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Malignant hyperthermia : current observations and findings

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MALIGNANT HYPERTHERMIA: CURRENT OBSERVATIONS AND FINDINGS

by

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"Malignant hyperthermia," "Fulminant hyperthermia," "Idiopathic malignant hyperpyrexia," or simply "MHT," as it is variously called, has become recognized as a distinct clinical entity associated with general anesthesia during the last ten to fifteen years. This explosive thermal idiosyncrasy is seen in apparently healthy patients, often undergoing elective operations; they are afebrile at the start of the operative procedure, and a variable time after induction, a rapid rise in body temperature is observed, usually greater than 1°F per fifteen minutes; the body temperature continues to rise in rapid progression to elevations over 106°F, and no etiology can be attributed to its cause; cardiovascular collapse and profound shock result in death in the majority of cases, and the autopsy fails to reveal the etiologic mechanism.

Malignant hyperthermia, as described in recent years, is probably not similar to the hyperthermia noted many years ago in association with the prolonged administration of diethyl ether, although the end result may be the same. The hyperthermia, convulsions, tachycardia, and cardiovascular collapse associated with deep planes of ether anesthesia occurred usually

in the hot summer months in operating rooms which were not air conditioned and which had a high relative humidity. Children were particularly prone to develop elevated temperatures under ether anesthesia, and "ether convulsions" have been described. A high incidence was noted in acutely ill patients having peritonitis or some other infectious process.

In October 1967 Wilson[1] reviewed the forty cases of MHT then reported in the literature. He found that the mortality rate was 73%, and the process occurred in an unusually young and healthy group of patients. Three-fourths of these patients were in physical status I or I-E, and the remainder were in II or II-E (American Society of Anesthesiologists' classification). The average age was 21.4 years (range: 15 months to 47 years), and patients under 14 years of age made up 41% of the total cases. There appeared to be no correlation to sex (53% were male). In two-thirds of the cases, halothane was used as the general anesthetic agent, and succinylcholine was given in 72% of the cases. In every case where succinylcholine was administered, there was an increase in muscle tone and/or extreme muscle fasciculations at the time it was given. The muscle fasciculations are due to rapid depolarization of the motor end-plate. The body temperatures varied between the survivors and the fatalities, being usually about 2°F higher in those cases with a fatal

outcome:

	Survivors:	Fatalities:
max.	110° F	112° F
min.	105° F	106° F
mean	106.7° F	108.5° F

The hyperthermia appeared two hours after induction in those who survived, and two and one-half hours after induction in those who did not survive. An interesting observation can be made concerning the type of operative procedure. A great proportion of the patients has musculoskeletal abnormalities; 19% of the operations were on the spine, 15% were orthopedic extremity operations, 11% were appendectomies, 11% were tonsillectomy and adenoidectomies, and 7% each were cholecystectomies, eye operations, and operations on the mandible. No definite etiology was established for a single case, and blood cultures were negative in every case reported. Autopsies performed showed only nonspecific changes of edema, congestion, and petechial hemorrhage in the major organs.

The recognition of MHT is usually made when the process is irreversible, and despite valiant efforts, the outcome is fatal. The following case, reported by Davies and Graves,[2] is typical of the course of MHT:

> The patient was a 24-year-old mother of three who was undergoing an elective cholecystectomy. Her previous history and physical examination were essentially negative, except for biliary tract disease. She had been well-sedated with secobarbital 100 mg, meperidine

> 100 mg, and hyoscine 0.4 mg. Her preoperative vital signs were stable, with a B.P. 120/80 and pulse 80 and regular. At 7:50 a.m., she had an uneventful induction with thiopentone 350 mg, and succinylcholine 50 mg was used for intubation. Anesthesia was maintained with N_2O and O_2 and halothane. When [the effects of succinylcholine were gone and] respirations returned, muscle relaxation was obtained with gallamine 120 mg; respirations were then maintained manually throughout the operation. At 9:45 a.m., an additional 40 mg gallamine were needed for closure of the peritoneum. At 10:15 a.m., the pulse rate increased to 160, ventilation became difficult, and the patient was a little off-color. The canister and bag were observed to be very warm, as was the patient's skin. The anesthesia machine was turned off, and only oxygen was given. Closure was completed rapidly by 10:30 a.m., at which time the rectal temperature was observed to be 104° F; spontaneous jerky respirations were apparent, and there was marked rigidity of the limbs with peripheral cyanosis. The rectal temperature rose to 108°F, even after tepid and alcohol sponging at 10:45 a.m. The patient's condition gradually deteriorated, and she died at 11:27 a.m. The pathologist's final diagnosis after autopsy was: acute pulmonary oedema, acute cerebral oedema, probable idiosyncrasy to anesthetic agent.

Relton and Creighton[3] list three cardinal features common to all cases of MHT: (1) hypertonicity of voluntary muscles, (2) hyperthermia, and (3) acidosis. The most universal and outstanding clinical finding in MHT is generally agreed to be the voluntary muscle rigidity, ofted preceding any recognized rise in body temperature. The rigidity appears as an abnormal response to succinylcholine in those patients who receive the drug, and repeated doses of succinylcholine fail to improve the hypertonicity. In cases where MHT develops and succinylcholine is not used, the hypertonicity occurs later in the course

of anesthesia.

There is a latent period of from thirty to two-hundred minutes after induction, after which the rising body temperature becomes evident. Both respiratory and metabolic acidosis accompany the muscular hypertonicity and hyperthermia. Diaphoresis, tachypnea, cardiovascular changes of asphyxia, excessive muscular fasciculation or hypertonicity after muscle relaxant, "dark blood" in the operative field in spite of adequate ventilation, increased body heat, or convulsions--all these should be considered as signs of impending MHT.

Heatstroke appears to be quite similar to the course of MHT. It occurs following heavy labor, sports competition, military maneuvers, or some such muscular strain during exposure to high environmental temperature and humidity. Heatstroke has a rapid onset and sometimes runs a fatal course. Dizziness, nausea, vomiting, diplopia, hot and dry skin, stupor, or coma are commonly associated with a temperature of 105° F or more, and coarse tremor, tachycardia, and hyperventilation are usually present; blood pressure is initially elevated and may drop to shock levels rapidly.[4] The pathological examination following heatstroke shows only nonspecific edema, petechial hemorrhages, and congestion of the major organs, including the brain. Normally the body loses heat by radiation,

conduction, convection, and evaporation. The failure to effectively lose excess heat and maintain normal body temperature is considered the cause for cardiovascular collapse and often death. The capillary bed in such an individual is initially dilated, and fluid is lost through the skin in an attempt to lose excess body heat by evaporation; this loss is principally free water and 0.25% sodium chloride, and can lead to extracellular volume depletion, both intravascular and interstitial, in a short time. It is perhaps at that point where intravascular and interstitial volume loss is significant that vasomotor collapse occurs. The body cannot lose any significant amount of additional heat, and body temperature rises, and a fatal course may ensue. It is often suspected that the thermoregulatory center in the anterior hypothalamus is no longer functioning, although this effect may be secondary. The coexistence of heat retention and possible depletion of intravascular and interstitial volume in heatstroke may have some relationship to the clinical picture of MHT, in this author's opinion. Patients are often kept NPO for eight to ten hours or more preoperatively, which is another factor which would predispose to dehydration and heat retention.

The effects of progressive hyperthermia upon the hemodynamic functions in dogs was demonstrated by Frankel[5] in 1963. He took eight dogs weighing from 16-27 kg

and immersed them in a tank of water after anesthetization with pentobarbitol, gradually increased the temperature of the water, and took serial measurements of the blood pressure, pulse, respirations, blood glucose, hemoglobin saturation, lactic acid, and blood gases. He found that there was a critical point, 105.8° F (41° C), at which significant changes could be observed in all parameters. At this critical point, excess lactates, of previously normal levels, began to accumulate rapidly (Fig. 1). The sudden and marked metabolic acidosis was followed quickly by cardiovascular collapse. The mean arterial blood pressure remained stable until 41° C was reached, and then declined markedly (Fig. 2). The respiratory rate (Fig. 3), minute volume (Fig. 3), and pulse rate (Fig. 2), all

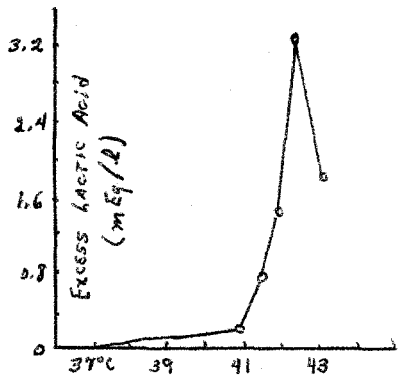

Fig. 1. Effect of Temperature on Excess Lactates.

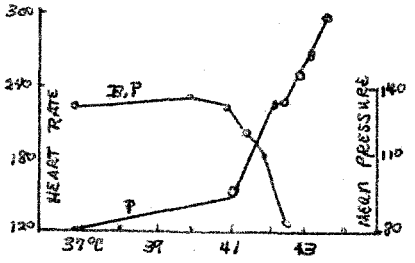

Fig. 2. Effect of Temperature on Blood pressure and Heart rate.

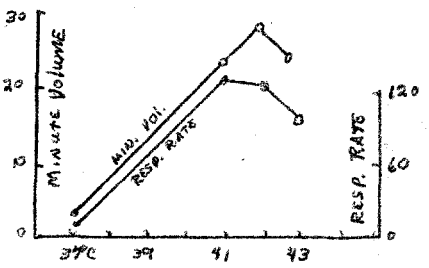

Fig. 3. Effect of Temperature on Respiratory Rate and Minute Volume.

increased up to the critical point, when the pulse became very rapid and the respiratory rate and minute volume showed a downward trend. The blood gases showed an initial rise in pO_2, a decrease in pCO_2 (corresponding to an increase in respiratory rate), and an initial increase in blood pH (Fig. 4). Hemoglobin

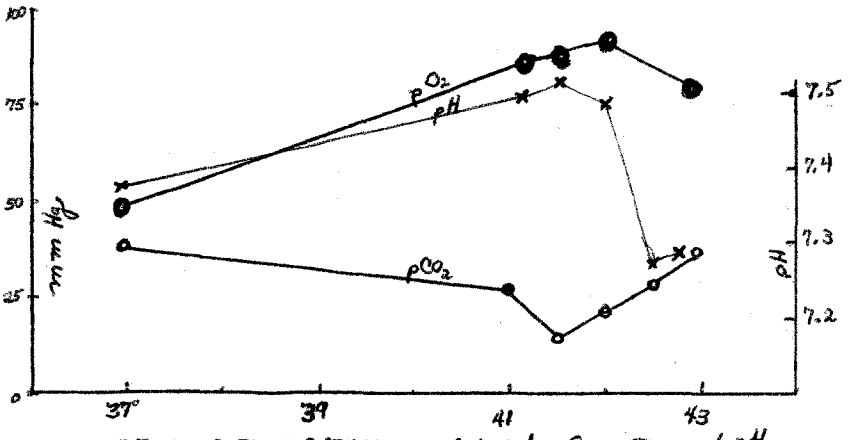

FIG. 4. Effect of Temperature on Arterial pO_2, pCO_2, and pH.

saturation remained stable. Shortly after 41° C, pH dropped markedly, and there was an increase in pCO_2. The earlier finding of lacticacidemia, followed rapidly by cardiovascular collapse, led Frankel to conclude that tissue hypoxia was present before the overt signs of cardiovascular collapse were manifest in the course of progressive hyperthermia. If a similar process were to occur in MHT, then we would expect acidosis and hypotension to be coincident with the appearance of significant hyperthermia. There are some differences between Frankel's dog experiment and what we might expect in MHT. Frankel described a rise in body temperature in association with an increase in

respiratory rate, minute volume, and pH, along with an increase in pO_2 and decrease in pCO_2. These changes in ventilation are prevented by the respirators, depressant action of general anesthetics, and adjuvant drugs.

Saidman[6] reports the presence of both metabolic and respiratory acidosis in MHT. He attributes the acidosis to the increased rate of metabolism seen with hyperthermia (7% increase in BMR for each 1°F elevation). Accordingly, oxygen demand is increased, but normal tissue perfusion is inadequate to meet the increase in metabolic rate, and hypoxia occurs; CO_2 is produced at an increased rate, and ventilation which is adequate for normal metabolism may be grossly inadequate for the increased CO_2 production. Excess CO_2 is eliminated in an increased amount, although not as rapidly as it is produced, and there is a lowering of the bicarbonate level and CO_2 combining power. In this way, inadequate perfusion and increased CO_2 production would account for the combined metabolic and respiratory acidosis which is seen in MHT, with an increased pCO_2 and CO_2 content, decreased bicarbonate level and CO_2 combining power, and lacticacidemia. Saidman lists the immediate complications of MHT as an interwoven group of events: acidosis, dehydration, hypovolemia, hypotension, and hypoxia. The hypotension and associated fall in tissue perfusion accentuate the tissue acidosis, and the acidosis, in turn, may produce

hypotension through the decreased responsiveness to catecholamines. Cardiovascular equilibrium is further compromised by hypovolemia, secondary to the dehydration from fluid loss through the skin and lungs; initially, the fluid loss is isotonic with the extracellular fluid, but eventually becomes hypotonic. The net loss of fluid results in a decrease in extracellular fluid volume and electrolyte abnormalities. The mortality of MHT is understandable, according to Saidman, if one considers the concomitant occurrence of all these events which upset normal human physiological processes.

From a review of the suspected causes for MHT in the literature, it can be seen that there is no one constant feature common to all cases of MHT which might be positively said to be the etiology. In considering the factors involved during anesthesia which might bring about such a condition as MHT, one must consider: (1) failure of the normal heat-losing mechanisms of radiation, conduction, convection, and evaporation; (2) genetic changes in mitochondrial enzymes; (3) increased heat production from muscle activity, as from an unusual reaction to succinylcholine; (4) endocrine or musculoskeletal abnormalities, such as myotonic dystrophy, pheochromocytoma, and thyrotoxicosis; (5) lesions of the central nervous system,

especially in the area of the anterior hypothalamus, or interference with the normal transmitter substances in this area; (6) the presence of infection, dehydration, hypoxia, antigen/antibody reactions, or abnormal liver enzymes; (7) introduction of pyrogens, perhaps causing physiologic alteration in body chemistry, as in uncoupling of oxidative phosphorylation.

An abnormality of the body's normal temperature-regulating system has been suspected in MHT, because of the rapid rise in body temperature and apparent collapse of the normal heat-losing mechanisms. The failure of the normal heat-losing mechanisms in their relation to environmental temperature, humidity, and the choice of anesthesia system used is explained by Clark,[7] who recorded temperatures at timed intervals on 212 patients undergoing operation and general anesthesia. He points out that radiation heat loss, while being the principal means of body heat loss at comfortable room temperature, becomes rapidly less effective above temperatures of 89°F, and is zero when room temperature equals skin temperature; the body can actually absorb radiant heat from bright overhead surgical lights or when the ambient room temperature exceeds skin temperature, and this may contribute to hyperthermia. Conduction, on the other hand, while ordinarily not an important means of heat loss, is the principal, most effective means of lowering body

temperature in the operating room, e.g., ice-bags, water-cooling mattresses, or the direct application or instillation of cold solutions in body cavities; body heat may be acquired in the operating room by patient contact to warm objects, such as the surgeon's hands. The amount of heat lost by convection, i.e., that heat lost by warming of the air that comes in contact with the body, was found by Clark to be quite small in most instances, and impaired by the presence of surgical drapes. Since fans are generally not permitted in the operating room, he doubted that loss of heat by forced convection would ever become acceptable as a means of lowering body temperature. In Clark's findings, evaporation through sweating at normal room temperature plays only a minor role in body heat loss; however, above 88-90°F, it is the principal means of heat loss, and above 94°F, it is essentially the sole means for normal body heat elimination. Heat loss through the evaporation of sweat is greatly retarded by high relative humidity, and in operating rooms which are not air conditioned, this may be an important factor in heat retention. Clark also mentions, as means of body heat loss, the water loss which occurs by the transudation of fluid through the skin, or insensible loss (capacity = 50cc'c/m^2/hr), and the loss of heat in respiration. In addition, there is loss of fluid by evaporation in body cavities and transudation of fluid

into injured tissues. The loss of heat in respiration is small and not of primary importance, but as Clark points out, should be considered in regard to the type of anesthesia system used and its effect on evaporation in the lung. A complete nonrebreathing system would not impede heat loss by water evaporation in the lung, whereas the inspired mixture in a complete rebreathing system would ordinarily be warmer and have a higher relative humidity, thus perhaps slightly decreasing heat loss by this mechanism. Postoperative hyperthermia has been reported where the sole cause was attributed to a faulty respirator which delivered air that was warmer than body temperature.[8]

In correlating heat retention and the failure of the normal heat-losing mechanisms in MHT, Saidman[6,9] gives as factors which cause a decrease in heat loss by evaporation: (1) the use of belladonna drugs; (2) the presence of certain exocrine anomalies (e.g., congenital absence of sweat glands); (3) patients with a short and stocky habitus; (4) high relative humidity; and (5) surgical drapes. Operating-room lights, poorly air-conditioned environment, and drapes are mentioned as factors which cause a decrease of heat loss by radiation or convection. According to Saidman, the normal heat-losing mechanisms are unable to get rid of the excess heat in MHT, and one of several factors may be the cause for the increased heat production:

(1) Various endocrinopathies, e.g. thyrotoxicosis and pheochromocytoma, will raise the metabolic rate and result in an increased heat production. (2) Any increase in muscular activity is accompanied by increased heat production, e.g. shivering in response to cold, struggling during light anesthesia, or the decreased compliance seen with certain anesthetics which represents an increase in muscular activity. (3) While general anesthetics in full dose abolish thermal regulatory power, they are not cooling agents as might be expected, and an abnormality of the central temperature regulating mechanisms in the anterior hypothalamus may be the basis for MHT. (4) Elevated temperature, which in itself results in increased metabolism and heat production, can further elevate temperature and metabolism.

Renwick and Hogg[10] relate the rate and amount of heat production by the body to the metabolic rate, and place 110°F as the critical point where the normal mechanisms will not take care of the excess heat and death will ensue unless artificial means to lower temperature are used. They list the following as factors of metabolism in MHT: (1) BMR--the basic metabolic rate is normally 40 cal./m^2/hr. (2) Muscular activity due to exercise or shivering can increase the metabolic rate of the body up to 150-200%. (3) Sympathetic activity can increase the metabolic rate to 50% above normal. (4) An increase in thyroxin production and activity

can double the metabolic rate. (5) As Saidman also pointed out,[6] an elevated temperature itself will cause an increase in the metabolic rate by increasing the metabolic heat production by about 7% for each degree Fahrenheit increase (Fig. 5); in this manner, there is a potentially vicious cycle, if the body's heat-losing mechanisms do not function to eliminate the excess heat production.

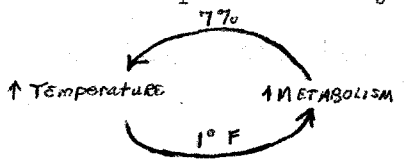

Fig. 5. Relationship of the mean Body Temperature to Metabolic Rate.

Renwick and Hogg suggest that the interference of the central heat-regulating mechanism may be the underlying cause for the increased body heat production seen in MHT. They support this argument by several observations. It is known that sweating is regulated by the anterior hypothalamus through impulses sent through the cord to the sympathetic outflow tract, and that pyrogens injected into the cerebral ventricles of animals will cause fever and shivering. For example, when serotonin is injected, shivering is produced, whereas the intraventricular injection of epinephrine or norepinephrine abolishes shivering. They point out that the concentration of serotonin, epinephrine, and norepinephrine is present in unusually high amounts in the hypothalamus. They theorize that because of these findings, body temperature may be a fine balance derived from

the release of serotonin, epinephrine, and norepinephrine in the anterior hypothalamus. According to this theory, when the body is exposed to cold, or the mean body temperature is lowered because of increased heat loss or decreased heat production, epinephrine and norepinephrine secretion would be decreased in the anterior hypothalamus; serotonin would be secreted in increasing amounts; peripheral vasoconstriction and shivering would take place, thus retaining and producing more heat. Were the temperature of the body to be elevated to normal by this mechanism, the release of epinephrine and norepinephrine would effect a stop in shivering and increase heat loss by peripheral vasodilatation. Renwick and Hogg suggest that the hypothalamus would retain its sensitivity to amines under general anesthesia, although temperature regulation is usually lost. Certain pyrogens could cause the release of amines, and may in this way explain the MHT seen under general anesthesia. They support this theory by observations of the pharmacological action of various anesthetic drugs injected intraventricularly in experimental animals. Pentobarbital causes an initial fall in temperature, followed by a rise to fever levels, and is associated with vigorous shivering, which is easily "turned off" by the administration of epinephrine or norepinephrine given intraventricularly. Similarly, other drugs have unusual effects when injected into

the cerebral ventricles, e.g. d-tubocurarine causes mydriasis, increase in blood pressure, shivering, increased respiratory depth and rate, and myoclonic jerks; acetylcholine will cause twitching and myoclonic movements.

Stephen[11] supports the theory that MHT may be caused by the introduction of certain drugs, or combination of drugs, which act as pyrogens in adjusting the thermostat of the hypothalamus upwards. He describes the regulation of body temperature as ultimately dependent not on receptors in the skin but on receptors in the hypothalamus, which respond to local temperature rises of 0.4° C or less by promoting skin vasodilatation, sweating, and increased respiration (e.g. panting), and to lowered body temperature by vasoconstriction and shivering. Stephen notes that some drugs may act on certain individuals as pyrogens which influence the release of serotonin, or render the hypothalamus more sensitive to it, thus perhaps causing marked elevations in temperature. He lists some substances which have been shown to be definitely pyrogenic: (1) 2,4 dinitrophenol (DNP), which has been shown to interfere with the formation of high energy bonds and which can lead to a lethal hyperthermia not unlike that of MHT. (2) Histamine, which causes an increase in body temperature, bronchospasm, and local reactions. It has also been shown

that there is a marked elevation of histamine and norepinephrine levels in plasma in hyperthermia. (3) It is known in some patients that succinylcholine is capable of causing an increase in body temperature by the release of histamine, as evidenced by urticarial wheals at the site of injection.

The possibility that there is an inherited sensitivity to certain drugs has been the focus of much interest in recent years. An unrecognized trait may underlie many cases of MHT. Denborough[12] described a local family in Melbourne, Australia, in which ten out of thirty-eight members who had received a general anesthetic died, apparently from the effects of the anesthesia. The family pedigree is outlined below (Fig. 6):

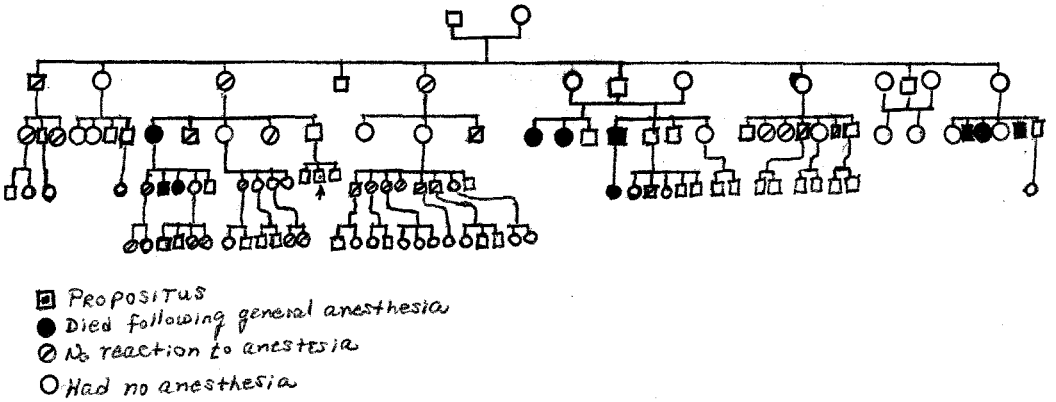

Fig. 6. Effects of Anesthesia in One Family

In all of the family members receiving general anesthesia, all but one received either ethyl chloride or ether; that one member received halothane, and

his case is well described. The patient was a 21-year-old male who was undergoing general anesthesia for a compound fracture of the tibia and fibula; the operative procedure was halted because of hypotension, elevated temperature, tachycardia, diaphoresis, and cyanosis. Consequent examination, including chest x-ray; EKG; urinary excretion of porphyrins, catecholamines, and corticosteroids; liver function studies; serum cholinesterase, proteins, calcium, phosphorus, and alkaline phosphatase, were all within normal limits. This patient had no untoward effects from subsequent injections of atropine and a procedure under spinal anesthesia. The sensitivity to anesthesia was regarded by Denborough as a familial inheritance of an incompletely penetrant dominant gene or genes.

The implication of succinylcholine in the etiology of MHT has been voiced by many observers.[13-18] In contrast to MHT, where pronounced muscle rigidity is observed, it has previously been shown that some persons show a marked over-reaction to the administration of succinylcholine by prolonged skeletal muscle flaccidity, and that these individuals have an atypical serum cholinesterase which has a very low affinity for hydrolyzing succinylcholine.[19] This condition is known to occur in 1:2800 (0.04%) of the population, and is gene-transmitted as the homozygous state; a

decreased cholinesterase activity is also noted in patients who are heterozygous for this gene and in those who have severe parenchymal hepatic disease or marked malnutrition. Certain drugs also inhibit serum cholinesterase; Dibucaine, because of its inhibiting effect, has been employed as a simple laboratory test to determine cholinesterase activity in plasma.

The apparent relationship between the administration of succinylcholine and skeletal muscular rigidity and hyperthermia is illustrated by several case reports in the literature. Cody[20] gives a case report of one patient who developed muscle rigidity following the administration of succinylcholine, and reviews the published reports of ten other cases with the same finding. He found that three of the total of eleven cases reviewed had known myotonia dystrophica. Seven of these cases were associated with hyperthermia, and all of the patients but two, both adults, had some musculoskeletal abnormality: retarded growth, scoliosis, etc. Cody concludes that unusual responses to succinylcholine may have occurred because the patients had early, undiagnosed myotonia dystrophica. He also feels that this is one cause for MHT.

Thut and Davenport[21] describe a case of fatal MHT in a five and one-half year old boy undergoing a tonsillectomy and adenoidectomy. They found the patient,

a "failure-to-thrive" case, in otherwise good health. The pre-operative status and induction were normal, until 15 mg of succinylcholine were administered, at which time violent generalized skeletal muscle spasm was observed; a further dose of 15 mg succinylcholine produced no change. The operative procedure was carried out, despite technical difficulty; but two hours later, hyperthermia, shock, and cardiac arrest appeared in rapid order, and in spite of all efforts to save him, the patient died. Thut and Davenport suggest that the hyperthermia was secondary to heat production from muscle rigidity, and that succinylcholine may have been the precipitating cause in the case described. They found no evidence at autopsy to support myotonic dystrophy as an underlying cause.

Lavoie,[22] in the same article, reports a case of MHT very similar to that described by Thut and Davenport. This occurred at the Maisonneuve Hospital in Montreal, where the patient was a 42-year-old, healthy, muscular male undergoing repair of a corneal wound under general anesthesia. The patient reacted to the succinylcholine (60 mg) with immediate sustained contractures of the jaw, neck and limbs, making intubation impossible. A further dose of succinylchone (60 mg) and decamethonium (4 mg), and an additional 100 mg Nembutal were given, and intubation was carried out in the next ten minutes.

Anesthesia was maintained with Fluothane-N_2O-O_2 in a partial rebreathing system, and the operative procedure went smoothly until forty-five minutes after induction, when the patient developed a rapid pulse (120), hyperthermia (107° F rectally), and consequently died following cardiovascular collapse.

Cullen[23] presented two cases of hyperthermia which show a possible connection with the use of succinylcholine. The first case, a thin, eight-year-old boy, had had a mild previous episode of hyperthermia postoperatively during hospitalization for splenectomy for traumatic rupture; on that occasion, he had received cyclopropane and succinylcholine drip. During the operation reported by Cullen, he underwent appendectomy under cyclopropane and succinylcholine drip. One hour postoperatively, he developed a rectal temperature of 107° F, but went on to recover completely. Cullen's second case involved a 32-year-old woman who had two procedures at the Queen Elizabeth Hospital in Montreal. The first procedure, a dilatation and curettage under Pentothal, Fluothane-N_2O-O_2 anesthesia, was uneventful. The second procedure was a total abdominal hysterectomy using the same agents plus the addition of a succinylcholine drip. Approximately one hour after induction, the patient went on the develop the clinical picture of MHT and died despite successful attempts to lower

body temperature and correct acidosis.

Relton[24] reported three cases of MHT occurring at Toronto's Hospital for Sick Children between June 1964 and December 1965, during which time 24,431 general anesthetics were given. The three patients presented, one of whom died, had developmental musculoskeletal abnormalities, the one having arthrogryposis, the second strabismus, and the third thoraco-lumbar scoliosis. The possibility of early or undetected myotonic dystrophy was considered, but a muscle biopsy taken from one patient was normal. All three cases showed marked skeletal muscle rigidity in association with the hyperthermia, and succinylcholine was implicated in the etiology of the hyperthermia, but was not a constant feature. All three had undergone previous operations under general anesthesia without any reported unusual outcome, and one patient had had two operative procedures while in the Toronto hospital during this time, one with and one without the administration of succinylcholine, and a MHT-like picture developed on both occasions. Relton concluded that succinylcholine was not the only cause for MHT.

In a recent article, Harrison[25] and his colleagues attempted to reproduce MHT without giving succinylcholine. They took thirty-four healthy six-to-eight-week-old Landrace pigs, weighing from 35 to 40 kg,

starved them for sixteen hours, and then anesthetized them, using N_2O (6 l), O_2 (3 l) and 1-3% halothane. They were able to reproduce an MHT-like course in six out of the thirty-four animals, all six of which expired. They concluded that succinylcholine is not the etiological factor, or the only one, which could produce the clinical picture of MHT, and instead, pointed out that since the pigs had received only N_2O, O_2, and halothane, there is probably a correlation between MHT and a fluorinated hydrocarbon (halothane) or N_2O. Harrison did not relate the fatal course of the six pigs to the general condition of the animals, which had been starved for sixteen hours; and we do not know their relative state of hydration. However, it would appear that some other factor than succinylcholine is present which causes MHT to develop.

Other agents used during general anesthesia, e.g. atropine, scopolamine, have been suggested as pyrogens responsible for MHT,[26-30] but they have generally not gained support because of the variability of agents used in general anesthesia and the absence of many of these suspected pyrogens in cases of recorded MHT. From a review of the MHT cases reported in the literature, it can be seen that there is no one agent, even a hologenated hydrocarbon, which is found in all instances. Therefore, MHT may develop after receiving a number of different drugs or anesthetic agents,

and we could expect that it should not be limited to anesthesia alone.

Several drugs, or combination of drugs, which are used outside of general anesthesia, can produce hyperthermia. Psychotherapeutic drugs which have specific biochemical effects on the central nervous system can bring about a hyperthermia not unlike that reported with anesthetics, even accompanied by muscle rigidity.[31] The similarity of MHT can be compared to a case reported by Bowen,[32] where a patient developed a fatal hyperthermia as a result of taking an imipramine derivative and MAO inhibitor simultaneously:

> . . . She gradually became comatose and showed signs of sympathetic over-stimulation with dilated pupils, flushed skin, perspiration, and rigid legs with ankle clonus. Her pulse was regular at 150, B.P. 130/70 mm Hg, temperature 40°C (104° F), and her respiration was shallow with increasing cyanosis . . . she had been taking phenelzine, desipramine, and chlorpromazine. She was transferred to a general hospital, where she died at 5 p.m. the same day. . . .

One substance, 2,4 dinitrophenol, has been shown, in laboratory animals, to produce a pathological process unmistakably similar to MHT in time and progression. Its method of action has been shown to be brought about by the uncoupling of high-energy bonds. This same method of action has become an attractive and popular theory for the cause of MHT. In 1966 Wilson[33] attempted to prove that certain anesthetic agents may act as "triggering substances"

to set off the uncoupling of oxidative phosphorylation and produce an MHT-like course. He took fifteen healthy adult mongrel dogs and anesthetized each of them with sodium pentobarbital 30 mg/kg intravenously and oxygen in a nonrebreathing system, and then again with halothane and oxygen in a nonrebreathing system, each time measuring complete cardiovascular, respiratory and blood gas parameters, as well as core temperatures under environmental temperature control. The dogs were then given DNP 5 mg/kg, and the animals were reanesthetized in the same manner. No significant difference was found between the two pentobarbital groups ($P = 0.4$), but in comparing the pentobarbital series with the halothane series there was a significant correlation ($P = 0.001$), and four of the animals died from the hyperthermia produced with halothane anesthesia after sensitization with DNP. Wilson concluded that a similar process could occur in MHT: Certain individuals who were sensitized, by whatever means, to the uncoupling process would develop an MHT-course when given halothane, and perhaps other anesthetic drugs as well.

The uncoupling of oxidative phosphorylation provides a consistent theory for the etiology of MHT, and several other substances besides DNP--viz., fluorinated compounds,[34] salicylamide derivatives,[35] and catecholamines,[36] have been reported to uncouple

high-energy bonds if administered in sufficient doses. However, the uncoupling process is not thought to occur in such hypermetabolic states as pheochromocytosis, thyrotoxicosis,[37] or diabetic ketosis; and D.R. Challoner[38] has suggested that these hypermetabolic states may be initiated through metabolic pathways that are not associated with high-energy phosphate metabolism. Therefore, the uncoupling process may not be present in such a hypermetabolic state as MHT either, or else it may be but one cause of many for hyperthermia.

Certainly, the direct administration of bacteria or toxins, by means of contaminated equipment or solutions, could bring about post-operative hyperthermia. Modell[39] reported, in 1966, the occurrence of six such instances of hyperthermia in patients undergoing operations at the United States Naval Hospital Hospital in Pensacola, Florida. In each instance, the hyperthermia developed from within one to two hours after emergence from general anesthesia, and was accompanied by hypotension and tachycardia. Blood cultures in five of the six patients grew out Alcaligenes fecalis; the sixth patient, who had a negative blood culture, had been treated preoperatively with antibiotics, because of a diagnosis of septic abortion. Although all six patients presented the same general features as MHT, they responded well to artificial

cooling methods and vasopressor drugs, and all recovered. The source of contamination was traced to four diluted solutions of Anectine, all prepared from the same package. The report of Modell is not characteristic of MHT. Instead of encountering an occasional case of hyperthermia, six such cases were seen within a short space of time; the appearance of hyperthermia did not occur until one to two hours after emergence from the anesthetic, and the temperatures of the patients were not as high as usually found in MHT, ranging only from 101-105°F; there were no reported difficulties with the induction or during the administration of general anesthesia, and it was only after the patient was awake in the recovery room that the hyperthermia was noted. While infection has occurred in several instances where inhalors and anesthetic equipment have been used,[40] many cases of MHT on record have failed to show positive cultures from equipment or solutions used, and contamination is not generally regarded as the etiology for MHT as it is usually described.

The mortality of malignant hyperthermia is understandably high, in light of the complications of acidosis, hypovolemia, hypotension, hypoxia, and dehydration seen during its course. In the patients who have recovered, a great number of remedies have

been employed; but certain steps should be taken in every full-blown case of MHT. (1) Rapid and effective cooling is necessary and must be initiated promptly; the pouring of diethyl ether or ethyl chloride directly on the skin,[24] packing the patient in ice,[6,11] installation of cold solutions (Ringer's or ice water) into the peritoneal cavity,[6,11] and ice water enema[11] have all been tried and have met with relatively good success in effectively lowering body temperature. The addition of chlorpromazine intravenously has been suggested as a means of decreasing shivering and at the same time increasing peripheral circulation.[6,24] (2) Hypoxia should be corrected by hyperventilation with 100% oxygen.[1,6,10,11,24] This should bring about increased arterial saturation and lowering of the elevated p_aCO_2. It is also suggested that the patient be placed immediately on a complete nonrebreathing system,[6] which might help lose heat through the lungs. Anesthesia may be maintained, as with halothane, since the O_2 delivered reaches nearly 100%, but the addition of even 25% N_2O may represent hypoxia if there is significant shunting.[6] (3) Large quantities of Lactated Ringer's is the treatment of choice for hypovolemia,[6] which is probably both intravascular and interstitial. The central venous pressure should be monitored to prevent overloading the circulation. (4) Acidosis may be of such a degree as to require large doses of intravenous sodium

bicarbonate. Steps to reduce acidosis should be taken immediately, and repeated arterial blood gas determinations for pH and pCO_2 should be made.[6,11] (5) If there is evidence of increased intracranial pressure after return to a normal temperature, some means of lowering this pressure, e.g. intravenous mannitol, urea, or hypertonic saline, should be used.[6,10] (6) Any known contributory factors, such as infection, should be treated. If hypotension is severe, vasopressor or cardiac stumulator drugs may be necessary, and if muscle rigidity is present, the use of curare has been suggested.[11]

The prevention of MHT is difficult, because many of its complications are already present before the elevation in body temperature is evident. Factors which should arouse suspicion, namely, an unusual anesthetic history, failure of succinylcholine to relax voluntary muscles, or any observed rise in body temperature during the course of general anesthesia, are not uncommon and never easy to evaluate. Perhaps the key to the prevention of malignant hyperthermia lies in the word "vigilance," which is inscribed in the seal of the American Society of Anesthesiologists. The ultimate prevention of this often fatal process awaits a better understanding of its nature.

SUMMARY:

From the above material it can be seen that no one etiology has as yet adequately explained the occurrence of malignant hyperthermia. It is usually seen in young, healthy individuals who are often undergoing an elective operation, and is manifested a variable time after induction of general anesthesia by a rapid and profound elevation in temperature, muscle rigidity, and acidosis. An abnormality of the central heat-regulating mechanism in the anterior hypothalamus, an unusual response to succinylcholine or other anesthetic agent, an underlying endocrine or musculoskeletal disorder, a gene-transmitted phenomenon, bacteremia, the uncoupling of oxidative phosphorylation, and possible failure of the normal body heat-losing mechanisms--all these have been suggested as causes for malignant hyperthermia. The treatment of MHT requires the immediate lowering of body temperature and correction of acidosis, but the complications of the often-fatal process are usually present when elevation in body temperature is first observed. There are few warning signs of impending MHT, and recognition rests on the perception and alertness of the anesthesiologist.

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