MALIGNANT HYPERTHERMIA: AETIOLOGY UNKNOWN!

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THE CLINICAL AND ROUTINE LABORATORY aspects of malignant hyperthermia have been amply documented in the literature.[1] There have been some attempts to investigate the aetiology of this syndrome,[2–13] but specific studies in man are scant. This is mostly due to the difficulty of obtaining the material required for research. The episodes are rare, and if one occurs, the patient is often in much too great danger of imminent death for any of the attending medical personnel to spare the time to take biopsies for research purposes. Moreover, the type of laboratory which is equipped and ready for an original investigation of this condition is not found in the average hospital, so that it may not appear to be worthwhile to take a specimen even if it is feasible. If the patient survives, he may not be available for elective investigation because of his only too natural hesitancy to undergo any further surgical procedures. If in spite of all he is still alive and still willing to serve, one cannot remove such large quantities of biopsy specimens as might be needed to obtain suitable dose-response curves for each of the many parameters that should be measured. There are some stimulating observations in pigs[2,6] and in dogs,[5] which seem to have the same malignant hyperthermia as occurs in man, but the degree of similarity between the hyperthermic reactions in these species remains to be established. We will therefore attempt here to choose between conceivable causes of malignant hyperthermia by contemplating the many clinical reports and the results of research in man and animals.

It is possible that malignant hyperthermia in man is not a single entity but in fact more than one disease. In this article we shall chiefly confine our consideration of possible aetiology to those cases characterized by rigidity, since these differ in many ways from those without rigidity.[1] In these cases we are most likely dealing with a syndrome of uniform aetiology.

CENTRAL OR PERIPHERAL AETIOLOGY?

Clinical findings do not favour a central cause. Heat losing mechanisms such as sweating and vasodilatation of skin vessels appear to remain competent in many patients.[1] In addition, patients who have received trauma to the hypothalamic temperature regulating centre do not display the extreme metabolic acidosis and hyperkalaemia[14] that has been observed in malignant hyperthermia. Furthermore, while patients suffering from severe heat stroke with irreversible damage to the temperature regulating centre do manifest metabolic acidosis and potassium intoxication, their muscles are frequently found to be flaccid, and rigidity occurs only as a terminal rather than an initial event.[15–22] Finally, if the setting of the

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hypothalamic thermostat had been suddenly altered so as to increase body temperature, the response in muscle would be shivering but not rigidity.

Very recently, Horsey[7] suggested that malignant hyperthermia might be secondary to an acceleration of 5-hydroxy-tryptamine (5-HT) release in the hypothalamus. He based this speculation on the finding of Feldberg and Myers[23–25] that an injection of 5-HT into the anterior hypothalamus of a cat raises body temperature. However, in Feldberg's experiment the hyperthermia was associated with shivering but not with rigidity.

Summers[10] has shown that inhalation of halothane by cats leads to hyperthermia and occasionally skeletal muscle stiffness when they have received beforehand an intraperitoneal injection of a monoamine oxidase (MAO) inhibitor such as tranylcypromine, pargyline, or nialamide. He attributed this temperature elevation to an abnormally great accumulation of 5-HT in the hypothalamus, which he assumed had been brought about by the combined actions of the MAO inhibitor and the halothane. However, this investigation is inconclusive for several reasons. First, the doses used were, on a weight for weight basis, several hundred times those employed therapeutically in humans. Second, the experiments were carried out by intraperitoneal injection and not by applying the drug to the region of the temperature controlling centre in the brain as Feldberg had done. As MAO inhibitors not only affect brain MAO but have additional actions throughout the body,[26–32] one can ascertain neither their site nor their mode of action when they produce a hitherto unknown effect.

The following observation seems to be conclusive. Satnick described a patient with malignant hyperthermia[33] who developed extreme rigidity everywhere except distal to a tourniquet. The tourniquet had been applied to the right forearm immediately after the injection of succinylcholine and before the administration of halothane. This arm remained flaccid throughout and after anaesthesia, even after removal of the tourniquet 90 minutes after the induction of the anaesthetic when the rest of the body was still stiff. This observation supports a peripheral cause in that the muscles not reached by halothane did not become rigid. Furthermore, the failure of rigidity to develop after removal of the tourniquet makes it unlikely that the cause could be a circulating material.

A tetanus can be relieved by d-tubocurarine[34,35] but the rigidity of malignant hyperthermia cannot be. As judged from inspection of the muscles of affected patients during surgery, the blood supply to the muscles must be ample, so there is no reason to doubt that d-tubocurarine can reach the end plate. Hence the principal defect seems to be distal to the neuromuscular end plate.

The administration of succinylcholine to patients affected with malignant hyperthermia is often followed by a prolonged and continuous muscle stiffness which may or may not be preceded by transient but violent muscle fasciculations. The muscle stiffness may merge imperceptibly into rigor mortis.[1] Such a smooth transition into rigor mortis can be more easily visualized from a contracture originating in the muscle fibre than from a neurogenically produced tetanic contraction.

Lastly, it appears that pigs may develop malignant hyperthermia.[2,6,36,37] In these animals, a peripheral defect has been directly demonstrated.[6] If the defects in man and pigs are identical, then malignant hyperthermia in man must occur on

the basis of a biochemical defect – not in the central nervous system but in the periphery.

Observations in Man on the Nature of the Peripheral Defect

At one time or another, malignant hyperthermia has been thought to be related to any of a number of peripheral metabolic diseases or specific defects. These deserve special discussion and serious consideration, since a central cause of malignant hyperthermia does seem far less likely than a peripheral one.

Relationship to myotonia dystrophica

Because of the relative rarity of malignant hyperthermia in older individuals, Cody suggested that this syndrome may be an early manifestation of undiagnosed myotonia dystrophica.[38] Myotonia dystrophica is an hereditary condition which is characterized by an inability to relax a muscle after its contraction. The primary defect is not known but the abnormality may involve both the motor end plate region and some site distal to the neuromuscular junction.[39–41] In patients with this disease, succinylcholine may cause a muscle contraction of short duration rather than the usual relaxation.

Cody proposed that the lack of a hyperthermic response in the older myotonic individual could be explained on the basis of insufficient muscle tissues to cause a dramatic heat production. However, the total lack of myotonia in any family with malignant hyperthermia and the short duration of the succinylcholine-induced stiffness in patients with myotonia render this theory unlikely. Furthermore, the recent detection at the Albert Einstein College Hospital in New York of a patient with malignant hyperthermia at the age of seventy[42] indicates that though the condition is rare in old age it is not absent.

Failing function of cell membrane

During malignant hyperthermia, enzymes, potassium, and myoglobin leak presumably from skeletal muscle cells, and red blood cells haemolyse prior to any significant temperature rise. We therefore considered the possibility of a generalized primary defect of cell membranes. Hence, Dr. P. Seeman[43] of this department has prepared red cell ghosts according to the method of Dodge *et al.*,[44] using blood from affected persons and their relatives. Measurements of the swelling properties of the ghosts and fragility tests of the red cells have failed to reveal any significant differences between normal subjects and patients, either in the absence or in the presence of various concentrations of halothane.[45]

We have investigated ATPase activity of erythrocyte ghosts, and the sodium and potassium transport in red blood cells on rewarming after cool storage. We were not able to show any significant difference in these parameters between samples from controls and those from affected patients.

Insufficient supply of ATP

Harrison *et al.*[6] have shown that the isolated muscle of pigs affected with a malignant hyperthermia develops a statistically significant diminution in ATP

content after exposure to a 4.0 per cent halothane vapour for a period of 30 minutes.

An adequate supply of ATP is essential for the muscle to remain in the relaxed state. Rigor mortis is one illustration of rigor due to decreased ATP production.[46] However, excessive ATP utilization could also lead to its shortage. Thus Harrison's observation permits numerous explanations, and one does not know whether it will apply to humans. This finding, nevertheless, must be counted as an essential discovery because it shows that *in vitro* investigation may be able to solve the puzzle of malignant hyperthermia.

Decreased muscle phosphorylase

It has been suggested that malignant hyperthermia may be due to insufficient ATP production secondary to the absence of muscle phosphorylase (Fig. 1).[47]

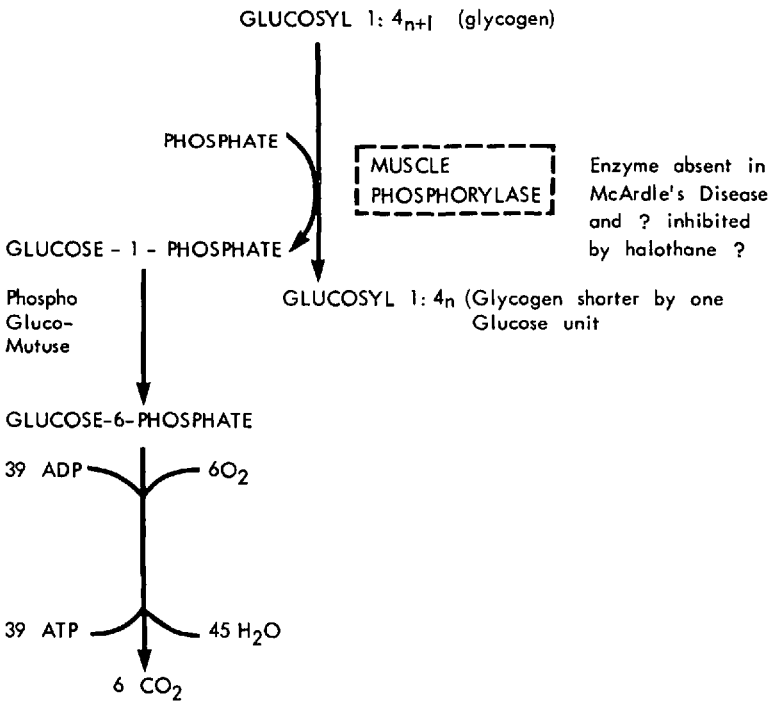

FIGURE 1. Mobilization of glycogen in skeletal muscle (ADP = adenosine-5'-diphosphate, ATP = adenosine-5'-triphosphate).

This rare familial form of glycogen storage disease is known as McArdle's disease. Those affected are unable to break down muscle glycogen and therefore rapidly deplete their glucose during exercise so that there is a generalized exhaustion of the available supply of the high energy phosphate bonds in the muscle. The energy supply necessary for the various transport and storage processes of the muscle membrane fails and the normal electrical activity of the membrane disappears. The muscle membrane becomes permeable to intracellular constituents,

and there is a leakage of myoglobin and enzymes into the plasma.[48–51] The muscle goes into a state of contracture, the exact mechanism of which is still obscure.

Epstein[47] has theorized that in patients with McArdle's disease the administration of depolarizing muscle relaxants might be expected to produce a clinical picture resembling that of malignant hyperthermia. However, extensive questioning of many members of several affected families, including one very large family in which twenty members have developed malignant hyperthermia during general anaesthesia,[52] has failed to detect any patients who have ever complained of red urine following exercise. Secondly, electron microscopy of skeletal muscle biopsies of several patients[1] suggest normal glycogen deposits. Thirdly, McArdle's disease is a recessive condition,[48,50] while malignant hyperthermia appears to be autosomal dominant,[1,52,53] and it has also been observed that enzyme defects almost never exhibit dominant inheritance.[54] Finally, McArdle's disease is not characterized by fever during episodes of contracture and myoglobinuria.[48,50,51] This absence of fever, however, may not be surprising, since, because of the inability to convert muscle glycogen to glucose, the rate of oxidation of glucose and the hydrolysis of ATP (exothermic reactions) must both be slower than normal.

Uncoupling of oxidative phosphorylation

Several authors have drawn attention to some similarities between malignant hyperthermia and poisoning by dinitrophenol (DNP) (Figs. 2 and 3).[5,13,55,56] Wang *et al.*[12] claimed that uncoupling of oxidative phosphorylation alone cannot adequately account for the enormous increase in heat production that has been observed in malignant hyperthermia, while on the other hand, when all the muscles of the body are maximally contracted, the metabolic rate of the whole body can increase to 1,500 to 2,000 per cent above the basal level.

In a case of exertional paroxysmal myoglobinuria reported a number of years ago by Kontes *et al.*,[57] uncoupling of oxidative phosphorylation appeared to be the best explanation for the clinical and laboratory abnormalities observed. Oxygen consumption was low in the basal state but accelerated in the normal manner during exercise, indicating that the capacity to utilize oxygen was unimpaired. As compared with a normal control there was increased energy expenditure during performance of muscular work, and a large proportion of this energy was derived from anaerobic metabolism, suggesting inefficient conservation of energy derived from oxidative metabolism. Arterial lactate rose to a higher level and arterial pyruvate fell to a lower level during exercise in the patient than in the control. Such accelerated glycolysis would be necessary, as it would be the only effective source for the rephosphorylation of ADP. However, in this patient, rigidity and apparently fever were both absent, while fatigue and weakness and even frank paralysis as well as muscle pain and swelling were very much in evidence during the acute attacks which followed muscle exercise.

Another patient described by Wijngaarden *et al.*[58] had non-thyroid hypermetabolism, an abnormal electromyogram, and generalized muscle wasting, hypotonia, and absent tendon reflexes. This patient was found to have an abnormally large and an increased number of skeletal muscle mitochondria. These mitochondria were "loosely coupled," i.e. they had a high rate of respiration which was not

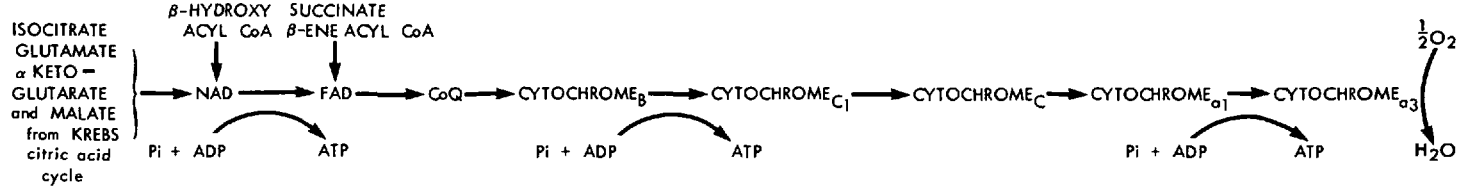

FIGURE 2. Normal coupled oxidative phosphorylation in the mitochondria (NAD = nicotinamide adenine dinucleotide, FAD = flavine adenine dinucleotide, CoQ = coenzyme Q).

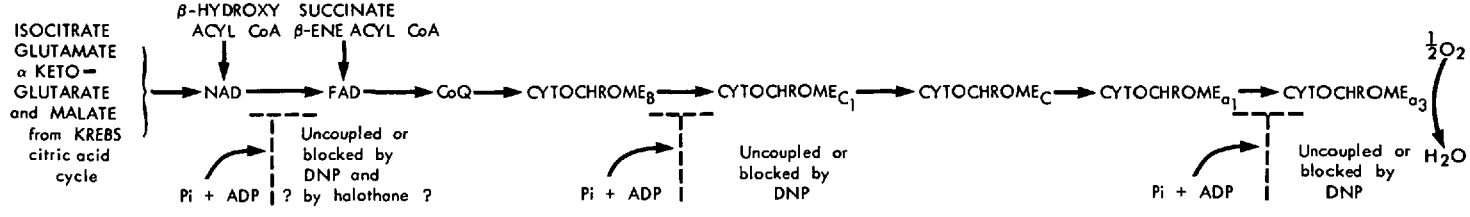

FIGURE 3. Uncoupled oxidative phosphorylation in the mitochondria. Note that while DNP (2,4-dinitrophenol) acts at three sites along the chain, halothane probably acts at only the first site.

further stimulated by the addition of ADP, but they were still able to phosphorylate ADP to ATP. Again the clinical features of this patient did not resemble those of patients with malignant hyperthermia. Prior to anaesthesia, patients with malignant hyperthermia do not exhibit hypermetabolism, muscle wasting, absent tendon reflexes or an abnormal EMG. Muscle weakness is localized and never generalized.

Thus it would appear that several distinguishing clinical features of syndromes known to be due to uncoupling of oxidative phosphorylation are different from the rigidity type of malignant hyperthermia. However, further work remains to be done. It would be interesting, for instance, to know how patients such as those described by Kontes *et al.* and by Wijngaarden *et al.* would react to general anaesthetic agents such as halothane. One would like to study the oxidative phosphorylation of a muscle specimen obtained from an affected patient during an acute episode of the non-rigid type of malignant hyperthermia.

Mitochondrial swelling did appear to be present in electron microscopy photographs made of the skeletal muscle of three patients with malignant hyperthermia reported by Carpenter *et al.*[59] However, this alteration could have been secondary to the hypoxia which is known to be present in malignant hyperthermia as evidenced by skin colour, arterial oxygen measurements, and post mortem findings.[1] Indeed Jennings *et al.*[60] have shown that the mitochondria of ischaemic cardiac muscle of the dog does become swollen and fragmented, with greatly reduced respiration, in the presence of ADP.

Intracellular calcium metabolism

Studies performed by Dr. N. S. Dhalla[4] on a patient recently detected in Winnipeg by Dr. J. Wade[61] seem to show that calcium uptake by the sarcoplasmic reticulum is less depressed in the presence of halothane than it is in normal patients. This observation and the observation of a low serum calcium in a number of the more severely affected patients who developed rigidity during the course of their disease lend some support to the theory that the primary defect consists of an alteration of the calcium storing or transporting properties of some membrane other than the sarcoplasmic reticulum.

The key role of calcium in the excitation-contraction coupling of skeletal muscle and therefore in the contractile state of the muscle has been amply documented (Figs. 4 and 5).[62–78] The contracted state is initiated by a high cytoplasmic calcium level. This could be brought about in various ways.

One could postulate that the primary defect lies in the membrane of the sarcoplasmic reticulum and that anaesthetic agents or muscle relaxants depress the uptake of calcium into the interior of these storage vesicles so that the level of calcium in the sarcoplasm remains above the critical level. Alternatively, one could postulate that the calcium storing or transporting properties of some other membrane such as the outer cell membrane or the membrane of the transverse tubules or the mitochondrial membrane are defective in the presence of anaesthetic agents or muscle relaxants. Calcium would then, following its natural concentration gradient, leak from these membranes into the cell cytoplasm so that its concentration in this compartment would remain permanently above the

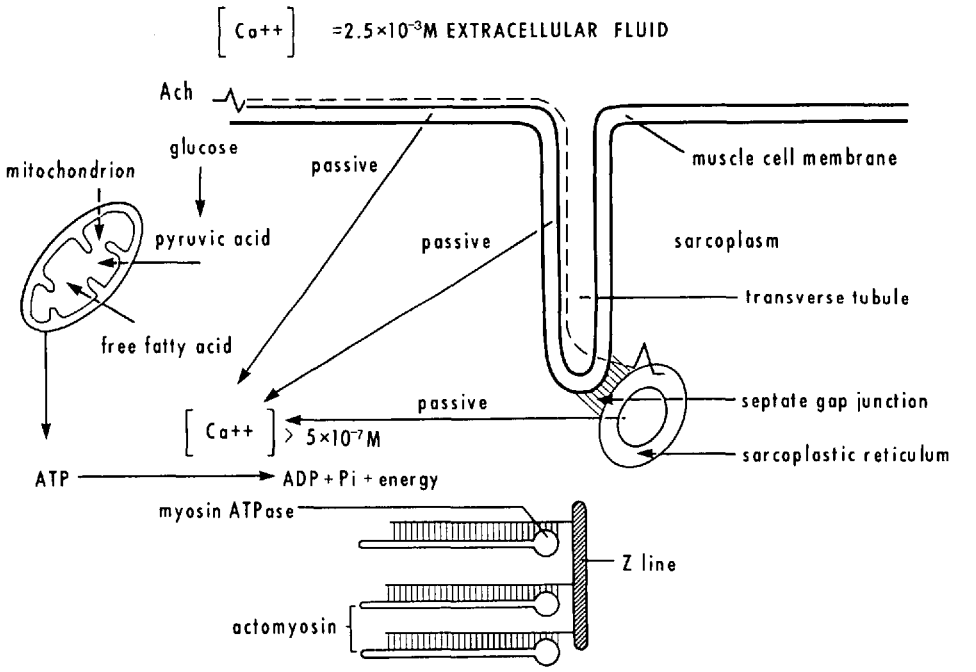

FIGURE 4. Schematic diagram of the role played by calcium in the contraction of skeletal muscle (Ach = acetylcholine).

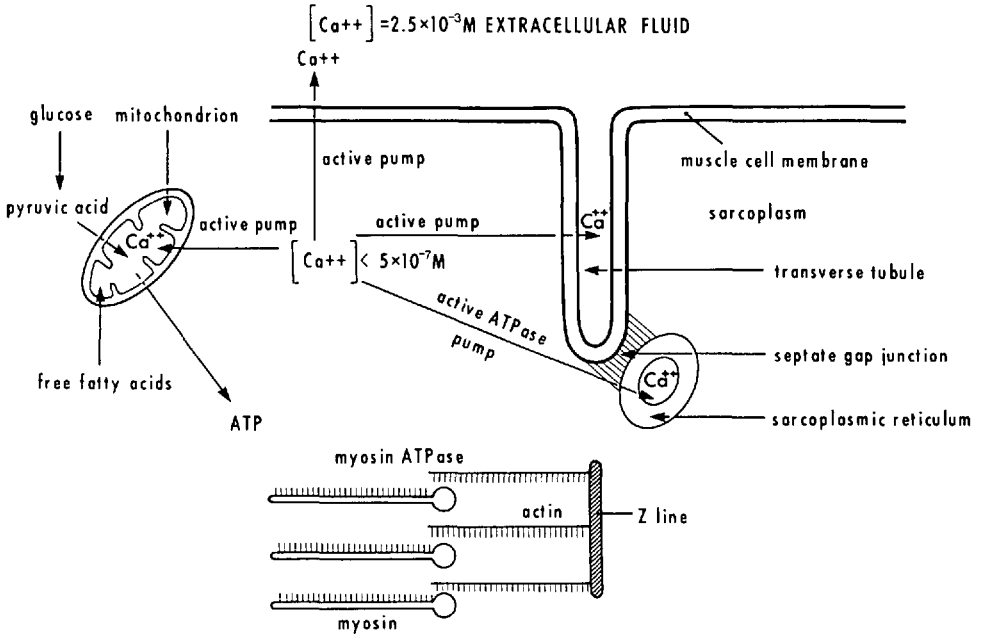

FIGURE 5. Schematic diagram of the role played by calcium in the relaxation of skeletal muscle.

critical level. The sarcoplasmic reticulum would now have to compensate to remove this excess calcium from the cytoplasm. The finding of Dhalla[4] would require an explanation of this nature.

In the presence of a high intracellular calcium concentration the contractile proteins actin and myosin would remain linked in the shortened state as actomyosin. There would be a continuous and rapid production of heat as ATP is broken down to ADP by myosin ATPase. The presence of excessive amounts of ADP would stimulate the various metabolic pathways necessary for the regeneration of ATP with further associated heat production and acceleration of oxygen consumption, carbon dioxide production, and lactacidosis. For example, oxidation of glucose and fatty acids to carbon dioxide and water in the mitochondria and conversion of phosphocreatine and ADP to ATP and creatine in the cytoplasm would be enhanced.

The accelerated rate of ATP production would not, however, be able to keep pace with the far more rapid rate of ATP breakdown. There would therefore be insufficient ATP to provide the energy for the various metabolic needs of the outer cell membrane, which consequently would become permeable to myoglobin, potassium, and various enzymes.[7,9]

Thus many of the known major changes present in the rigidity type of malignant hyperthermia could be accounted for by the theory that potent inhalational anaesthetic agents and muscle relaxants in some way alter the calcium storing or transporting properties of a cellular or intracellular membrane.

Such a theory surmounts a serious difficulty associated with the "uncoupling of oxidative phosphorylation" theory – namely that a highly ionized quaternary amine such as succinylcholine would have to be able somehow to traverse one or more lipid membranes. If the "calcium" theory is correct the succinylcholine could act directly on the outer cell membrane, or on the transverse tubular membrane, an invagination of the outer cell membrane, or on the membrane of the sarcoplasmic reticulum, which, being separated from the membrane of the transverse tubules only by a septate space, is actually electrotonic with it.

Animal Data and Their Relevance to the Human Disease

Wilson *et al.*[13] and Gatz *et al.*[5] administered both DNP and halothane to dogs. This combination of drugs did produce a high fever and in Gatz's experiments also other clinical and laboratory changes characteristic of malignant hyperthermia, including rigidity.

We administered dinitrophenol to rabbits and to rats in various doses. The addition of halothane did not heighten muscle tone.[5,6] These findings agreed with a similar study carried out on chickens by Viguera and Conn.[11] Gatz *et al.*,[5] in their investigations on dogs, used a reversed procedure by first giving halothane and then adding 5 mg/kg of DNP. It thus remains to be seen whether the differences between the results of various investigators are due to differences of experimental techniques or to species differences.

Most revealing have been the observations on malignant hyperthermia in the Landrace pigs. Clinically the syndrome in man is indistinguishable from that in

TABLE I*

EFFECT OF HALOTHANE ON BLOOD COMPOSITION IN THE PIG†

	Time (min)						
	−60	−3	+3	+8	+21	+31	+80
Oesophageal temp.(°)	38.3	38.4	38.6	39.0	42.0	43.0	44.1
Na^+ (mEq/L)	136	142	142	154	151	154	155
K^+ (mEq/L)	4.5	4.6	4.5	5.4	8.2	8.4	11.4
Glucose (mg/100 ml)	68	68	68	78	112	125	150
Total protein (g/100 ml)	6.5	6.5	6.3	6.9	7.7	7.9	6.3
Ca^{2+} (mg/100 ml)	10.8	11.1	10.3	11.7	13.5	12.9	10.5
Mg^{2+} (mEq/L)	1.12	1.44	2.16	2.40	2.00	2.24	2.56
Pi (mg/100 ml)	9.6	9.4	9.1	14.5	25.8	29.3	31.7
Lactate (mEq/L)	1.63	1.43	1.70	7.00	19.9	20.9	18.0
Pyruvate (mEq/L)	0.15	0.16	0.17	0.27	0.18	0.20	0.21
"Excess lactate" (mEq/L)	0.62	0.35	0.56	5.18	18.7	19.5	16.6
pH	7.36	7.36	7.07	6.92	6.60	6.60	6.82
Po_2 arterial (mm Hg)	120	350	340	265	200	215	78
Po_2 venous (mm Hg)	46	55	52	51	28	58	47
Pco_2 arterial (mm Hg)	49	49	68	119	268‡	168‡	153‡
Base excess (mEq/L)	+3.0	−1.5	−3.2	−7.2	−21.5	−22.0	−22.0

*After Berman *et al.*, Nature *225*: 654 (1970).[2] Reproduced with permission of the authors and the editors of Nature.

†Halothane 3% v/v in O_2 was given from 0 to 8 minutes.

‡Calculated from total blood CO_2 and pH.

pigs. The pigs exhibit hyperthermia and rigidity, and, as in man, the causative agents have been mostly halothane and succinylcholine. As in man, the condition is usually fatal. Finally, as in man, predisposition is inherited and the pattern of inheritance is by autosomal dominance.

The biochemical observations presented most recently by Berman *et al.*[2] are shown in Table I. The data can be scrutinized from various points of view, as to time of onset and time and magnitude of maximal change. In terms of onset, there were four distinct changes occurring within three minutes after the start of the administration of halothane. These are the rise in lactate, the fall in pH, increased arterial Pco_2, and last, but not least, the rise in plasma magnesium. By contrast, plasma protein and plasma calcium showed slower and more modest rises which were parallel in terms of timing and of percentage change. The rise of protein concentration indicates a shift of water into the intracellular space, and this seems to account for the change of calcium concentration (this interpretation of the calcium shift in Table I is different from that proposed by the authors). During the final stage of the experiment the largest alterations from the control period concerned hydrogen ion, plasma potassium, inorganic phosphate, glucose, lactate, and blood gases.

According to Berman *et al.*[2] the initial rise of body temperature of affected pigs was somewhat faster in the liver than in muscle, and the liver temperature exceeded muscle temperature at all times until death. Strangely enough, the skin temperature fell, indicating a lack of blood flow in the skin. When isolated muscle of affected pigs was exposed to halothane *in vitro*, its ATP content quickly dropped in contrast to that of control muscle from unaffected pigs.[6]

These data are more complete than any of the data in man or in dogs, and for that reason a comparison is difficult. A possible discrepancy lies in the observation

that there was only a modest rise of plasma calcium in pigs, perhaps secondary to a fluid shift, while the human data showed a distinct and significant fall in plasma calcium levels. This looks like a fundamental difference of an important physiological parameter (see Figs. 4 and 5). However, a final decision can be made only after further investigation of the time factor in man and in pigs. If both showed an initial excess and a final deficit of plasma calcium, apparently opposite effects could depend on the time of sampling. Magnesium levels have not been measured in man, nor are there good data on lactic acid or blood glucose; most glucose determinations were made after glucose infusion and are therefore not relevant. Other parameters which changed most dramatically in pigs, namely potassium, pH, and blood gases, changed in man and in dogs in similar directions. Calcium and magnesium levels have not been measured in dogs.

One is left, therefore, with the conclusion that changes in electrolytes are prominent in both man and affected pigs. There is no evidence of any differences between man, pigs, and dogs in regard to carbohydrate metabolism during malignant hyperthermia. Observations in dogs suggest that uncoupling of oxidative phosphorylation plays a role. What the primary factor is, remains to be discovered. One has to accept gratefully the opportunities offered by the availability of animal data but one cannot use them to the exclusion of human data.

Summary

The aetiology of malignant hyperthermia still remains obscure, but the search is narrowing. Clinical and experimental evidence available to date indicate that the site of the defect is peripheral and not central. Absence of muscle phosphorylase, impaired ATPase activity of cell membranes, and the defect in myotonia dystrophica do not appear to be causative factors, at least not in those cases associated with rigidity. Metabolic defects in man known to be associated with mitochondrial alterations and an uncoupling of oxidative phosphorylation cause clinical symptoms which are not observed among patients predisposed to malignant hyperthermia. However, a combination of halothane and dinitrophenol in dogs has produced a syndrome with many features of malignant hyperthermia.

The malignant hyperthermia which occurs on the basis of a genetic defect in Landrace pigs is not only clinically identical with the human syndrome, but also identical in many of the biochemical features. Changes in carbohydrate metabolism as indicated by lactic acid accumulation are prominent in pigs and presumably in man. A difference in plasma calcium might represent a fundamental distinction if an artefact can be excluded and therefore needs to be carefully explored. The most puzzling observation in pigs, namely a 50 per cent increase in plasma magnesium within minutes of exposure to halothane, demands measurements of that parameter in man.

Résumé

L'étiologie de l'hyperthermie maligne demeure encore incertaine, cependant la recherche cerne la vérité de plus en plus. En ce moment, les constatations expéri-

mentales et cliniques disponibles nous incitent à croire que le point défectueux est périphérique plutôt que central. Du moins, en ce qui concerne les cas qui présentent de la rigidité; il ne semble pas que le facteur causal soit ou l'absence d'union de la phosphorylation oxidative, ou l'absence de phosphorylase du muscle, ou un trouble de l'activité de l'ATP des membranes cellulaires ou le défaut dans la dystrophie myotonique.

L'hyperthermie maligne observée sur la base de défauts génétiques chez les porcs Landrace est identique non seulement au syndrome clinique humain, mais aussi à plusieurs aspects biochimiques. Les modifications du métabolisme des hydrates de carbone comme l'indique l'accumulation de l'acide lactique est un point prédominant chez les porcs et, nous le présumons, chez l'homme. Une différence dans le taux de calcium plasmatique peut constituer une distinction fondamentale si l'on peut exclure un artefact et, alors, il faut faire des recherches minutieuses. L'observation la plus troublante chez les porcs consiste en une augmentation de 50 pour cent du magnesium plasmatique en deça de quelques minutes après l'inhalation d'halothane; chez l'humain, il nous faut mesurer ce paramètre.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Council of Canada (grant MA-2441) and by a grant from Ayerst Laboratories.

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