Medicine Grand Rounds
Parkland Memorial Hospital
September 5, 1974

MALIGNANT HYPERTHERMIA

Malignant Hyperthermia - A pharmacogenetic disease occurring during general anesthesia with strong inhalation anesthetics, usually in conjunction with muscle relaxants, characterized by rapid rise of body temperature to extreme levels and rigidity of skeletal muscles.

History:

In the first edition of Guedel's book, Inhalation Anesthesia (1937) - six cases are described.

1940 - Report of a case (2).

1960 - The start of modern recognition of the syndrome. Denborough and Lovell described a family with a propensity to anesthetic deaths associated with hyperthermia (3).

By 1970, almost 200 cases had been recorded (4).

1. Guedel, A.E. Inhalation Anesthesia. New York, Macmillian, 1937, p. 133.

2. Burford, G.E. Hyperthermia following anesthesia. Anesthesia 1:208, 1940.

3. Denborough, M.A. and Lovell, R.R.H. Anesthetic deaths in a family. Lancet 2:45, 1960.

4. Britt, B.A. and Kalow, W. Malignant hyperthermia: A statistical review. Can. Anesth. Soc. J. 17:293, 1970.

5. Gordon, R.A. History of the syndrome of malignant hyperthermia. In: International Symposium on Malignant Hyperthermia. Eds., R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill., 1973, p. 5.

Clinical Description:

1) In a typical case, both succinylcholine and halothane are used.

2) First abnormality may be increased muscle fasciculation following succinylcholine injection.

3) In many cases, rigidity of maseter muscles noted after succinylcholine injection.

4) After induction, most consistent early signs are unexplained tachycardia, tachypnea, flushing of the skin. (Temperature has already risen at this point.)

5) Mottled cyanosis of the skin. Venous blood darkened. Excessive sweating. Hot CO_2 cannister. Hot patient. (Temperature in the 40-43° C range.)

6) Blood Chemistries. An acidosis: Lactate and pyruvate increased (seldom have excess lactate). Respiratory acidosis: Serum phosphorus, magnesium increased. Blood glucose increased. Uric acid probably up. Severe elevation of serum potassium concentration (well into the cardiotoxic range). Late fall in P_2O_2.

7) Myoglobinuria usually occurs; seldom have oliguric renal failure in surviving patients. Intravascular coagulation may occur.

8) Without therapy, death occurs at about one hour or before. Usually preceded by cardiac arrhythmias. Mortality somewhere between 60-70%.

Roughly equal male-female incidence.

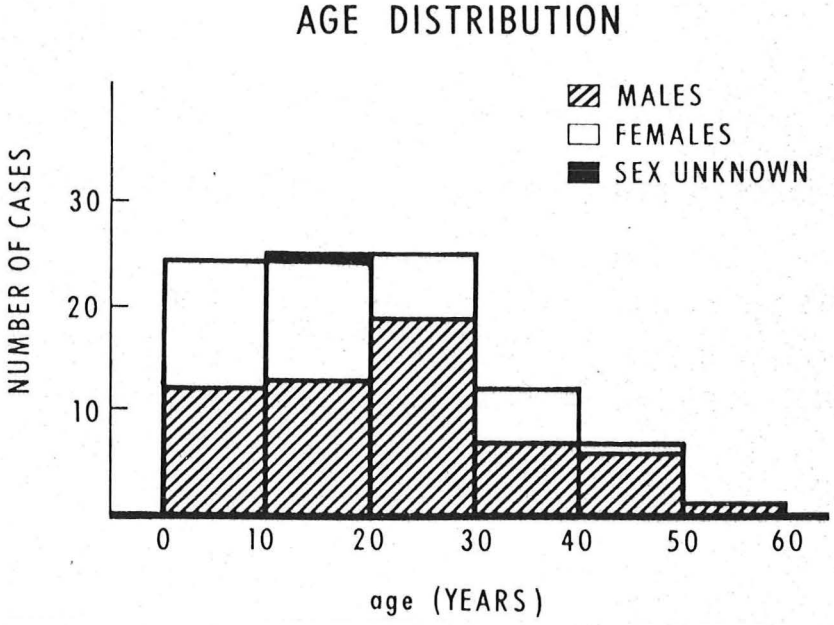


Figure 1 (From reference 4)

Musculoskeletal disorders are common in susceptible patients. Many are undergoing orthopedic operations at time of hyperpyrexia.

Kyphoscoliosis
Herniated Nucleus Pulposis
Congenital Hernia
Strabismus
Congenital Ptosis

These disorders appeared in about 25% of the first 100 cases. However, the incidence rate of these disorders is about 20% in the population (4). (See references 34 and 35).

Incidence:

Actual calculation has only been made one time (4).

In 74,000 children and teenagers in Toronto's Hospital for Sick Children, the incidence was 1:14000. (95% confidence limits 1:7000 and 1:4000).

There are large case loads, however, that have reported no incidence of hyperthermia.

Malignant hyperthermia has been seen in all races.

6. Britt, B.A. and Kalow, W. Hyperrigidity and hyperthermia associated with anesthesia. Ann. N.Y. Acad. Sci. 151:947, 1968.

In this early report, Britt and Kalow first introduced the concept that there were "rigid" and "non-rigid" patients with anesthetic induced hyperthermia. They still insist upon this distinction. (See reference 92 They believe that rigid may be one disease, and non-rigid another, with fundamentally different genetic lesions.

7. Britt, B.A. and Gordon, R.A. Three cases of malignant hyperthermia with special consideration of management. Can. Anesth. Soc. J. 16:99, 1969.

Of the three cases, 2 fatal.

Points out the importance of temperature correction in measurements of blood pH and pCO_2 in these patients.

Rosenthal's equation for correction of pH to body temperature:

(a) $pH_t = pH_{37} + 0.0147\ (37-t)$

Siggarad-Andersen's correction for pCO_2:

(b) $pCO_{2_t} = \text{antilog}\ (\log pCO_{2_{37}} - 0.21\ (37-t))$

(a) Rosenthal, T.B. The effect of temperature on pH of blood and plasma *in vitro*. J. Biol. Chem. 173: 25, 1948.

(b) Siggaard-Andersen, O. The XYZ of blood acid-base chemistry. Proc. Assoc. Clin. Biochem. 2:137, 1963.

It can be seen that if possible, it is easier to set the pH and pCO_2 to the patient's body temperature. There are also theoretical reasons why this is better than any type of correction.

8. Beldavis, J., Small, V., Cooper, D.A., and Britt, B.A. Postoperative malignant hyperthermia: A case report. Can. Anesth. Soc. J. 18:202, 1971.

One of the best case reports in that laboratory data was collected early in the course. Somewhat unusual patient in that hyperthermia did not begin until almost 1 1/2 hours of anesthesia. Temperature reached 112° F. With onset, urine turned red. First blood drawn showed pCO_2 70 mmHg, pH 7.04 and serum $[K^+]$ of 6.8.

9. Wilson, R.D., Dent, T.E., Traber, D.L. et al. Malignant hyperpyrexia with anesthesia. J.A.M.A. 202:111, 1967.

The report covers 12 instances of malignant hyperthermia seen at Galveston and discusses the 28 patients in the literature at that time. One of the first to point out the similarity of these patients to laboratory animals that had received agents for uncoupling oxidative phosphoration.

10. Gibson, J.A. and Gardiner, D.M. Malignant hypertonic hyperpyrexia syndrome. Can. Anesth. Soc. J. 16:106, 1969.

Report of two fatal cases in children with rather typical courses. In one, D-tubocuramine had no effect on established muscle rigidity.

11. Stephen, C.R. Fulminant hyperthermia during anesthesia and surgery. J.A.M.A. 202:106, 1967.

Review of the syndrome with the presentation of a child that recovered.

12. Denborough, M.A., Forster, J.F.A., Hudson, M.C. et al. Biochemical changes in malignant hyperpyrexia. Lancet 1:1137, 1970.

Stresses the rise in serum phosphorus and potassium concentration together with the fall in total serum calcium concentration. Notes that serum CPK can be very high. SGOT and LDH also elevated.

13. Arens, J.F. and McKinnon, W.M.P. Malignant hyperpyrexia during anesthesia. J.A.M.A. 215:919, 1971.

It is difficult to tell, but syndrome was probably recognized early. Nevertheless anesthesia and surgery were continued. The patient did recover, however, after an episode of oliguric renal failure which the authors almost certainly misdiagnosed as cortical necrosis.

14. King, J.O. and Denborough, M.A. Malignant hyperpyrexia in Australia and New Zealand. Med. J. Aust. 1:625, 1973.

Between 1955 and 1971, there were 16 cases in Australia and 3 in New Zealand. Only 2 gave a history of anesthetic deaths. Rigidity was present in 15 cases. 12 patients died (63%).

15. Newson, A.J. Malignant hyperthermia: Current trends in treatment. New Zealand Med. J. 77:81, 1973.

Somewhat behind in treatment, but a good review nevertheless. Stresses the occurrence of congenital musculoskeletal defects in these patients.

16. Relton, J.E.S., Britt, B.A. and Steward, D.J. Malignant hyperpyrexia. Brit. J. Anaesth. 45:269, 1973.

17. C.R. Stephen. Typical cases of malignant hyperthermia. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 11.

Other types of fever during or following anesthesia:

Ether convulsions - No doubt some of these cases were true malignant hyperthermia.

18. Morio, M. and Kohana, G. Ether convulsion and malignant hyperthermia during anesthesia. Hiroshima J. Anesth. 7:1, 1971.

These authors investigated case histories of so-called ether convulsion and found that many were no doubt associated with high environmental temperature. Concluded that less than half of these older cases were the result of the malignant hyperpyrexia syndrome.

19. Conn, J.W. and Seltzer, H.S. Spontaneous hypoglycemia. Am. J. Med. 19:460, 1955.

20. Tornblom, N. Hyperinsulinism with fatal postoperative hyperthemia. Acta. Med. Scand. 170:757, 1961.

The post surgical fever following removal of an insulinoma can be both malignant and fatal. Its cause is not altogether clear but does not appear related to malignant hyperthermia.

Likewise, fever following pheochromocytoma surgery appears to be more of a result of "physiological uncoupling" and not kin to malignant hyperthermia.

21. Solomons, C.C. and Myers, D.N. Hyperthermia of osteogenesis imperfecta and its relationship to malignant hyperthermia. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 319.

22. Aldrete, J.A., Padfield, A., Solomon, C.C. and Rubright, M.W. Possible predictive tests for malignant hyperthermia during anesthesia. J.A.M.A. 215:1465, 1971.

There has occurred, during surgery, mild fever in patients with osteogenesis imperfecta - nothing like the syndrome of malignant hyperthermia. The above authors, however, have noted increased serum pyrophosphate concentrations in: 1) patients with osteogenesis imperfecta; 2) patients with malignant hyperthermia; and 3) family members of patients with malignant hyperthermia.

Genetics:

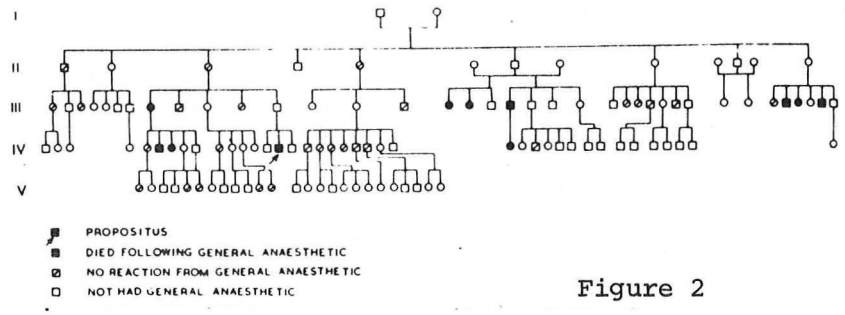


Figure 2

The family depicted above was that reported by Denborough et al. (23). The report grew out of studies of their original patient with malignant hyperthermia (3).

There are now many large pedigrees for malignant hyperthermia. The following short pedigree shows the associated elevated CPK serum levels in one family reported by Kalow and Britt (24).

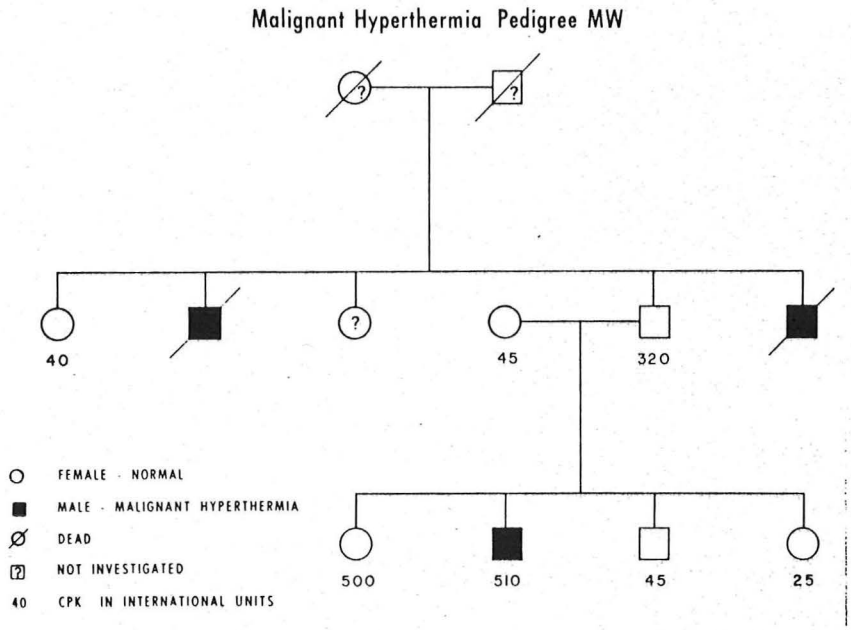


Figure 3 (From reference 4)

23. Denborough, M.A., Forster, J.F.A., Lovell, R.R.H. et al. Anesthetic deaths in a family. Brit. J. Anaesth. 34:395, 1962.

24. Kalow, W. and Britt, B.A. Inheritance of malignant hyperthermia. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 67.

The evidence is overwhelming that malignant hyperthermia is inherited as an autosomal dominant trait.

25. Britt, B.A., Locher, W.G. and Kalow, W. Hereditary aspects of malignant hyperthermia. Can. Anaesth. Soc. J. 16:89, 1969.

This paper presents the Wisconsin Family (CW) with arguments for and against various types of inheritance. The conclusion reached is an autosomal dominant type inheritance

26. Barlow, M.B. and Isaacs, H. Malignant hyperpyrexial deaths in a family. Brit. J. Anaesth. 42:1072, 1970.

27. Isaacs, H. and Barlow, M.B. The genetic background to malignant hyperpyrexia revealed by serum creatine phosphokinase estimations in asymptomatic relatives. Brit. J. Anaesth. 42:1077, 1970.

These two papers report 3 fatal instances of malignant hyperthermia in a South African family and the finding of elevated CPK's in family members.

28. Isaacs, H. and Barlow, M.B. Malignant hyperpyrexia occurring in a second Johannesburg family. Brit. J. Anaesth. 45:901, 1973.

Four generations of a second South African family studied. One 14 year old male lived through two episodes of malignant hyperthermia.

29. Britt, A.B. Malignant hyperthermia: A pharmacogenetic disease of skeletal and cardiac muscle. New Eng. J. Med. 290:1140, 1974.

30. Wedley, J.R. and Jaffe, E.C. Malignant hyperpyrexia and the dental outpatient. Anaesthesia 28:46, 1973

Presents limited data from two families. Stresses the possible difficulty in obtaining an accurate family history. One family carried a letter stating that their members were probably allergic to ether - they didn't like to let this information out, even to doctors (or dentists).

With the genetic aspects of the syndrome well grounded and with the finding that family members, presumably susceptible family members, had high serum CPK's, several studies were reported concerning the value and meaning of CPK determination.

30a. Isaacs, I.W. and Barlow, M.B. Malignant hyperpyrexia during anesthesia; Possible association with subclinical myopathy. Brit. Med. J. 1:275, 1970.

Family members with no "clinical abnormality" rather frequently showed elevated serum CPK's. Several sudden and unexplained deaths had occurred in the family.

31. Isaacs, H. and Barlow, M.B. Malignant hyperpyrexia. Further muscle studies in asymptomatic carriers identified by creatinine phosphokinase screening. J. Neurol. Neurosurg. Psychiat. 36:228, 1973.

32. Zsigmond, E.K., Starkweather, W.H., Duboff, G.S. et al. Abnormal creatine phosphokinase isoenzyme pattern in families with malignant hyperpyrexia. Anesth. Analg. Curr. Res. 51:827, 1972.

Interestingly found that in affected individuals the nerve isoenzyme, BB > muscle isoenzyme, MB. In normal individuals the opposite is true.

Myopathy:

The families with the genetic defect allowing the development of malignant hyperthermia have been said to manifest a "subclinical" myopathy. It is clear, however, that in some instances the myopathy is far from subclinical. Moreover, when more than just the serum CPK is examined, rather frequent abnormalities of muscle are found.

Muscle Biopsy:

1. Most frequent abnormal finding is small fibers interspersed with normal size fibers.

2. Variable numbers of central nuclei.

3. Abnormalities of mitochondria (myelinization).

Although perhaps "sub-clinical" many patients with malignant hyperthermia have had irregular hypertrophy and atrophy of muscle groups.

As it stands at this time, there is no question of the existence of myopathy in many patients (probably, the Australian patients have the highest incidence), but there are families without any signs of myopathy, including elevated enzymes and abnormal muscle morphology.

33. Denborough, M.A., Ebeling, P., King, J.P. and Zapf, P. Myopathy and malignant hyperpyrexia. Lancet 1:1138, 1970.

This family must be said to have overt myopathy although perhaps not clinically severe.

34. King, J.O., Denborough, M.A. and Zaph, P.W. Inheritance of malignant hyperpyrexia. Lancet 1:365, 1972.

Among other musculoskeletal abnormalities, a number of patients with myopathy were found. One group with some members having myotonia congentia. Also studied were five young males with short stature, cryptorchidism, pectus carivatum, lumbar lordosis and thoracic kyphosis. These had similar facies. This description and photographs of the youths prompted the following letter in Lancet.

35. Pinsky, L. The XX-XY Turner phenotype and malignant hyperthermia. Lancet 2:383, 1972.

The author commented that in addition to the description given, the young men could be seen from their photographs to have, in one case, a low posterior hairline and a webbed neck. This constellation of physical abnormalities made him think of the XX-XY Turner phenotype or Noonan's syndrome.

36. Isaacs, H., Free, G. and Mitchell, J. Histological, histochemical and ultramicroscopic findings in muscle biopsies from carriers of the trait for malignant hyperpyrexia. Brit. J. Anaesth. 45:860, 1973.

In two South African families muscle histology would suggest a myopathy with neurologica factors - variation in muscle fiber size - activity at nerve endings showing both degeneration and regeneration. Also said to have noted mitochondrial and membrane abnormalities. Small fibers tended to be type 1. Central nuclei common.

37. Berhardt, D. and Schiller, H.H. Malignant hyperthermia under general anesthesia: Abnormal histochemical and electron microscopic muscle findings in combination with pathological serum CPK values evidencing existence of primary myopathy. Anesthesist (Berl) 22:367, 1973.

38. Schiller, H.H. Histochemical abnormalities of muscle in malignant hyperpyrexia. Z. Neurol. 203:265, 1973.

In these two abstracted articles, the authors report two families. In one, the muscle morphology is entirely normal. In the other, the most interesting finding is that by the Ca-EDTA method, decreased myofibrillan ATPase content was found.

39. Denborough, M.A., Dennett, X. and Anderson, R. McD. Central core disease and malignant hyperpyrexia. Brit. Med. J. 1:272, 1973.

From a member of a previously studied family, muscle biopsy showed clear evidence of central-core disease. Authors believe this lesion may have been seen but not appreciated in some of the Landrace pigs. Core found in 50% of type 1 fibers.

40. Harriman, D.G.F., Sumner, D.W. and Ellis, F.R. Malignant hyperpyrexia myopathy. Quart. J. Med. (New Series) 62:639, 1973.

41. Ellis, F.R., Keaney, N.P., Harriman, D.G.F. et al. Screening for malignant hyperpyrexia. Brit. Med. J. 3:559, 1972.

Because the serum CPK value varies markedly in family members, these authors suggest that in family members who require anesthesia, a motor point muscle biopsy be done and an *in vitro* test with halothane be used - contraction with the anesthetic means a susceptible patient.

Have noted clinically that family members, as well as patients, frequently display hypertrophy and/or atrophy of various muscle groups; frequently have diminished or absent deep tendon reflexes (may be unilateral), but in general, all are asymptomatic.

Thus far:

1) A reaction, during general anesthesia, consisting of rigidity and hyperthermia appears in some patients.

2) The tendency to susceptibility to this syndrome appears to arise from a pharmogenetic defect where the inheritance is autosomal dominant.

3) Many of the patients and family members have some evidence of at least a subclinical myopathy.

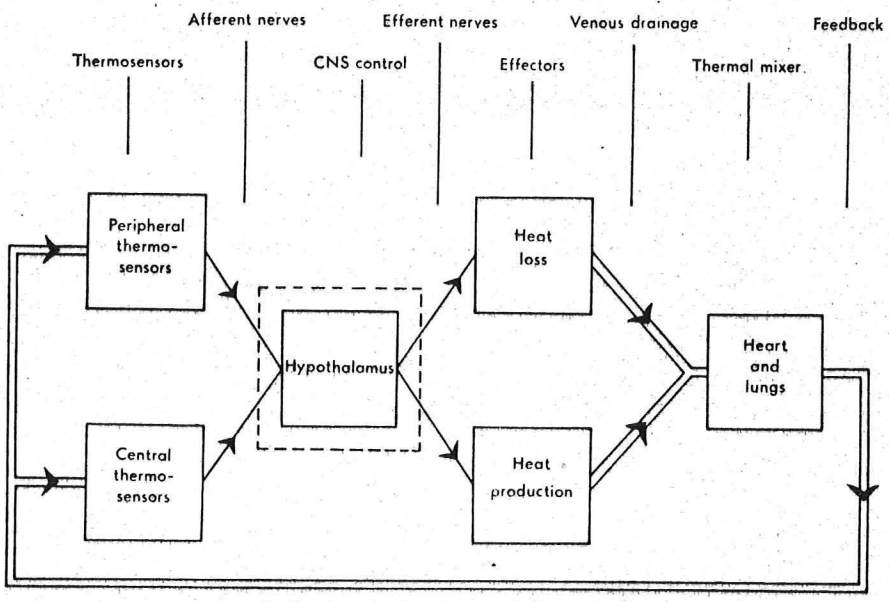
Need to evaluate mechanisms of hyperthermia and muscle rigidity.

1) Is hyperthermia central or peripheral?

2) From mode of inheritance might suspect a single protein defect - likely affecting cell membrane function.

3) Very likely lesion is neuromuscular or muscular.

Hyperthermia:



Single connecting lines indicate nervous pathways; double lines indicate circulatory pathways. The interrupted line round the hypothalamic component of the system represents the blood–brain barrier.

Figure 4 (From reference 42)

Most drugs affecting body temperature do so in reference to ambient temperature. Pyrogens effect temperature by resetting of the thermal regulatory "set-point". Drugs may release pretransmitters or transmitters (prostoglandins, acetylcholine, noradrenalin, 5-hydroxytrylophane) and thereby alter body temperature. Serious hyperthermia can occur with amphetamine type drugs and nomoamine oxidase inhibitors (43-45).

In most instances, hyponotic, sedative (usually in toxic doses) and general anesthetics tend to reduce the central control of body temperature. The individual is rendered essentially poikilothermic. Generally then, in these circumstances body temperature falls.

42. Cremer, J.E. and Bligh, J. Body temperature and responses to drug. Brit. Med. Bull. 25:299, 1969.

43. Borbély, A.A., Baumann, I.R. and Waser, P.G. Amphetamine and thermoregulation: Studies in the unrestrained and curarized rat. Naunyn-Schmiedeberg's Arch. Pharma. 281:327, 1974.

44. Weis, J. On the hyperthermic response to d-amphetamine in the decapitated rat. Life Sci. 13:475, 1973.

45. Krisko, I., Lewis, E., and Johnson, J.E. Severe hyperpyrexia due to tranylcypromine (Parnate) - amphetamine toxicity. Ann. Int. Med. 70: 559, 1969.

46. Benzinger, T.H. Clinical temperature: New physiological basis. J.A.M.A. 209:1200, 1969.

Most authors agree that the hyperthermia in malignant hypothermia is not central in origin.

Britt and Kalow give the following points as evidence against a central hyperthermia (47):

1) Absence of shivering

2) Triggering by relaxants

3) Observations on a limb under tourniquet (26, 48)

47. Kalow, W., Britt, B.A., Terreau, M.E. and Haist, C. Metabolic error of muscle after recovery from malignant hyperthermia. Lancet 2:895, 1970.

48. Satnick, J.H. Hyperthermia under anesthesia with regional muscle flaccidity. Anesthesiology 30:472, 1970.

> Although a patient developed all the signs of severe malignant hyperthermia, the muscles distal to a limb tourniquet remained flaccid throughout.

Although there is no doubt that the heat is produced peripherally, there is essentially no evidence either way to allow adequate evaluation of the role of the CNS in malignant hyperthermia. It would certainly not be surprising to find membrane defects in the CNS, genetically determined, similar to those suspected in peripheral tissues.

It would appear to be a reasonable assumption to conclude that marked heat production associated with muscle contraction together with some form of uncoupling of energy transduction and consequent increased heat production, alone or together, are responsible for the hyperthermia.

Muscle Physiology - A Review:

(Figures 5-10 from reference 49)

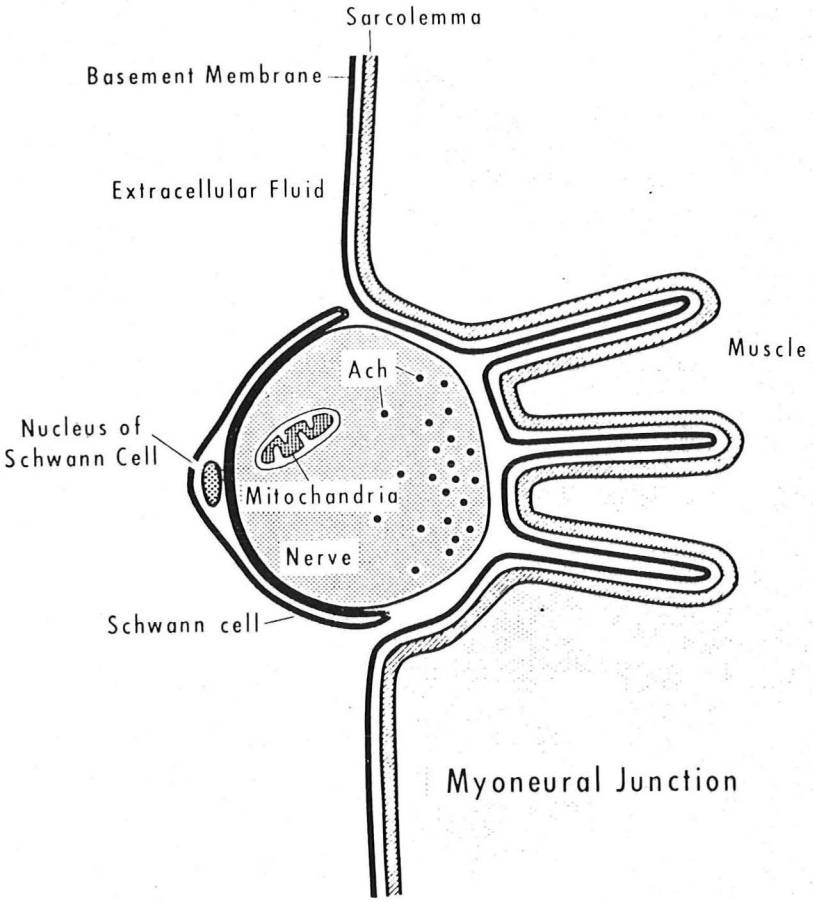
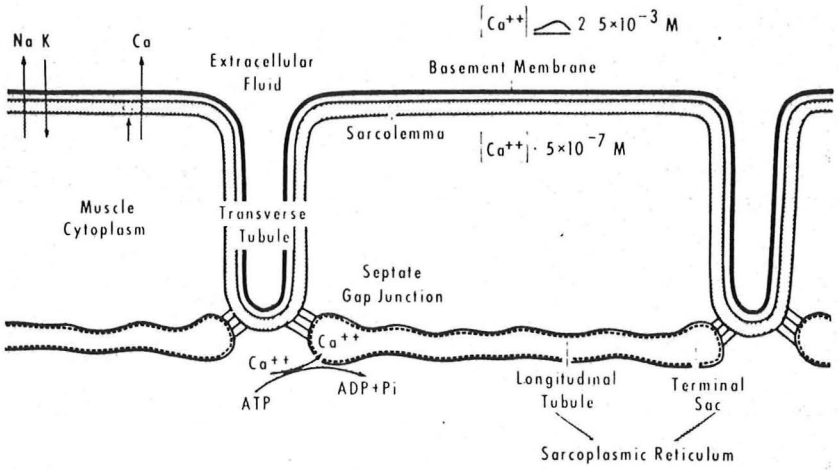
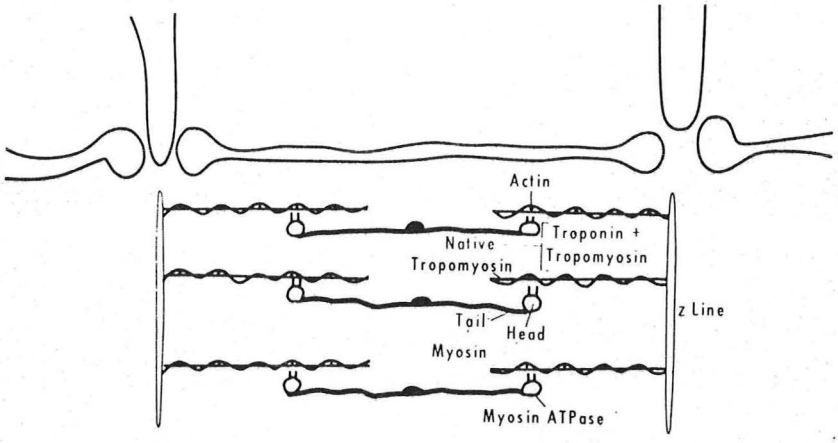


Figure 5



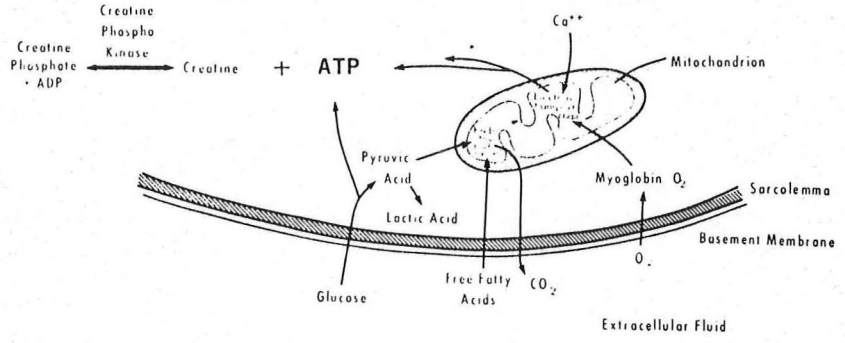
Sarcolemma and Transverse Tubules
Sarcoplasmic Reticulum during Muscle Relaxation

Figure 6



Myofibrils during Muscle Relaxation

Figure 7



The Mitochondrion and Ancillary Reactions

Figure 8

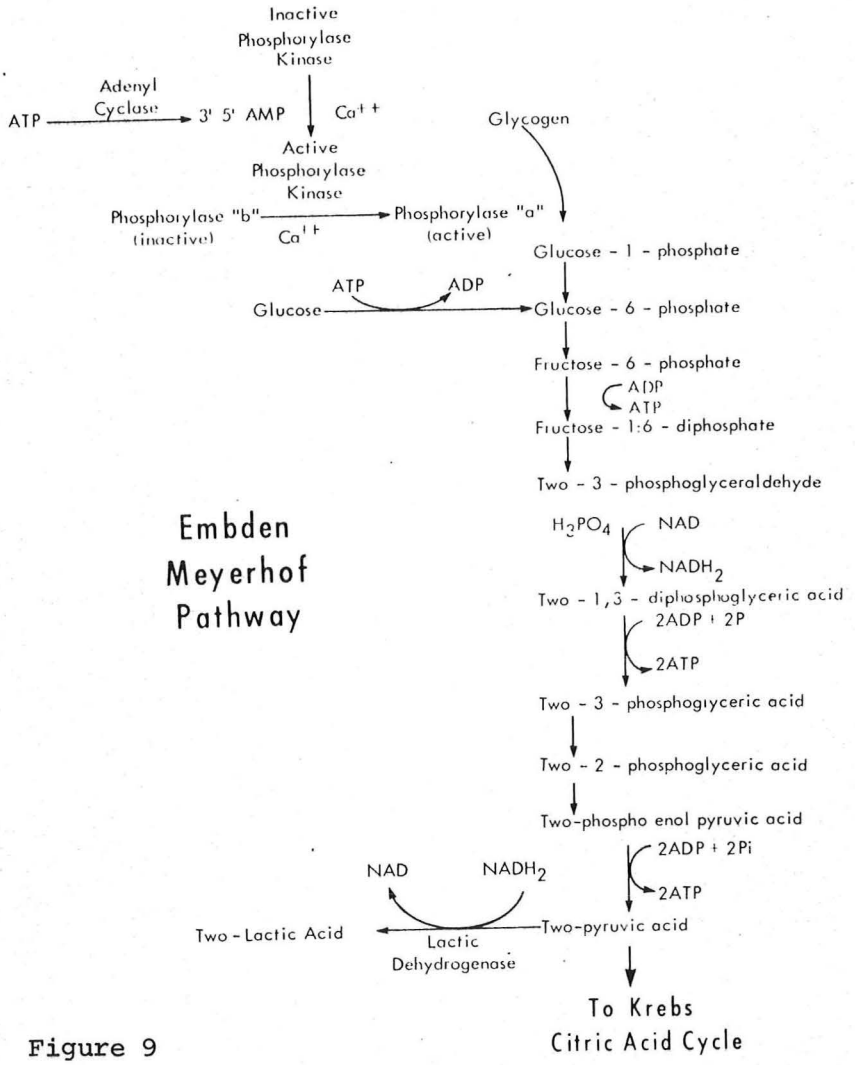


Figure 9

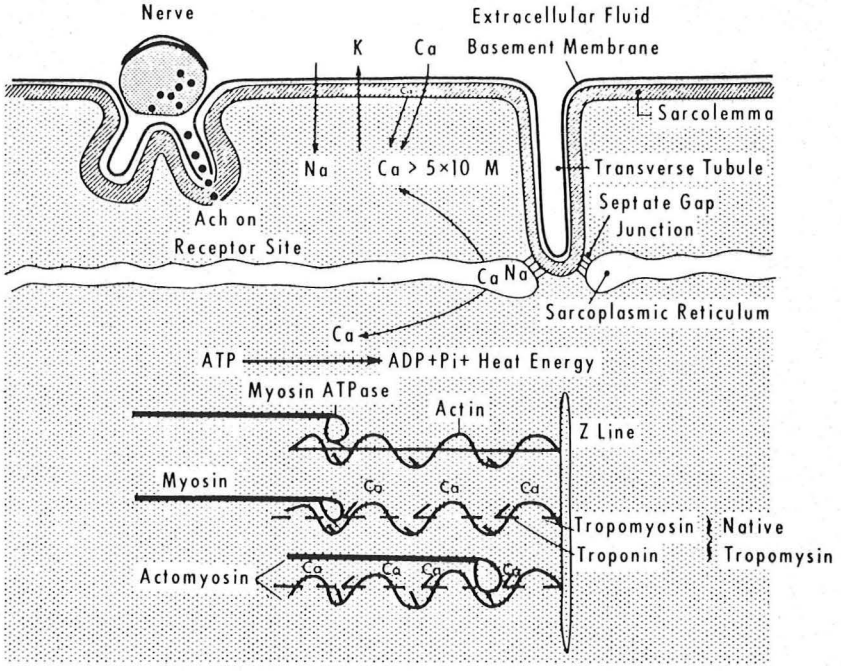


Figure 10

Muscle Contraction

49. Britt, B.A. Fundamentals of muscle structure and function. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 117.

This is the best short essay on muscle physiology written; it is almost totally correct. Although only 10 1/2 pages long, 183 references are cited.

50. Katz, B. Nerve, Muscle and Synapse. New York. McGraw Hill, 1966.

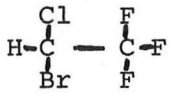
51. Bendall, J.R. Muscles, Molecules and Movement. New York. Heinemann Educational Books, 1969.

Two very fine, easily read, short books on muscle physiology.

Halothane - Succinylcholine:

Although more than half of the reported cases of malignant hyperthermia are associated with the use of halothane, well documented cases have occurred with all strong inhalation anesthetics.

Halothane, 2-Chloro, 2-Bromo, 1,1,1-Trifluoroethane,



is a simple halogenated aliphatic hydrocarbon with high fat solubility, almost insoluble in water (approx. 345 mg/100 ml - Merk Index). It is liquid to 51° C and is vaporized for use as an inhilation anesthetic. Generally in a gas mixture of 20% N_2O - 80% O_2 enough halothane is added to bring its concentration in the mixture to from 1 to 5%.

52. Brodkin, W.E., Goldberg, A.H. and Kayne, H.L. Depression of myofibrillar ATPase activity by halothane. Acta Anaesth. Scand. 11:97, 1967.

One of several reports that suggests that halothane can depress cardiac muscle contractility. Here the authors find that this is the result of decreased muscle fiber ATPase activity for both heart and skeletal muscle.

53. Zimmerman, H.J., Kendler, J. and Koff, R.S. Intraperitoneal halothane administration: Evidence of hepatic and muscle injury. Proc. Soc. Exp. Biol. and Med. 138:678, 1971.

Found that halothane, in large doses, released hepatic and muscle enzymes (skeletal and/or cardiac?).

Succinylcholine is a depolarizing neuromuscular blocking agent that, usually together with halothane, has been used in well over half the cases of malignant hyperthermia. Again, however, as with halothane, it does not appear to be an absolute essential to the production of malignant hyperthermia.

Normal Response to Succinylcholine:

1) Most of the drug is destroyed in blood stream or lung bed.

2) Some reaches motor end plates.

3) Attachment to receptor protein produces depolarization.

4) The muscle contracts.

5) The muscle relaxes.

6) The muscle remains depolarized until,

7) Residual succinylcholine is hydrolyzed.*

8) The muscle repolarizes.

*Malignant hyperthermia is not related to the disease characterized by deficient or atypical plasma or pseudocholinesterase where in a very long paralytic response to injected succinylcholine is seen. Like malignant hyperthermia, this disease is also a pharmacogenetically determined state (54,55).

54. Kalow, W. and Staron, N. On distribution and inheritance of atypical forms of human serum cholinesterase, as indicated by dibucaine numbers. Can. J. Biochem. Physiol. 35:1305, 1957.

55. Kalow, W. Succinylcholine and malignant hyperthermia. Fed. Proc. 31: 1270, 1972.

Beecher regarded succinylcholine as a toxin. That it is inately toxic is disputed by most pharmacologists and anestheseologists today.

56. Cooperman, L.H. Succinylcholine-induced hyperkalemia in neuromuscular disease. J.A.M.A. 213:1867, 1970.

57. Smith, R.B. Hyperkalemia following succinylcholine administration in neurological disorders: A review. Can. Anaesth. Soc. J. 18:199, 1971.

Succinylcholine is known to raise serum [K^+] to dangerously high levels in burn and severely traumatized patients. In addition, it causes a rise in potassium in patients with denervated muscle; a rise

apparently proportional to the muscle mass denervated, and inversely proportional to the length of time of denervation.

58. Theye, R.A. The effect of succinylcholine on canine gastroenemius muscle oxygen consumption. Anesthesiology 32:537, 1970.

Appears to solidly show that O_2 consumption increases 50-60%. Suggested reason: continued "firing" of the motor end plate.

59. Airaksinen, M.M. and Tammisto, T. Myoglobinuria after intermittent administration of succinylcholine during halothane anesthesia. Clin. Pharm. Therap. 7:583, 1966.

The year previously these authors reported ↑ serum CPK in ophthalmic surgery with halothane and repeated doses of succinylcholine. In this instance, out of 24 patients having this type of surgery, 7 had dark urine which almost certainly was the result of myoglobin. Patients given single doses of succinylcholine or repeated doses with anesthetics other than halothane did not show myoglobinuria.

60. Tammisto, T., Leikkonen, P. and Airaksinen, M. The inhibitory effect of d-tubocurarine on the increase of serum-creatine-kinase activity produced by intermittent suramethonium administration during halothane anaesthesia. Acta Anaesth. Scand. 11:333, 1967.

This is far from clearcut. Serum [K] rose even with curare. CPK did not, but perhaps there was one case of myoglobinuria in the curare group. See reference 61.

61. Perkoff, G.T., Abernathy, R. and Ruiz, M. Effect of succinylcholine on creatine phosphokinase (CPK) in anesthetized dogs. J. Lab. Clin. Med. 74:153, 1969.

In these experiments succinylcholine with halothane anesthesia (plus N_2O - O_2) resulted in elevated serum levels of CPK in dogs, much more marked in the female. (To think, we may have sex-linked motor end plates.) This result not blocked by d-tubocurarine. CPK fell with halothane alone.

There is one theory for the production of malignant hyperthermia based upon the action of depolarizing neuromuscular blockade. This is the proposal of Auerbach and his co-workers (62).

Postulate: The receptor protein for the motor transmitter (ACH) is genetically altered so that it becomes allosterically sensitive to depolarized (succinylcholine) state.

Sequence:

1) Succinylcholine attaches to receptor protein producing depolarization as in normal individual.

2) The muscle contracts.

3) The altered receptor protein can no longer bind succinylcholine.

4) The muscle relaxes.

5) The muscle repolarizes.

6) Repeat of steps 1 through 5 resulting in tentanic contraction until,

7) Residual succinylcholine is hydrolyzed.

62. Auerbach, V.H., DiGeorge, A.M., Mayer, B.W. et al. Rhabdomyolysis and hyperpyrexia in children after administration of succinylcholine. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 30.

Pigs:

There are, in several types of domesticated pigs, three recognized stress syndromes (63).

1) Porcine stress syndrome (PSS).

2) Pale, soft, and exudative pork (PSEP).

3) Malignant hyperthermia susceptible (MHS).

Breed	Syndrome
Danish Landrace	PSEP
English Landrace	PSEP
	MHS
Poland China	PSEP
	MHS
	PSS
American Landrace	MHS
Pietrain	PSS
	MHS
	PSEP

PSS - Induced by: Transportation, sudden increase in ambient temperature, mild exercise and fighting

Characterized by: Progressive tachypnea, rise in body temperature, alternative areas of blanching and erythema in the skin. Collapse and death with immediate rigor mortis.

PSEP - After slaughter, meat (loin especially) is noted to be soft, pale, and to contain an exudate.

MHS - Anesthetic induced hyperthermia with marked muscle rigidity resulting in rapid death (almost 100%) in < 60 minutes.

Syndromes may be essentially one in the same, but this is not certain. MHS is an excellent animal model for malignant hyperthermia in man. MHS is a genetic defect with autosomal dominant characteristics.

63. Nelson, T.E. Porcine stress syndromes. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 191.

MHS syndrome appears clinically indistinguishable from the human syndrome, but does appear to be more severe.

64. Short, C.E. and Paddleford, R.R. Malignant hyperthermia in the dog. Anesthesiology 39:462, 1973 (letter).

Three year old male "pure bred" pointer developed, with halothane anesthesia, a temp > 108° F and muscle stiffness with rapid death. Two siblings had modest elevations of serum CPK (3 others did not). Father may have had slight elevation.

65. Hadlow, W.J. Myopathies of animals. In: The Striated Muscle. Eds. Carl M. Pearson and F.K. Mostofi. Williams and Wilkins Co., 1973. pp 391-395.

A stress myopathy, seen in draft horses and in thoroughbred race horses appears to have a genetic background. Association with malignant hyperthermia is uncertain. High incidence of renal failure. Racing greyhounds likewise appear to have what may be a genetically determined stress myoglobinuria. In cattle and sheep there is an entity termed "Transport Myopathy" which appears to be similar to PSS in swine. Insufficient data are available to be certain, at this time, of relationship to malignant hyperthermia of these entities.

66. Holmes, J.H.G. and Ashmore, C.R. A histochemical study of development of muscle fiber type and size in normal and "double muscled" cattle. Growth 36:351, 1972.

    An inherited abnormality associated with stress induced lactate acidosis and muscle necrosis almost certainly not related to malignant hyperthermia syndromes.

The likelihood of human "stress syndromes" akin to malignant hyperthermia existing shall be discussed below.

67. Denborough, M.A., Hird, F.J.R., King, J.O. et al. Mitochondrial and other studies in Australian Landrace pigs affected with malignant hyperthermia. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 229.

    Mitochondria of MHS pigs react no differently to halothane than those from other pigs.

68. Berman, M.C., Harrison, G.G., Bull, A.B. and Kench, J.E. Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. Nature 225:653, 1970.

    Muscle glycogen - 0.56 to 0.20 gm/100 ml.

    ATP - 2.7 to 2.8 mg/100 ml.

    O_2 consumption rose 20-40% per °C rise in core temperature. Normal 12-18%/°C rise.

    CO_2 production disproportionately increased. RQ rises (to 1.69 in one experiment).

pO_2	350 to 200 mmHg
pCO_2	45 to 268 mmHg
pH	7.36 to 6.6

69. Jones, E.W., Kerr, D.D., Nelson, T.E. Malignant hyperthermia - observations in Poland China pigs. In: International Symposium Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 198.

    The clinical picture of malignant hyperthermia appears to be identical to that seen in the Landrace pig. Poland China pigs are more apt to show exercise stress, however (as are the Pietrain swine).

Figures 11-13 from reference 67.

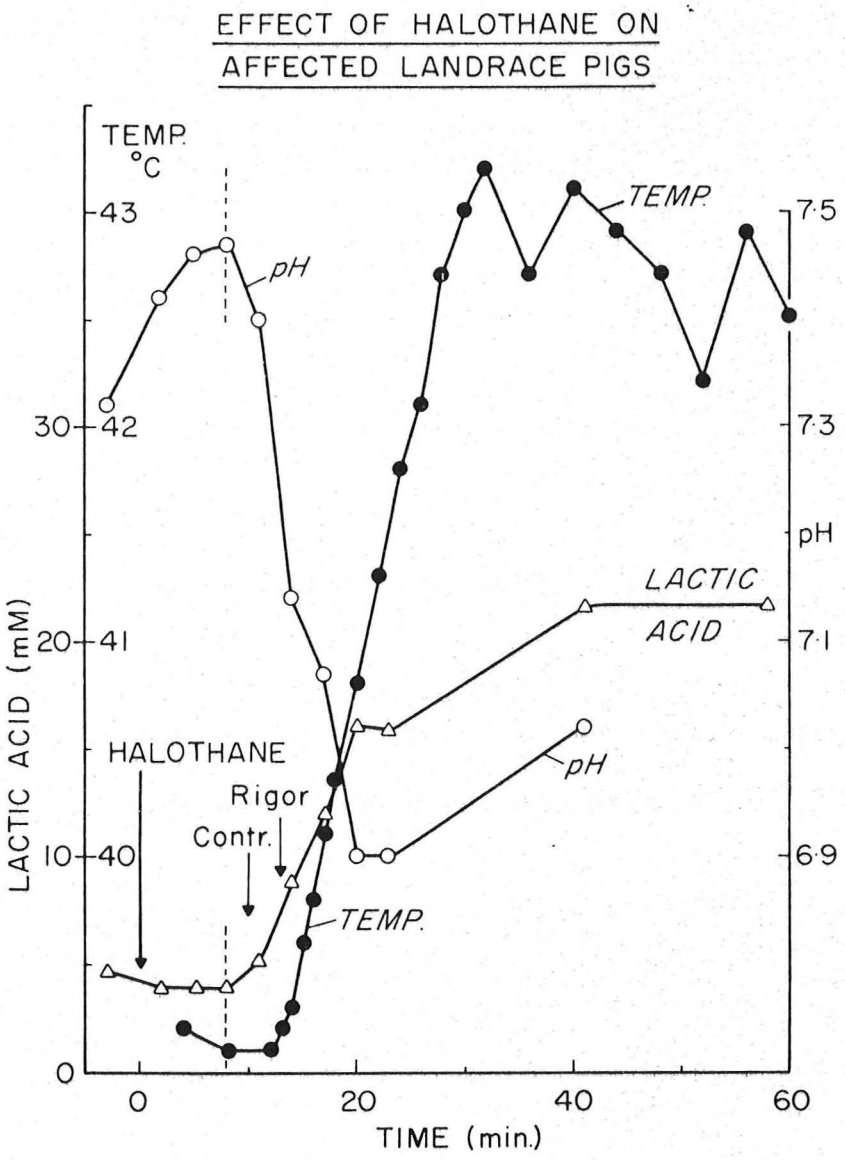


Figure 11

EFFECT OF HALOTHANE ON
AFFECTED LANDRACE PIGS

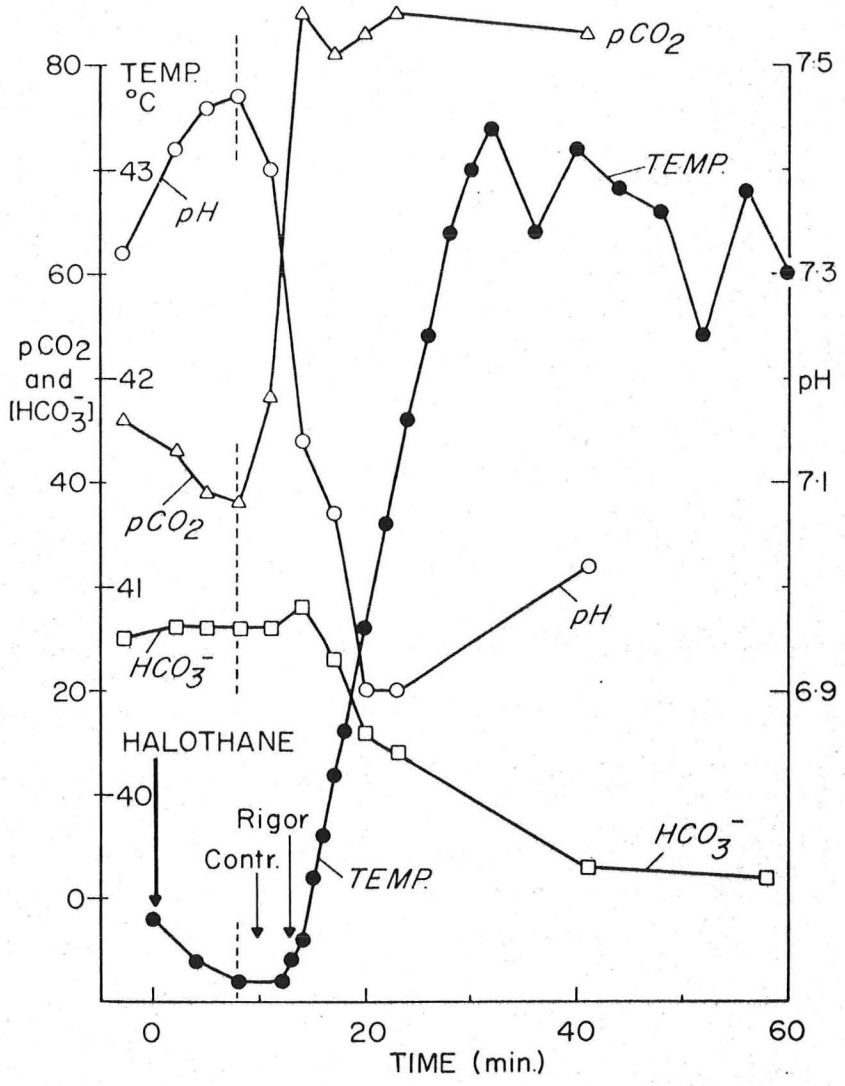


Figure 12

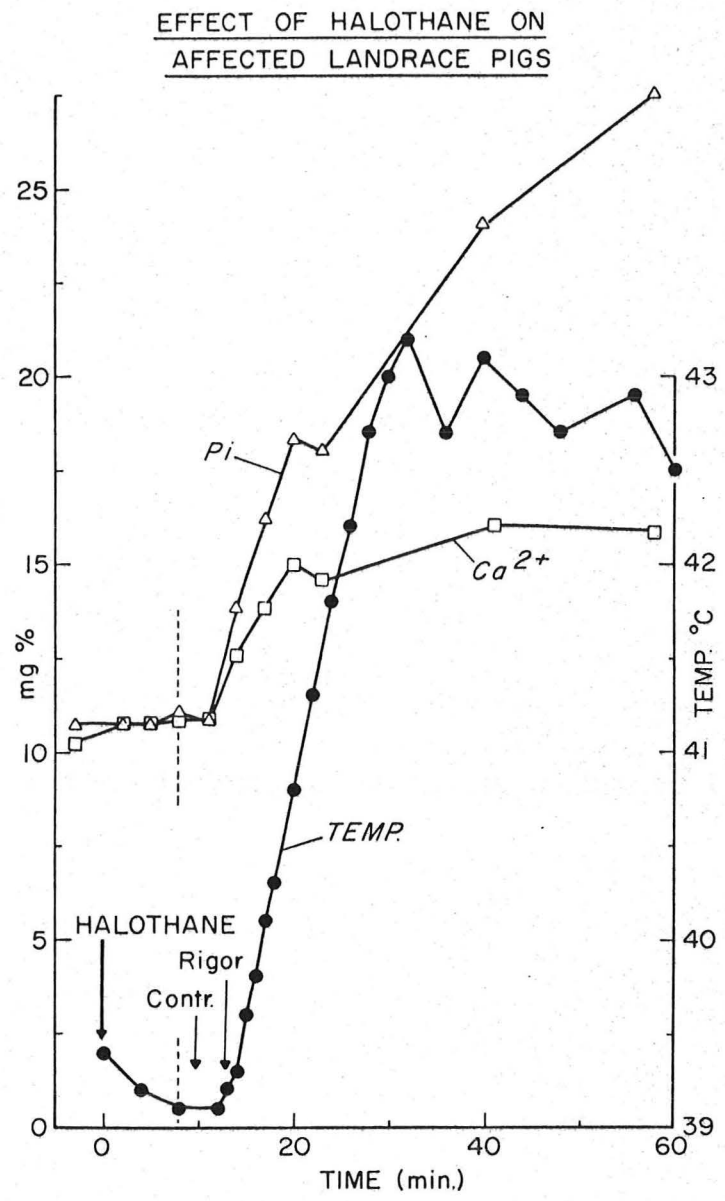

EFFECT OF HALOTHANE ON
AFFECTED LANDRACE PIGS
25
20
15
10
5
0
mg %
43
42
41
40
39
TEMP. °C
Pi
Ca 2+
TEMP.
HALOTHANE
Rigor
Contr.
0
20
40
60
TIME (min.)

Figure 13

Mechanisms of Malignant Hyperthermia:
(See also reference 62)

1) Uncoupling - A metabolic state characterized by increased O_2 utilization and CO_2 production with inefficient transduction of energy to useful work and therefore accompanied by the production of large amounts of heat.

Chemicals that produce uncoupling laboratory animals, cell suspensions, and/or isolated mitochondria are generally water insoluble, highly fat soluble weak organic acids (proton donors). 2,4-Dinitrophenol is more or less a prototype chemical. Inhalation anesthetics and neuromuscular blocking agents do not fit in this category.

Nevertheless, the striking, rapid rise of body temperature in malignant hyperthermia was recognized by Wilson and co-workers (reference 9) as being remarkably similar to the course of laboratory animals given Dinitrophenol.

70. Wang, J.K., Moffitt, E.A. and Rosevear, J.W. Oxitative phosphorylation in acute hyperthermia. Anesthesiology 30:439, 1969.

For a variety of reasons, these authors concluded that a DNP type of uncoupling was not a thermodynamically reasonable explanation for malignant hyperthermia. However, their reasoning might be open to criticism.

71. Britt, B.A., Kalow, W. and Endrenyi, L. Effects of halothane and methoryflurane on rat skeletal muscle mitochondria. Biochem. Pharmacol. 21: 1159, 1972.

Both these anesthetics, in fact, depressed O_2 uptake in mitochondria when at "clinical" concentrations. At higher concentrations methoryflurane showed some ability to uncouple.

72. Britt, B.A., Kalow, W. and Endrenyi, L. Malignant hyperthermia and the mitochondria in human patients. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 387.

Mitochondria from 3 patients and 4 normal controls showed much the same characteristics as rat mitochondria.

The conclusions from references 67 and 68 would also be that classical uncoupling of mitochondria is not brought about by halothane anesthesia even in susceptible animals. Moreover, uncoupling would not itself explain muscle contraction.

73. Gatz, E.E., Schoettger, J.D., Morgan, J.G., et al. Etiology and control of malignant hyperpyrexia. Fed. Proc. 30:442, 1971.

74. Gatz, E.E. The mechanism of induction of malignant hyperpyrexia based on *in vitro* to *in vivo* correlation studies. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 399.

Gatz is an outspoken proponant of uncoupling as the etiology of malignant hyperthermia. In the following reference, experiments were done to which Gatz was a party, that would seem to put his concepts of etiology to rest.

75. Kerr, D.D., Jones, E.W., Nelson, T.E. and Gatz, E.E. Treatment of malignant hyperthermia in swine. Anesth. Analg. Curr. Res. 52:734, 1973.

It was Gatz's contention that in uncoupled animals, hyperventilation with 100% O_2 drove oxidation and heat production and resulted in death. Here in 12 paired experiments, pigs undergoing malignant hyperthermia were hyperventilated with air or O_2.

Hyperventilation improved mortality, but there was no significant difference in mortality between air and O_2 ventilation.

75a. Brooks, G.A., Hittelman, K.J., Faulkner, J.A. and Beyer, R.E. Temperature skeletal muscle mitochondrial functions, and oxygen debt. Am. J. Physiol. 220:1053, 1971.

75b. Mitchelson, K.R. and Hird, F.J.R. Effect of pH and halothane on muscle and liver mitochondria. Am. J. Physiol. 225:1393, 1973.

The above two papers point out that when studied at the supposed intracellular conditions, (e.g., high temp, 45° C, and low pH) mitochondria have a markedly increased O_2 uptake. In the case of a low pH, the O_2 uptake is actually increased by halothane.

2) Catecholamine release - Only a mention can be made of this, but if it were true and significant, it could be that malignant hyperthermia was similar to amphetamine intoxication.

76. Hall, G.M. and Lister, D. Procaine and malignant hyperthermia. Lancet 1208, 1974 (letter).

These authors claim evidence in MHS pigs of high circulating catecholamines during hyperthermia induced by anesthesia. Their data, they say, are to be published later.

3) Substrate cycling of fructose-6-phosphate -

77. Newsholme, E.A. and Start, C. Regulation in Metabolism John Wiley and Sons, New York. 1973, pp 121-124.

78. Newsholme, E.A. et al. The activities of fructose diphosphatase in flight muscles from the bumble-bee and the role of this enzyme in heat generation. Biochem. J. 128:89, 1972.

Newsholme has proposed that the occurrance of the enzyme fructose-1,6-diphosphatase produces together with phosphofructokinase the possibility of a futile cycle:

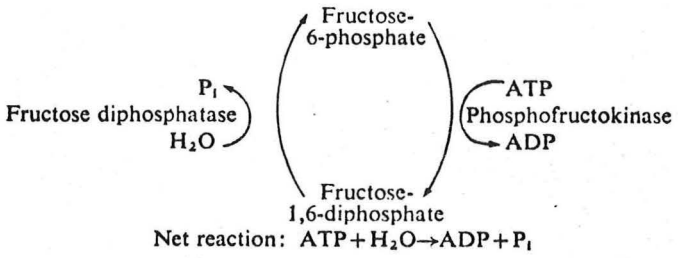


Figure 14

In the liver, and in muscle, this cycle might be a controlling influence on glucose metabolsim. He further proposed that in the breast muscle of the bumblebee, this cycle could be activated at rest to produce heat necessary for keeping flight muscles at 30°C, the temperature requirement they have for contraction.

79. Clark, M.G., Bloxham, D.P., Holland, P.C., and Lardy, H.A. Estimation of the fructose 1,6-diphosphatase-phosphofructokinase substrate cycle and its relationship to gluconeogenesis in rat liver *in vivo*. J. Biol. Chem. 249: 279, 1974.

80. Bloxham, D.P., Clark, M.G., Holland, P.C. and Lardy, H.A. A model study of the fructose dyphosphatas-phosphofructokinase substrate cycle. Biochem. J. 134:581, 1973.

81. Bloxham, D.P., Clark, M.G., Goldberg, D.M., Holland, P.C. and Lardy, H.A. The theoretical estimation of substrate cycling *in vivo*.. Biochem. J. 134:586, 1973.

Lardy and his co-workers devised methods that could quantitate the degree of substrate cycling in this system. With this method, the rate of substrate cycling was estimated in bumble-bees (82) and in the muscle of MHS pigs (83).

82. Clark, M.G., Bloxham, D.P., Holland, P.C. and Lardy, H.A. Estimation of the fructose diphosphatase-phosphofructokinas substrate cycle in the flight muscle of *Bombus affinis*. Biochem. J. 134:589, 1973.

83. Clark, M.B., Williams, C.H., Pfeifer, W.F., Bloxham, D.P., Holland, P.C., Taylor, C.A. and Lardy, H.A. Accelerated substrate cycling of fructose-6-phosphate in the muscle of malignant hyperthermic pigs. Nature 245:99, 1973.

Muscle from MHS pigs subjected to halothane anesthesia showed a decrease in ATP, increase in inosine, and a 30 to 80-fold increase in the rate of substrate cycling.

Although the "futile cycle" hypothesis would no doubt explain the hyperthermia, it does not explain muscle contraction. In fact, Lardy concludes that in the case of the bumble-bee, the futile cycle is turned off by contraction; specifically by the increase in Ca^{++} concentration that occurs with contraction.

Moreover, Lardy's methods for quantitating the cycle in liver have been questioned (84, 85) and perhaps more critical assessment of his techniques are necessary.

84. Hue, L. and Hers, H-G. On the use of [^{3}H, ^{14}C] labeled glucose in the study of the so-called "futile cycles" in liver and muscle. Biochem. Biophys. Res. Comm. 58:532, 1974.

85. Hue, L. and Hers, H-G. Utile and futile cycles in liver. Biochem. Biophys. Res. Comm. 58:540, 1974.

86. Uyeda, K. and Luby, L.J. Studies on the effect of fructose diphosphatase on phosphofructokinase. J. Biol. Chem. 249:4562, 1974.

This study suggests possibilities that the interaction of these two enzymes might control the rate of a futile cycle. What various concentrations of Ca^{++} might do to the interactions of these enzymes might be of significance regards malignant hyperthermia.

4) Muscle membrane defect -

This proposed defect would effect the sarcolema and the endoplasmic reticulum (sarcoplasmic reticulum) membrane. It might also be found in the mitochondrium membrane. The error, presumably produced by abnormal protein structure, would, in the presence of a strong inhalation anesthetic, result in the ability of the sarcolema, sarcoplasmic reticulum, and perhaps mitochondria to retain Ca ion either because of a failure of active pumping or because of the development of an overwhelming back-leak.

The high sarcoplasmic concentration of the anesthetic susceptible muscle would initiate contraction and the oxidation of glycogen stores (96), the combination of which would result in hyperthermia and rigidity.

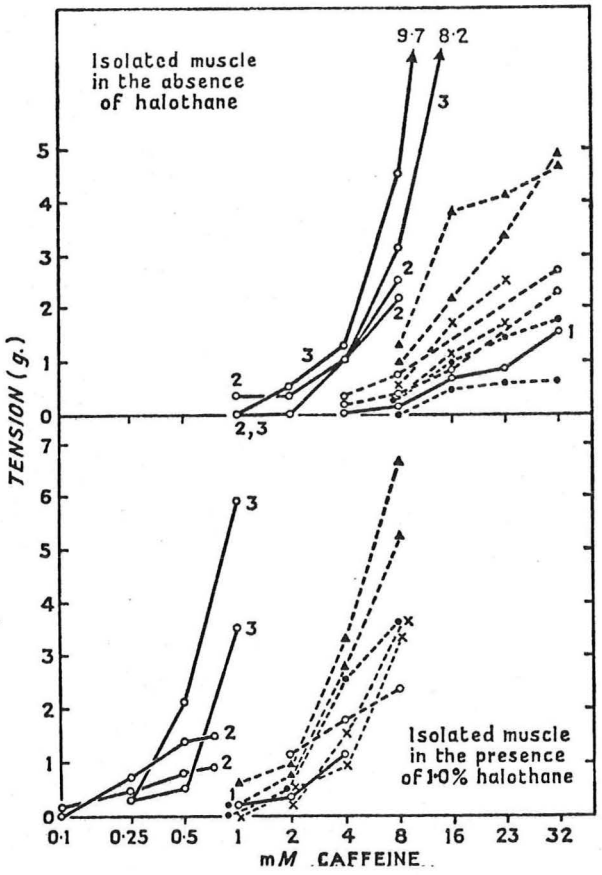


Figure 15

(From reference 47)

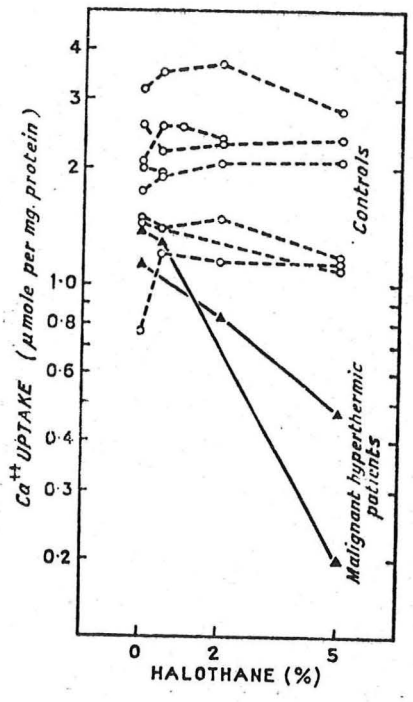


Figure 16

87. Brucher, R.F., Williams, C.H., Popinigis, J. et al. *In vitro* studies on liver mitochondria and skeletal muscle sarcoplasmic reticulum fragments isolated from hyperpyrexia swine. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 238.

Similar defect in sarcoplasmic reticulum of MHS pigs have been found.

(Figures 17 and 18 from reference 87)

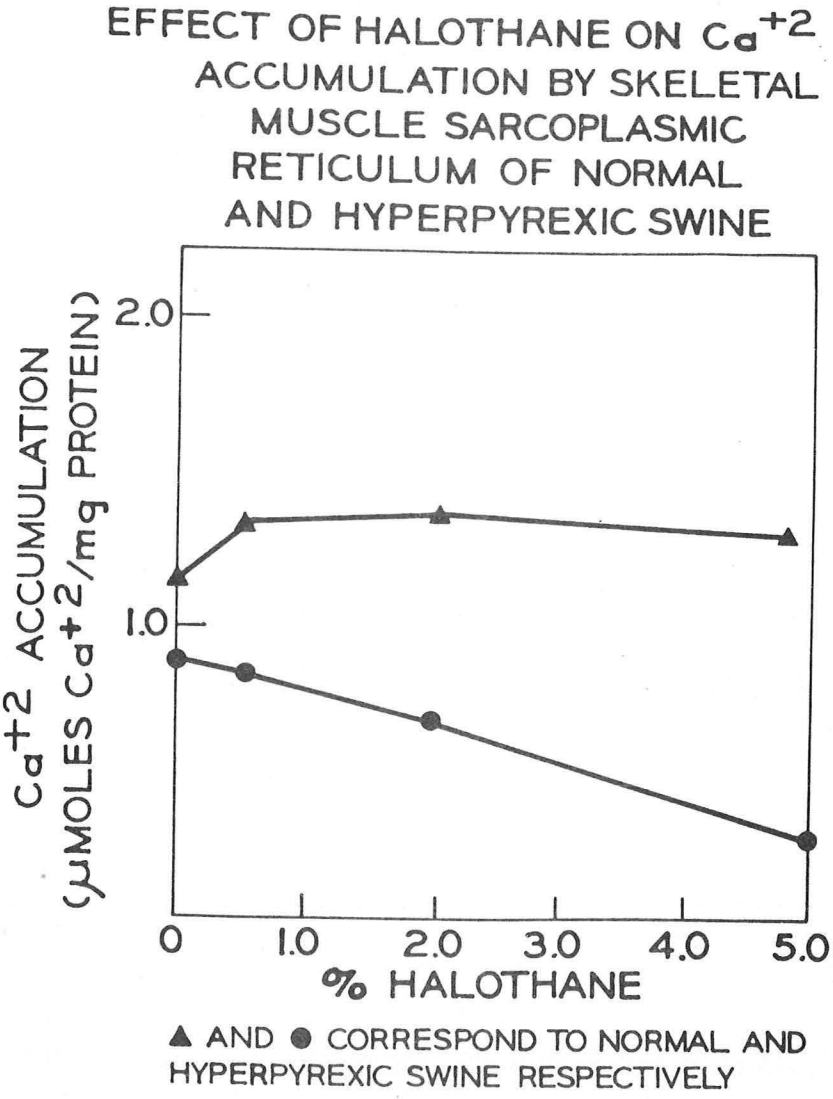


Figure 17

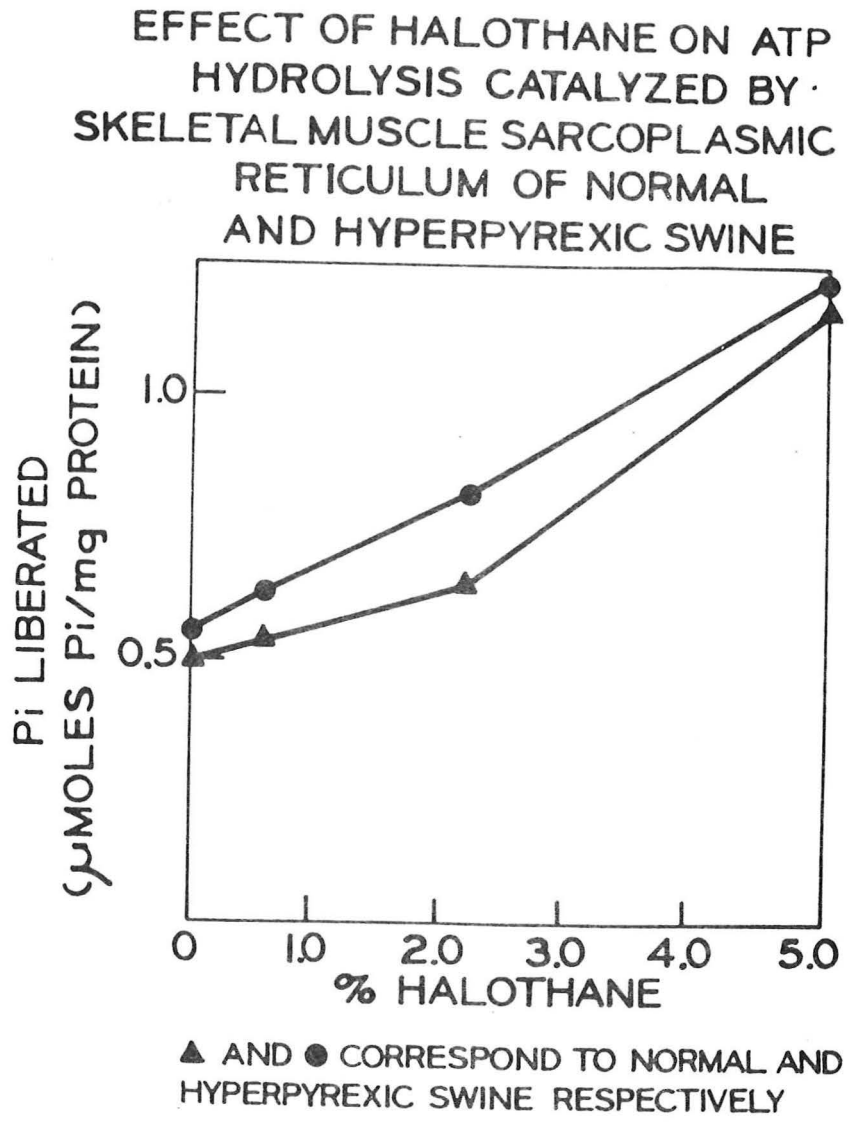


Figure 18

Similar findings have been found by other groups in both humans and MHS pigs (88-91).

88. Harrison, G.G. Recent advances in the understanding of anaesthetic-induced malignant hyperpyrexia. Anaesth. (Berl) 22:373, 1973.

89. Greaser, M.L., Cassens, R.G., Hoekstra, W.G. et al. Calcium accumulating ability and compositional differences between sarcoplasmic reticulum fraction from normal and pale soft exudative porcine muscle. J. Anim. Sci. 28:389, 1969.

90. Venable, J.H. Skeletal muscle structure in Poland China pigs suffering from malignant hyperthermia. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 208.

91. Ryan, J.F., Donlon, J.V., Malt, A.R. et al. Cardiopulmonary bypass in the treatment of malignant hyperthermia. New Eng. J. Med. 290:1121, 1974.

Sarcoplasmic Reticulum

	ΔPi μM/ng/min	Ca Uptake μM/ng/min
During MH (41° C)	0.10	0.06
During Neuroleptanalgesia	0.6	0.5
Normal	0.5 - 0.8	0.4 - 0.8

92. Britt, B.A., Kalow, W., Gordon, A., et al. Malignant hyperthermia: An investigation of five patients. Can. Anesth. Soc. J. 20:431, 1973.

Finally, Britt and Kalow have added to their previous studies and appear to confirm their findings.

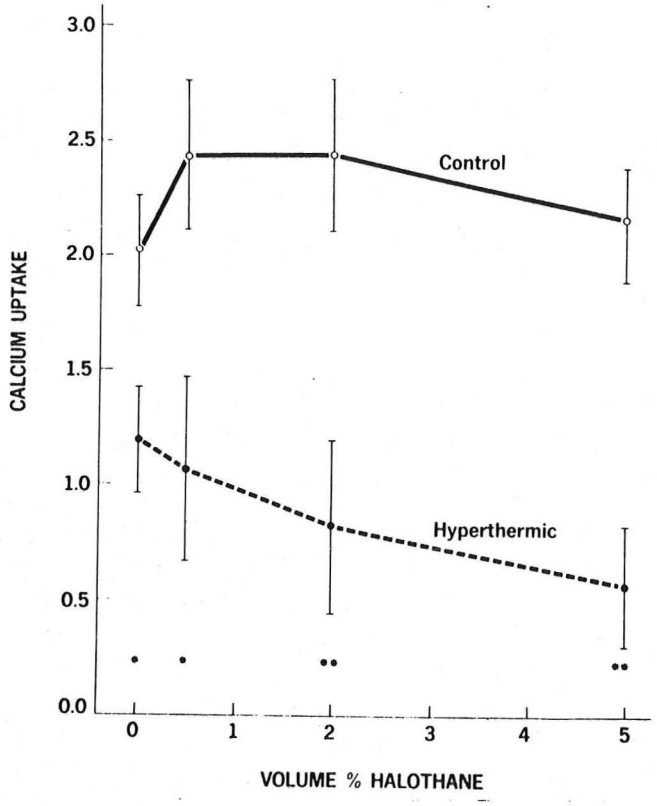


Figure 19 (From reference 92)

But not all studies of the sarcoplasmic reticulum show decreased Ca ion uptake, especially in pigs (93-95).

93. Berman, M.C. and Kench, J.E. Biochemical features of malignant hyperthermia in Landrace pigs. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 287.

Ca uptake by SR was actually enhanced in MHS pigs.

94. Steward, D.J. and Thomas, T.A. Intracellular calcium metabolism and malignant hyperpyrexia. In: International Symposium on Malignant Hyperthermia. Eds. R.A. Gordan, Beverley A. Britt, Werner Kalow. Charles C. Thomas, Springfield, Ill. 1973, p. 409.

Again from MHS Poland China pigs, no depression of SR Ca uptake by halothane.

95. Dhalla, B.S., Sulakhe, P.V., Clinch, N.F., Wade, J.G. and Naimark, A. Influence of fluothane on calcium accumulation by heavy microsomal fraction of human skeletal muscle. Biochem. Med. 6:333, 1972.

Here, the SR from a human patient was more resistant to the action of halothane than was a normal control.

96. Herlmeyer, L.M.G., Meyer, F., Haschke, R.H. and Fischer, E.H. Control of phosphorylase activity in a muscle glycogen particle. J. Biol. Chem. 245:6649, 1970.

Calcium ion converts inactive phosphorylase "b" to active phosphorylase "a". See Figure 9.

97. Miller, R.N., Smith, E.E. and Hunter, F.E. Halothane-induced alterations in energy-dependent and energy-independent membrane carrier functions in isolated rat liver mitochondria with some electron microscope correlations. In: Cellular Biology and Toxicity of Anesthetics. Ed. B.R. Fink. Baltimore, Williams and Wilkins. 1972.

In addition to an increased sarcoplasmic Ca ion concentration resulting from abnormal SR function, mitochondria may potentiate this increase in concentration by a failure to actively accumulate Ca. This factor may become of more importance as the pH falls and temperature increases.

Treatment:

Many of the references thusfar cited deal with non-specific measures of prevention and treatment of malignant hyperthermia. Newer and specific measures shall be taken up here.

In reference 91 a case is described that was successfully treated by cooling by means of cardiopulmonary bypass equipment. It was estimated that total body heat loss was 11 K cal/min during the bypass.

98. Berman, M.C. Role of preoperative management in development of malignant hyperthermia. Lancet 2:743, 1973.

> This author pleads for less "stress" of patients prior to anesthesia and surgery. Points out that some MHS pigs are also capable of developing hyperthermia on a stress basis only. May be important, particularly in patients requiring anesthesia that are suspects with regards malignant hyperthermia.

Although the physiology may not be altogether clear, "hyperventilation" has seemed to reduce the mortality in MHS pigs (75). If nothing more, hyperventilation should lower pCO_2, increase blood pH and thereby perhaps blunt lethal effects on the CNS and heart.

The major interest regards treatment at this time is concerned with the role of local anesthetics (or their derivatives) or so-called membrane stabilizers.

99. Feinstein, M.B. Inhibition of caffeine rigor and radiocalcium movements by local anesthetics in frog sartorius muscle. J. Gen. Phys. 47:151, 1963.

> Caffeine, which is capable of releasing Ca ion from the SR causes contraction and increased O_2 uptake. Procaine and tetracaine at about 5 mM concentration were found to prevent Ca ion release, increased O_2 uptake, and contraction in muscles exposed to caffeine.

100. Novotny, I. and Biancki, C.P. The effect of xylocaine on oxygen consumption in the frog sartorius. J. Pharmacol. Exp. Therap. 155:456, 1967.

> Although xylocaine may be a membrane stabilizer for the sarcoplasma, it can not block increased O_2 consumption resulting from caffeine as does procaine. This is the result of its different pK_a. (lidocaine 7.85, procaine 8.95).

On the basis of these observations, the treatment of malignant hyperthermia was directed towards the stabilization of the SR membrane by either procaine or procaine amide. The idea appears to have occurred to several persons at the same time. One excellent three paragraph discussion of why procaine might be useful is given in reference 101.

101. Strobel, G.E. Treatment of anesthetic-induced malignant hyperpyrexia. Lancet 1:40, 1971. (letter).

102. Harrison, G.G. Anesthetic-induced malignant hyperpyrexia: A suggested method of treatment. Brit. Med. J. 3:454, 1971.

Another early advocate of procaine. Had good results in pigs. Interestingly cunae blocked the action of succinylcholine in MHS pigs, but halothane brought out the full syndrome anyway.

103. Moulds, R.F.W. and Denborough, M.A. Procaine in malignant hyperpyrexia. Brit. Med. J. 4:526, 1972.

In their human muscle test with halothane in muscle from an individual susceptible to malignant hyperthermia, procaine prevented contracture.

104. Noble, W.H., McKee, D. and Gates, B. Malignant hyperthermia with ridigity successfully treated wtih procainamide. Anesthesiology 39:450, 1973.

The patient was cooled, given HCO_3^-, etc. and in addition 200 mg procainamide, I.V., over a five minute period. Hard to think this amount would have any great effect.

Interesting blood chemistries reported in this patient. After 445 mM of $NaHCO_3$:

pH	7.10
pCO_2	247 mmHg
CO_2	27 mM/L
K	3.5 mEq/L
pO_2	99 mmHg

105. Barrett, J.T. Recovery from malignant hyperthermia: Case report. New Zealand Med. J. 77:84, 1973.

Ice, heparin, and mannitol were used in treatment. Procainamide in a dose of 32 mg/kg B.W. (2.4 gms) was given IV. Although not discussed, lidocaine, for PVC, was given early - may have worsened the patient's status.

Not all reports hail procaine therapy:

106. Hall, L.W., Trim, C.M. and Woolf, N. Further studies of porcine malignant hyperthermia. Brit. Med. J. 2:145, 1972.

In three pigs, each with MHS, each given procaine in a different dose, differently - no benefit seems to have resulted.

Hall and Lister (reference 76) pointed out that concentration in muscle to prevent caffeine contraction required 1.83 to 5 mM of procaine. Claim highest blood level in human = 0.41 mM (96 µgm/ml) after 5 minutes following a 4 gm injection. As they believe high circulating catecholamines are etiologically important in malignant hyperthermia - local anesthetics may block their peripheral action.

107. MacLaghlan, D. and Forrest, A.L. Procaine and malignant hyperthermia. Lancet 1:355, 1974 (letter).

> After a rather small dose, (600 mg IV over 20 minutes) procaine appeared to produce an intractable hypotension.

108. Brown, L.L. and Britt, B.A. Malignant hyperthermia. So. Med. J. 67: 799, 1974.

> This is really a report of 2 cases of malignant hyperthermia where procaine was not used. However, this treatment is discussed and the suggested dose is:
>
> > Procaine or amide - 1 gm as 100 mg doses over "several minutes" while monitoring ECG.

Possible Human "Stress Syndrome" Related to Malignant Hyperthermia"

> There is at present little evidence to support a human stress syndrome related to malignant hyperthermia. However, cases of exertional myoglobinuria were reviewed for this possibility.

109. Kontos, H.A., Harley, E.L., Wasserman, A.J., et al. Exertional idiopathic paroxysmal myoglobinuria. Am. J. Med. 35:383, 1963.

> The case reported had recurrent myoglobinuria. He had congenital convergent strabismus of the right eye, hypertrophic calf muscles and muscle biopsy showed variation in muscle size. No significant family history. No mention made of body temperature.

110. Diamond, I. and Aquino, T.I. Myoglobinuria following unilateral status epilepticus and ipsilateral rhabdomyolysis. New Eng. J. Med. 272: 834, 1965.

> Patient admitted with body temperature of 107.2° F after 2 hours of left sided convulsion. Perhaps had myoglobinuria on six previous occasions, however, no mention of fever. "Normal" muscle from the right side shows irregular fiber size, but this is difficult to evaluate.

111. Berg, P. and Frenkel, E.P. Myoglobinuria after spontaneous and induced fever: Report of a case. Ann. Int. Med. 48:380, 1958.

The case reported here had myoglobinuria with mild febrile illnesses. Myoglobinuria was also seen following induced fever (102° F). Six hours after elective surgery he developed a temperature of 100° F lasting several hours. This was likewise accompanied by myoglobinuria.

112. Vertel, R.M. and Knochel, J.P. Acute renal failure due to heat injury. Am. J. Med. 43:435, 1967.

Two of the 10 patients reported here presented with rigid muscles in addition to high temperature and myoglobinuria.