, in addition, were suffering from a myopathy similar to that described by Barnes. They also showed elevated blood CPK levels. We have investigated two other families in which malignant hyperpyrexial deaths have occurred and have found a similar pattern of high CPK activity occurring over several generations. Exact data on the gene frequency of this CPK abnormality is not as yet available. The frequency of the malignant hyperpyrexial reaction under anaesthesia has been placed at 1/14,000 by Britt and Kalow (1970).

A correlation between high CPK and susceptibility to malignant hyperpyrexia has been confirmed by Berman, du Toit, and Kench (1971) in Landrace pigs and by Jones (1971) for Poland-China swine. This could be a most valuable correlation as it indicates a method by which

FIG. 9. EDTA ATPase reversal stain, showing dark staining type I fibres. × 75.

FIG. 10. Phosphorylase stain, showing dark staining type II fibres. × 300.
Malignant hyperpyrexia

KEY

MALE

FEMALE

Serum Creatine Phosphokinase (C.P.K.) normal

C.P.K. females 60 and over males 80 and over

Survived malignant hyperpyrexia

Died from malignant hyperpyrexia

Died of natural causes

Muscular skeletal abnormalities

FIG. 11. Ludik family.

liquid nitrogen. Sections were cut to a thickness of 10 μ on a cryostat at −25° C. These sections were subjected to routine haematoxylin and eosin (H and E), and a modified trichrome stain (Engel and Cunningham, 1963). The histochemical study included phosphorylase (Takeuchi and Kuriaki, 1955), ATPase (Padykula and Herman, 1955), EDTA ATPase (Drews and Engel, 1966), succinic dehydrogenase (Pearse, 1957), and NAD diaphorase (Scarpelli, Hess, and Pearse, 1958). Modifications to the ATPase and EDTA ATPase were carried out according to Dubowitz (1971).

Muscle from asymptomatic carriers with high CPK activity showed evidence of destruction of single muscle fibres (Figs 3 and 4). In most sections the abnormal muscle fibres were scattered apparently at random and in some areas there was evidence of considerable cellular infiltrate (Fig. 5). In one case the pattern of degeneration of the muscle fibres was grouped in a manner highly suggestive of primary neuronal pathology (Figs 6 and 7).

The histochemical study revealed areas of excessive grouping of individual fibre types but for the most part the staining reactions were normal (Figs 8, 9, 10). The glycogen content was normal and there was no evidence of nemaline rod formation. The muscle of the uninvolved members of the family was histologically normal.

ASSOCIATION WITH MUSCULOSKELETAL ABNORMALITIES

The overall incidence of malignant hyperpyrexia would at first appear to be higher in cases who have undergone minor orthopaedic procedures but, on closer scrutiny of the cases involved, it is obvious that there are large families afflicted with the predisposition to develop malignant hyperpyrexia who have no increase in musculoskeletal abnormalities, as in the family of Britt et al. (1969) and the family of Isaacs and Barlow (1971). In some other families there is a high incidence of musculoskeletal abnormality and in
these families there appears to be some link between the inheritance of the musculoskeletal disorder and the trait for malignant hyperpyrexia. The musculoskeletal abnormality cannot be used as a marker for malignant hyperpyrexia, as some members of these families without the musculoskeletal abnormalities showed elevated levels of CPK (Isaacs and Barlow, 1971). Such a dissociation has been found in a family under investigation at present (Fig. 11), where the common musculoskeletal abnormalities are ptosis, high arched palate, and dislocated patellae. The commoner musculoskeletal disorders which have been associated with malignant hyperpyrexia are ptosis, strabismus, dislocated patellae, dislocated shoulder, kyphoscoliosis, high arched palate, and various types of hernias (Britt and Kalow, 1970).

TREATMENT

The most important aspect of treatment depends on the awareness of the disorder and thus a continuous recording of the temperature during anaesthesia. Any rise in temperature above 37.8°C (100°F) calls for an urgent end to the anaesthetic. The patient must be cooled by applying ice externally and, if available, ice water can be applied internally, either rectally or intraperitoneally. The Wangensteen gastric cooling apparatus was effectively used by Ryan and Pepper (1970). Care must be taken, however, to see that the patients are not cooled excessively, as hypothermia creates additional problems. The hypoxia is treated by hyperventilation with 100% oxygen. Sodium bicarbonate is given intravenously to combat the acidosis but excessive administration must be avoided. A close watch must be kept on the serum potassium, which may rise to dangerous levels before treatment and may rapidly fall to low levels with treatment. Intravenous calcium chloride has been of benefit in a few cases in correcting the bradycardia (Hogg and Renwick, 1966), but this is best avoided until the more specific therapy outlined below has been given. The blood volume must be maintained by means of fluid replacement. Pressor agents are best avoided, if possible, as there is theoretical evidence that they may aggravate the heat-producing state (Keaney and Ellis, 1971). This objection does not apply once procainamide or procaine has been administered. Frusemide and/or mannitol may be used to maintain adequate production of urine. There does not seem to be any place for the use of anticoagulants or cardiac glycosides—in fact, this latter group of drugs may be harmful.

The most important aspect of therapy, however, apart from immediate cessation of the anaesthetic and cooling, is the administration of intravenous procainamide (Kalow, Britt, Terreau, and Haist, 1970; Beldavs, Small, Cooper, and Britt, 1971). Katz (1970) used lignocaine successfully in one case but there is experimental evidence suggesting that this substance should not be used (Strobel and Bianchi, 1971). After these publications, Harrison (1971) found that intravenous procaine could abort the hyperpyrexial reactions in pigs. Procaine offers, therefore, an alternative to procainamide and Harrison suggests the following dosage: a loading dose of 30–40 mg/kg intravenously followed by an intravenous infusion of 0.2 mg/kg/min until the muscle rigor relaxes. With this regimen isoprenaline has been necessary to maintain the blood pressure and, of course, electrocardiographic monitoring is a standard procedure. It is possible that a much smaller dose will prove to be equally effective and so avoid the severe hypotensive effect.

LATE PHASE

The phase of late treatment corresponds with the time when the temperature has been brought down to normal with a return of respiratory and cardiovascular functions to normal. At this stage, electrolyte disturbances must be watched and corrected, with particular attention to the serum potassium which may fall precipitously.

A close watch must be kept on the renal output, as oliguria and renal failure may develop. It may be necessary to control the renal failure by means of haemodialysis until renal function recovers.

Because of the intense muscular wasting and weakness which follows recovery from malignant hyperpyrexia, prolonged rehabilitation by way of physiotherapy, employing splintage, passive movements, and later active exercise is most important.
DISCUSSION

There are several interesting aspects of muscle disease that emerge from the study of malignant hyperpyrexia.

It is our opinion that malignant hyperpyrexia is always associated with a myopathic process, usually subclinical, as revealed by CPK studies (Isaacs and Barlow, 1970a). Furthermore, we have now shown that the muscle of susceptible members of the family reported by us (Isaacs and Barlow, 1971) may be histologically abnormal. The histological examination of muscle from a known carrier whose CPK was normal was found to be abnormal (Fig. 7). Before obtaining this histological evidence, we had considered this case to be an example of suppressed expressivity of the disorder but it is now obvious that either the myopathic lesions are too few at any one time to produce a rise in serum CPK or there must be modifying factors in this patient which have prevented a rise in serum CPK, though the myopathy exists. It remains to be seen whether the normal serum CPK indicates a lessened susceptibility to develop malignant hyperpyrexia. Such modification may also be playing some part in determining the relative rarity of malignant hyperpyrexia in the elderly.

Further evidence of myopathy in families prone to develop malignant hyperpyrexia has been published by Denborough et al. (1970). In addition to their confirmation of the value of CPK in carrier detection, they found clinical evidence of myopathy. Steers et al. (1970) found evidence of a myopathy in their susceptible family similar to that described by Barnes (1932). King, Denborough, and Zapf (1972) have suggested that susceptible individuals may show one of a number of specific myopathies consisting of a group with a dominantly inherited myopathy, a group who have myotonia congenita, and a third group with physical abnormalities and a progressive congenital myopathy. The second group implicating myotonia congenita with malignant hyperpyrexia will require substantiation as 45 patients with myotonia dystrophica and 11 patients with myotonia congenita, studied retrospectively by one of us (H.I.), were found to have survived a total of 68 general anaesthetics and there was no history of hyperpyrexial deaths in their families.

LaCour, Juul-Jensen, and Reske-Nielsen (1971) suggested that the myopathic changes found in their cases were secondary to both central and peripheral neurological disease. Their biopsies revealed evidence of degeneration and regeneration in motor nerves which also showed evidence of excessive sprouting and an increased number of endplates. The pattern of atrophy seen in Figs 7 and 8 from a known carrier of this disease lends support to this concept.

After the application of CPK screening in man, elevated CPK levels were found in susceptible pigs by Berman et al. (1971) and Jones (1971). Harrison et al. (1969) have shown that the muscle of susceptible Landrace pigs shows an abnormal fall in the level of ATP on exposure to halothane vapour. Venable (1971) has shown electron microscopic evidence of myopathy in susceptible strains of Poland-China pigs in the aipyrexial state. The abnormalities varied from distorted myofibrillar patterns to areas of frank degeneration. The combined evidence of enzyme, biochemical, and microscopic abnormalities indicates that an underlying myopathy is active in susceptible pigs as well.

In considering the aetiology of malignant hyperpyrexia, the basis of the abnormal heat production is all important. A central neurologically mediated cause for the rise in temperature does not have much support, as the heat-regulating mechanisms appear to be intact until an advanced and sometimes preterminal stage has been reached. Sweating, vasodilatation, and tachypnoea occur as the temperature rises but, as the overall heat production in this disease far exceeds that of normal physiological heat production, the processes of heat dissipation are inadequate. Hyperthermia of central neurological origin would not give rise to the extreme hyperkalaemia and metabolic acidosis that occur fairly early in this disease.

That the muscle tissue is ultimately independent of the nervous system in this process of abnormal production of heat is exemplified by one of the cases dying of malignant hyperpyrexia at the Coronation Hospital. The patient was undergoing surgery to the lower limb and before the injection of suxamethonium a tourniquet had been applied to this limb. This occlusion of perfusion caused the limb to remain flaccid as though it were protected from the noxious
effects of the suxamethonium and subsequent halothane inhalation. The rest of the body became rigid and contributed to the enormous heat production. Though the site of heat production in malignant hyperpyrexia is largely from muscle and independent of neurological influence, one cannot exclude some prior predisposing or modifying effect that the nervous system may have produced in the muscle.

Agents which block neuromuscular transmission do not protect the muscle from malignant hyperpyrexia nor do they alleviate the condition once established. Harrison (1971) has found that the prior administration of curare prevents the triggering action of succinylcholine but does not block the effects of halothane in susceptible Landrace pigs. Theye (1970) has shown that dogs anaesthetized with halothane show an increased oxygen consumption after the administration of succinylcholine to the extent of 50–60% in the first 20 minutes. After this period an increased oxygen consumption of 20% above normal is maintained. The initial massive increase was shown to be due to end-plate generation of action potentials causing contraction of the muscle fibres; the sustained increase results from an altered energy requirement of the muscle itself. The sustained increased heat production is subsequent to the entry of succinylcholine into the muscle cell and this altered oxygen consumption is not influenced by blocking agents. The initial massive fasciculation which suxamethonium administration induces may be damaging to the muscle and Kalow (1971) considers that the mass release of potassium after this depolarization is indicative of damage to the sarcolemma. Tammisto and Airaksinen (1966) have shown increases in serum levels of CPK after administration of suxamethonium. The increased heat production as seen in dogs and outlined above does not account for the heat of malignant hyperpyrexia.

There are similarities between the rigidity of the muscle in malignant hyperpyrexia and experimentally produced muscle contractures. Malignant hyperpyrexia occurs in humans as already stated in two forms; the common form accounts for about 80% of the cases and is associated with muscular rigidity, the remaining cases showing no evidence of alteration in muscle tone.

When halothane and dinitrophenol are administered to dogs they develop a state of muscular rigidity associated with excessive heat production. It has been stated that the heat production in these circumstances is due to uncoupling of oxidative phosphorylation (Wilson, Nicols, Dent, and Allen, 1966; Gatz, Hull, Bennett, and Jones, 1970). Uncoupling of oxidative phosphorylation alone, however, does not seem to offer the entire explanation for the heat production in malignant hyperpyrexia (Wang, Moffitt, and Rosevear, 1969), and increased or accelerated glycolysis (anaerobic metabolism) would be necessary to ensure an effective source for the rephosphorylation of ATP (Britt and Kalow, 1970). Britt and Kalow (1967) showed that halothane did not increase the dinitrophenol contracture in rats and rabbits, nor in the case of chickens (Vigueria and Conn, 1967). 2,4-dinitrophenol blocks the second and third ATP formation of the respiratory chain of the mitochondrion while halothane tends to inhibit the first ATP formation according to Miller and Hunter (1971) and, as such, is not considered a true uncoupling agent. Halothane is an anaesthetic with a mild positive charge and so tends to reduce the membrane permeability to calcium and sodium but it has the effect of displacing the calcium, which is bound to the cell membrane and sarcoplasmic reticulum. It is, nevertheless, reasonable to accept that the greatest source of heat in malignant hyperpyrexia is produced by uncoupling of oxidative phosphorylation. Such energy release, as shown by Williams (1971), can be achieved by cations such as calcium which are able to penetrate the mitochondrial membrane as calcium or as lipid soluble complexes which move into the mitochondria and disrupt the chemo-osmotic potential. This situation in turn disturbs the proton gradients disrupting the equilibrium of the primary energy conservation systems of the mitochondria. Halothane has, in addition, a direct though non-specific effect upon the mitochondrial membrane, affecting the lipid phase, and in this way may pave the way for other substances, again, possibly calcium, to initiate the uncoupling process.

Apart from the contracture and heat production which is associated with poisoning by dinitrophenol, additional and vital information has been obtained by comparing the rigid form
of malignant hyperpyrexia with caffeine-induced rigor. Caffeine contracture of muscle in vitro has been well documented by Sandow (1970) who was able to show that this contracture occurs in consequence of the release of calcium into the sarcoplasm, thereby initiating ATPase activity. Weber and Hirtz (1968) claimed that the increased sarcoplasmic concentration was achieved by the release of calcium from the sarcoplasmic reticulum, while Weber (1968) correlated the events with an uncoupling of sarcoplasmic reticulum ATPase activity effecting the re-accumulation of calcium.

From all the evidence available there can be no doubt that the sarcoplasmic reticulum is involved in malignant hyperpyrexia. The calcium is released from this site after depolarization of the cell membrane and T-tubules and it forms part of the excitation-contraction coupling mechanism. The sarcoplasmic reticulum, by virtue of its ability to regulate the release of calcium into the sarcoplasm, exerts metabolic control over muscular contraction directly and thereby indirectly over glycolgenolysis, ATP formation, and heat production. The sarcoplasmic reticulum has been analysed by MacLennan (1971) who has found two proteins which appear to be involved in calcium transportation. One is ATPase, its activity depending upon magnesium and ATP concentration as well as calcium concentration. The second is a soluble protein called calciquestrin which he extracted from the sarcoplasmic reticulum and showed to be capable of binding up to 43 moles of calcium per mole. Once in the sarcoplasm, calcium interacts with troponin complex, which in the relaxed state is bound to the actin filaments, and frees binding sites which then cross-bridge with myosin and set in action the sliding contraction process. Reaccumulation of calcium by the sarcoplasmic reticulum results in relaxation and a return to the resting state.

Britt and Kalow (1970) were the first to suggest that, as a result of various anaesthetic substances, the sarcoplasmic reticulum was unable to re-accumulate the calcium from the sarcoplasm. In order to test this hypothesis, Kalow et al. (1970) decided to test the susceptibility of human muscle to caffeine contracture and examined muscle taken from three volunteers who had survived a malignant hyperpyrexial reaction. The isolated muscle was mounted so that isometric tension could be measured while the muscle was bathed in a solution resembling human plasma. The muscle was electrically stimulated and the responses to caffeine and halothane administration were noted. Muscle strips of two of the three patients who had previously developed the rigid form of malignant hyperpyrexia showed increased susceptibility to develop caffeine contracture when compared with normal controls. This increased susceptibility was enhanced by halothane. They were also able to show that the accumulation of calcium by the sarcoplasmic reticulum was lowered by the administration of 5% halothane in two of the susceptible cases, while it remained normal in the controls. These results are in keeping with earlier work of Sabawala and Dillon (1968) who demonstrated that halothane was able to enhance the twitch response in human muscle after direct stimulation, suggesting that halothane may have similar action to caffeine and act by blocking the return of calcium to the sarcoplasmic reticulum. The failure to demonstrate halothane-induced contracture in the one specimen of susceptible muscle by Kalow et al. (1970) may be due to the fact that their experiment was carried out at physiological temperatures, as suggested by Keaney and Ellis (1971). Ellis, Harriman, Keaney, Kyei-Mensah, and Tyrrell (1971) have been able to demonstrate that halothane is capable of inducing a reversible contracture in susceptible muscle. Strobel and Bianchi (1971) produced contracture in isolated frog sartorius muscle by administering halothane to the muscle which had been previously exposed to caffeine. This action of halothane, as pointed out by Kalow, is similar to the effect seen after the administration of ether which was demonstrated by Fiehn and Hasselbach (1969).

Kalow et al. (1970) conclude that malignant hyperpyrexia with rigidity is caused by an inborn metabolic error in skeletal muscle which renders the muscle susceptible to disturbances of intracellular calcium distribution. They further suggest that malignant hyperpyrexia without rigidity is a different disease and that both are inherited as autosomal dominant abnormalities and both are equally lethal. This opinion, however, is not acceptable to us as we find it difficult to reconcile the fact that both forms of malignant hyper-
pyrexia have occurred in the same family and we prefer to regard both forms as a manifestation of the same basic underlying abnormality which is modified by sarcoplasmic, mitochondrial, or other factors as yet unknown which presumably would alter the intracellular environment in a particular direction at that particular time. Animal experimentation to the present time has not given any indication as to what the difference may be as only the rigid form occurs.

Little is known of the way caffeine exerts its effect on sarcoplasmic reticulum but in recent years a few points of importance have emerged. Caffeine is capable of blocking phosphodiesterase, the degradation pathway for cyclic adenosine mono-phosphate (AMP) resulting in increased concentrations of intracellular cyclic AMP (Rasmussen, 1970; Sutherland, 1970). For this reason, an objection was raised to the use of isoprenaline and related pressor substances as a form of therapy for hypotension during malignant hyperpyrexia, as these substances increase cyclic AMP by their stimulatory action on adenylcyclase. Increased concentration of the cyclic AMP has been proposed as a basis for the generation of the heat process in malignant hyperpyrexia by Pollock and Watson (1971). Harrison et al. (1969), however, infused 1:100,000 adrenalin into a susceptible pig without triggering a hyperpyrexial reaction. Other drugs such as amine-oxidase inhibitors and imipramine act by stimulating adenylcyclase and blocking phosphodiesterase respectively (Abdulla and Hamadah, 1970). The net result is an increase in intracellular cyclic AMP and both drugs have been known to produce hyperpyrexial syndromes. It would be tempting to group all these hyperpyrexial syndromes together but there is insufficient evidence for this and it must yet be shown that patients with non-anaesthetic reactions belong to families with either a clinical history or biological evidence of malignant hyperpyrexia. Patients with different hypermetabolic states such as hyperthyroidism, the hypermetabolic syndrome of Luft, Ikkos, Palmieri, Ernster, and Afzelius (1962), osteogenesis imperfecta (Aldrete, Padfield, Solomon, and Rubright, 1971) and the syndrome of continuous muscle-fibre activity (Isaacs, 1961) have shown no predisposition to develop malignant hyperpyrexia. Neither have patients with megaconial or pleoconial muscle mitochondrial abnormality (Shy, Gonatas, and Perez, 1966) or with abnormal lipid storage and abnormal mitochondria (Bradley, Hudson, Gardner-Medwin, and Walton, 1969; Isaacs, 1972) shown any such tendency. Cases with Duchenne type muscular dystrophy have been shown to have abnormalities in the sarcoplasmic reticulum by Samaha and Gergely (1969) but these patients are not prone to develop malignant hyperpyrexia. All this evidence tends to indicate the rather specific nature of the sarcoplasmic reticulum abnormality in malignant hyperpyrexia. A febrile state that warrants close study with the possibility of correlation with malignant hyperpyrexia is the liver necrosis and unexplained fever after halothane administration (Sharpstone, Medley, and Williams, 1971).

The correlation of malignant hyperpyrexia with caffeine contracture has had far-reaching benefits in that it opened the way for a most important therapeutic approach. As far back as 1963 Feinstein was able to show that the rigorous induced by caffeine could be blocked by the administration of procaine. Weber and Hirttman (1968) recorded that procaine in vitro could block the onset of caffeine rigor and was also capable of reversing the early effects of caffeine rigor if administered at this stage. Katz (1970) administered lignocaine to a case of malignant hyperpyrexia in an attempt to correct a cardiac arrhythmia and noted a dramatic drop in temperature. An equally dramatic response was obtained by Kalow et al. (1970) in a case where procaainamide was given in a total dose of 1,100 mg. This case has been written up in great detail by Beldavs et al. (1971). These dramatic responses led Strobel and Bianchi (1971) to examine the merits of both lignocaine and procaainamide in the prevention of caffeine contracture in the frog sartorius muscle. They found that procaainamide had a blocking action, while lignocaine stimulated the caffeine responses. These findings were in keeping with the work of Bianchi and Bolton (1967) and Bianchi (1968).

Harrison (1971), following on the success of Katz (1970) and Kalow et al. (1970) with lignocaine and procaainamide respectively, used procaine in susceptible Landrace pigs. Not only was procaine found useful in protecting the muscle from malignant hyperpyrexia induced by halothane and succinylcholine but it also helped
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to reverse the fully established syndrome, enabling two out of five pigs to survive. Ellis et al. (1971) were able to show that procaine hydrochloride was able to prevent and reverse the halothane-induced muscle contracture in susceptible muscle strips.

Though it seems likely that an effective therapy has become available in the form of procainamide or procaine this should not be taken as an indication to relax vigilance with regard to prophylaxis. Careful interrogation of the patient with regard to anaesthetic deaths in the family is of paramount importance. The fact that a patient with such a history has had a previous uneventful anaesthetic is no safeguard and in fact may sensitize the patient in some way to subsequent anaesthetic challenge. Several tests which may point to susceptibility are available and the most widely used is the serum creatine phosphokinase (Isaacs and Barlow, 1970a). Aldrete et al. (1971) have shown that estimations of serum pyrophosphate are equally reliable. Subjects who carry the abnormal trait, with few exceptions, show an elevation of the serum CPK and it seems logical to correlate the degree of susceptibility with the height of the CPK, though a normal or only slightly elevated serum CPK should not lull the anaesthetist into a false sense of security.

If serum creatine phosphokinase is used as a general screening test there will be some false positives, as several otherwise normal members of the population who give no family history of muscular dystrophy or malignant hyperpyrexia will be found to have elevated levels which may reflect some other unrelated non-specific defect (Emery and Spikesman, 1970). However, we would suggest that these cases remain suspect and should not be challenged with drugs or anaesthetics without caution. If need be, muscle histology per se, as shown in this paper, or exposure of muscle strips to halothane (Harrison et al., 1969) or halothane and caffeine (Kalow et al., 1970) as described could presumably solve the problem.

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REFERENCES


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