Malignant Fever during and Following Anesthesia

John F. Ryan, M.D.,* and E. M. Papper, M.D.†

Malignant fever is a recently-noted, usually-fatal complication of anesthesia and surgery. Five cases representing the authors' experience since August, 1966 are described. Serial physiologic changes occurring during the early phases of the sudden fever are reported for the last two patients. Both patients had received succinylcholine and developed muscular rigidity. Salient findings include metabolic acidosis, hyperkalemia and myoglobinemia. Successful intragastric cooling with a Wangensteen Hypothermia Unit is described. Possible etiologic factors, which may include genetic defects, disturbances of cellular metabolism, and hypothalamic derangement, are discussed. (Key words: Malignant hyperpyrexa; Intragastric cooling; Muscular rigidity.)

ACUTE HYPERPYREXIA during anesthesia and during and immediately following surgical operation is a serious complication. The rapid onset of high fever is often unexpected and unpredictable, with a mortality rate of 70 to 80 per cent.

Burford reported three cases of hyperthermia, one fatal, in all of which the patients had temperatures above 106 F.2 Denborough et al., in a remarkable study, reported ten patients from a family of 38 who died during anesthesia.2 Three of the ten patients died postoperatively during convulsions with high temperatures. Stanley and Pal described death allegedly due to phenetidine (Nardil) and imipramine (Tofranil) in an ambulatory patient with a temperature of 43 C.3 Saidman reported two cases, one fatal, of hyperthermia and metabolic acidosis.4 Nine cases of hyperpyrexia, usually associated with either halothane or methoxyflurane and the use of succinylcholine—most of them in children—were reported in the Canadian Anaesthetist Society Journal.2-10 Most of these patients became rigid after administration of succinylcholine. Satnick described the case of a patient with hyperthermia and muscle rigidity in which a tourniquet on an extremity prevented the development of muscle rigidity in the extremity.11 Wilson et al.12 and Stephen12 reviewed 40 and 12 cases, respectively, with a combined mortality rate of 73 per cent. Ruscio and Marcus14 also Cody15 reported their findings, bringing the total of the cases of hyperthermia generally associated with muscle rigidity reported in the literature to 68.

The five cases described below represent the experience of the Department of Anesthesiology at the Columbia-Presbyterian Medical Center since August, 1966. The last two case reports describe some of the physiologic changes during the early phase of the sudden fever. A novel approach to rapid cooling using the Wangensteen Gastric Hypothermia Unit was successful in one of these cases. It overcomes the enormous heat production which, especially in adults, has been difficult to manage by external or other cooling devices.

Patient 1. A 30-year-old white man, in good health except for low back pain, underwent spinal fusion on August 30, 1966. Premedication consisted of secobarbital (Seconal), 100 mg, meperidine (Demerol), 50 mg, and scopolamine, 0.5 mg, an hour before anesthesia. Anesthesia was induced with 2.5 per cent thiopental (Pentothal), 300 mg, intravenously. Succinylcholine (Anectine), 100 mg, was used to facilitate tracheal intubation, with no abnormal response noted. The patient was placed in the prone position and anesthesia maintained with nitrous oxide (3 liters) and oxygen (2 liters) and halothane (0.6–1.0 per cent), with controlled respirations. Increase in pulse rate and tachypnea were noted approximately three hours after induction of anesthesia. The rectal temperature was above 100 F at this time. The surgical operation was completed as rapidly as possible. In the recovery room, despite vigorous external cooling, the rectal temperature rose to 108 F. The EKG showed ventricular tachycardia. Lidocaine (Xylocaine), 200 mg, was given intravenously. In spite of this, ventricular fibrillation occurred. External cardiac massage and DC defibrillation restored normal sinus rhythm.

* Assistant Professor.
† Professor and Chairman; Director, Anesthesiology Service, The Presbyterian Hospital, New York, New York 10032. Present address: University of Miami School of Medicine, Miami, Florida 33132.

Received from the Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, 630 West 168th St., New York, N. Y. 10032. Accepted for publication November 20, 1969.
The patient subsequently developed fibrinolysis, requiring 16 g of fibrinogen and a fibrinolysis inhibitor, epsilon-aminocaproic acid (Trasylol), in addition to fresh blood. The wound was re-explored and packed in an attempt to control bleeding. The patient became anuric and died 36 hours later with renal failure, hyperkalemia and ventricular arrhythmias. Gross pathological examination showed only cerebral edema. Cultures of the patient's blood and transfused blood were negative.

Patient 2. A 58-year-old woman entered the hospital with a chief complaint of lower abdominal pain and distention. Initial laboratory studies showed: hemoglobin, 10.7 g/100 ml; leukocyte count, 13,350; serum bilirubin, 0.25 mg/100 ml; alkaline phosphatase 58 King-Armstrong units; serum glutamic oxaloacetic transaminase (SGOT), 35 units and serum glutamic pyruvic transaminase (SGPT), 8 units. After premedication with secobarbital, 100 mg, meperidine, 50 mg, and atropine, 0.5 mg, intramuscularly, anesthesia was induced with thiopental, 225 mg, and succinylcholine, 100 mg, to facilitate intubation. Cyclopropane and oxygen were administered. d-Tubocurarine, 15 mg, was given for muscle relaxation, with assisted respirations. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for endometrial carcinoma. The patient recovered from anesthesia and was alert, but complained of feeling cold. On admission to the recovery room the rectal temperature was 99.2 °F initially, and the pulse rate 140 beats/min. During the next hour the temperature rose to 103 °F. Cooling measures with rectal aspirin, ice bags, chlorpromazine (Thorazine), 50 mg, intravenously, and a cooling blanket were instituted. Despite these measures the temperature rose to 105.3 °F, then declined to normal over the next two hours. On the first postoperative day the leukocyte count was 17,850. Blood cultures were negative. A direct Coombs test was negative. Convalescence was subsequently satisfactory.

Patient 3. A woman was admitted to the Otolaryngological Service with a diagnosis of chronic tonsilitis. The rectal temperature was 100.4 °F the day before surgical operation. On the morning of operation it was 99.2 °F. The leukocyte count was 7,250, hemoglobin 9.4 g/100 ml. After administration of thiopental, 275 mg, and succinylcholine, 100 mg, intravenously, a second dose of succinylcholine (40 mg) was needed to relieve muscle rigidity in order to perform laryngoscopy and intubation. Anesthesia was maintained with nitrous oxide (3 liters), oxygen (2 liters) and halothane (0.5-1.3 per cent) in a circle system. Anesthesia time was an hour and 15 minutes. After a mild episode of emergence delirium in the recovery room, the patient had a shaking chill. Rectal temperature was 101.2 °F and was monitored continuously thereafter. During the next two and a half hours, rectal temperature rose to 104.6 °F despite chlorpromazine, 25 mg, intravenously, alcohol baths, cooling blankets and ice bags over the iliac, carotid and popliteal areas. Temperature returned to normal over the next several hours. The patient received cephalothin (Keflin), 0.5 g, chloromycetin, 0.5 g, hydrocortisone, 100 mg, all intravenously. The leukocyte count postoperatively was 12,800. The patient was alert, alebrile and ambulatory the following day, and was discharged three days later.

Patient 4. A 35-year-old woman was admitted on May 18, 1968 for tonsillectomy after recurrent bouts of tonsillitis. Past history was unremarkable except for a two-month history of leg cramps and muscle weakness. The patient had no abnormal neurologic or orthopedic findings but had responded dramatically to psychiatric therapy with complete relief of muscle symptoms six weeks prior to admission. The diagnosis at that time had been anxiety reaction. Physical examination revealed a robust 5'10", 185-pound woman who was normal except for obesity. Results of routine laboratory studies of blood and urine were normal. On the afternoon of May 19, after premedication with secobarbital, 100 mg, and atropine, 0.4 mg, anesthesia was induced with thiopental, 275 mg, intravenously. After the intravenous injection of succinylcholine, 100 mg, the jaw was noted to be rigid; no fasciculation occurred. An additional 80 mg of succinylcholine was then injected, and the mandible could be opened to permit intubation. Anesthesia consisting of halothane (0.7-1.5 per cent), nitrous oxide (3 liters) and oxygen (2 liters) was given. An additional 60 mg of succinylcholine was required for the insertion of the mouth gag. Respirations were controlled and the level of anesthesia appeared adequate. At the end of the 35-minute procedure, with spontaneous respirations present, a Kussmaul type of respiration was observed. After about ten minutes, while the patient was still intubated and in the operating room, the skin was noted to be warmer than before. She was taken to the recovery room. The rectal temperature was 101 °F. A thermistor probe was inserted rectally, and a Block-Aid Monitor showed no evidence of neuromuscular blockade, i.e., there was a strong twitch response with no posttetanic facilitation and no fade of tetanus. The EKG revealed normal sinus rhythm with peaked T waves. The patient, still unconscious, was placed on a cooling blanket, blood was drawn for electrolyte and blood gas determinations, and oxygen was given via the endotracheal tube. After these procedures, which took approximately five to seven minutes, the temperature was 103 °F. On admission to the recovery room, the blood pressure was 120/80 mm Hg and the pulse rate 140 beats/min. After ten minutes the blood pressure was 180/110 mm Hg and the pulse rate 190 beats/min. External cooling continued and d-tubocurarine, 12 mg, and chlorpromazine, 25 mg, intravenously, were given; controlled ventilation was begun with 100 per cent oxygen. The temperature climbed rep-
idly to above 105.8°F in approximately 20 minutes. Ventricular arrhythmias appeared and the blood pressure fell to 40 mm Hg systolic, then became unobtainable. Closed-chest massage was begun and ice-chilled sodium chloride and water were instilled through gastric and rectal catheters, together with surface cooling, with no effect on the hyperthermia. At this point reports of the results of blood studies were obtained. Serum potassium was 8.5 mEq/l, the pH of arterial blood was 7.15, with a base excess of −16.5 mEq/l. Sodium bicarbonate, 150 mEq, was administered intravenously. The Wangerstein Gastric Hyperthermia Unit was then inserted via direct esophagoscopy. Inflow temperature was 2°C. The rate of flow was approximately 1.0 l/min. For almost ten minutes the fluid returning from the stomach remained at 20°C, then began to fall, as did the patient’s rectal temperature. When the rectal temperature reached 106.2°F, normal sinus rhythm returned and the blood pressure was 40 mm Hg systolic. Arterial blood had a pH of 7.35 and a base excess of −3.2 mEq/l. Serum potassium was 6.2 mEq/l just after the return of the patient’s circulation. A second dose of d-tubocurarine, 6 mg, was given intravenously, and assisted ventilation continued with a pressure-limited respirator. Over the next half hour the rectal temperature fell to 103°F and blood pressure rose to 80–90 mm Hg systolic, with normal sinus rhythm on the electrocardiogram. Arterial blood had a pH of 7.45. The serum potassium three hours later had fallen to 2.3 mEq/l. Approximately six and a half hours after admission to the recovery room, the patient responded to commands. The trachea was extubated four hours later. The patient was given morphine sulfate, 6 mg, intravenously, in three divided doses over the next three hours to alleviate severe muscle pains in the legs and arms. Urinary output was never less than 100 ml/hour. The urine was red and analysis disclosed that it contained myoglobin. Serum potassium levels remained low during the evening but rebounded to a level of 6.1 mEq/l at 9:00 a.m. the next morning. (This is similar to a case reported by Purkis.24) There was slight metabolic and respiratory alkalosis from bicarbonate administration and controlled ventilation. The leukocyte count the following day was 33,000, with 93 per cent neutrophils. Creatine phosphokinase was elevated and myoglobinuria persisted for three days. SGOT levels reached a peak of 940 units and remained elevated for seven days. Anteroseptal T-wave changes in V₅ and V₆ persisted for two weeks, and electroencephalographic abnormalities of low-voltage slow activity, and some low-voltage fast activity, persisted for eight weeks. An electromyogram one week postoperatively revealed acute myopathic changes compatible with muscular destruction. Biopsy of the left gastrocnemius muscle revealed acute myopathic changes scattered randomly in the muscle fibers, with degeneration, vacuolation and some fibrocytic activity with disintegration of muscle fibers. Following discharge, the patient returned to her previous activity.

Patient 5. A 5-year-old boy was admitted to the hospital for repair of undescended testicles. Past history and family history were normal except for occasional otitis media and decreased vision in the right eye. The patient also had herpes simplex on admission. He was premedicated for the first operation (November, 1967) with secobarbital, 40 mg, scopolamine, 0.3 mg, and morphine, 3 mg, intramuscularly. An hour and 15 minutes later he was brought to the operating room asleep. Anesthesia was induced and maintained with cyclopropane and oxygen without incident. The patient also received succinylcholine, 40 mg, intravenously, during induction, and left orchiectomy of three hours’ duration proceeded uneventfully. The patient was readmitted three months later for right orchiectomy. Premedication consisted of secobarbital, 55 mg, and atropine, 0.5 mg, intramuscularly, at 12:20 p.m. Anesthesia was induced with cyclopropane and oxygen at 2:00 p.m. Anesthesia was maintained with 1.5 per cent halothane with nitrous oxide (3 liters) and oxygen (3 liters) by mask. At 4:50 p.m., owing to the extension of the surgical incision into the abdomen, the patient was given succinylcholine, 20 mg, intravenously. The jaw became tight, he was given an additional 40 mg, and the trachea was intubated without difficulty. Pulse rate and blood pressure remained stable between 100 and 110 beats/min and 110/70 mm Hg and 100/50 mm Hg, respectively. The operation was halted due to the possibility of the occurrence of hyperthermia while a cooling blanket was positioned and temperature monitoring with an esophageal thermometer was begun. The temperature at 5:00 p.m. was 99.2°F. At 6:00 p.m. the temperature was 101°F. It rose to 103°F in the next 45 minutes, then fell with vigorous cooling to 100°F over the next hour. In the recovery room, serum potassium was 5.8 mEq/l; arterial pH 7.28; PaO₂ 30 mm Hg; the base excess −11.0 mEq/l; oxygen saturation 99 per cent. Three hours later serum potassium was 4.0 mEq/l. On the first postoperative day the creatine phosphokinase level rose to 393 units and myoglobin was present in the urine and serum. The leukocyte count was 24,000 and SGOT, 312 units. Creatine phosphokinase remained elevated for days. Myoglobinemia disappeared in one day but myoglobinuria persisted for three days. The patient was discharged. Postoperative neurologic and electromyographic examinations have disclosed no abnormalities.

Discussion

Acute malignant hyperpyrexia during anesthesia appears to be a problem that has been noted only recently. The majority of the reported cases have occurred since 1960. Since
a number of anesthetic agents, old and new, have been associated with this phenomenon, and since a genetic component appears to be implicated in some cases, why were there not cases reported prior to the sixties? Were deaths attributed to other causes (e.g., "ether convulsions"), or just not noted? Both possibilities seem unlikely.

The etiology of the acute febrile response is not known. Explanations for this high fever during anesthesia fall into three groups: 1) genetic defects, 2) disturbances of cellular metabolism, and 3) hypothalamic derangement.

The study of a family of 38 by Danborough et al.2 and Britt and Kalow's17 detailed report of a family in Wausau, Wisconsin, strongly suggest that genetic abnormalities play a very important etiologic role. The Wausau family's genetic pattern was one of autosomal dominance with reduced penetrance and variable expressivity. Fifty per cent of siblings were affected and transmission was not x-linked. Hall et al.18 have reported that succinylcholine "triggers" hyperthermic reactions in pig litter mates.

Two theories supporting an increase in total body heat production due to cellular metabolic disturbances have been advanced. The first describes an "uncoupling" of oxidative phosphorylation as a possible cause. Wilson et al.19 found that administration of 2,4-dinitrophenol to dogs during halothane anesthesia resulted in a significant increase in temperature. Four of the animals died of hyperthermic reactions. The ability of the uncoupling of oxidative phosphorylation alone to produce sufficient heat to account for hyperthermia has been discussed by Wang et al.,20 who pointed out that uncoupling agents would have to increase oxygen metabolism many-fold by secondary effects on energy metabolism to result in hyperthermia.

Challoner21 described a second pathway of oxidative metabolism via mitochondria, involving a well-known ADP-ATP system. Using oligomycin to block ADP formation, he suggested that in disease states these secondary pathways are stimulated through the adrenergic system to increase lipolysis and oxygen uptake.

A third etiologic factor was suggested by Saidman et al.—a derangement of hypothalamic temperature-regulating centers attributable to sustained muscular activity following administration of succinylcholine.

The five cases reported here point to no single etiologic factor. They present several novel aspects of acute hyperpyrexia. The first case follows the now-classical pattern during anesthesia, i.e., tachycardia, tachypnea, sudden hyperthermia and either immediate death or subsequent death from brain damage, active fibrinolysis,16 electrolyte imbalance and/or anuria. Unlike the last three patients, this patient had no abnormal response to succinylcholine.

The second case might well be dismissed as not being a case of acute hyperpyrexia; yet, the patient did develop a high fever rapidly in the recovery room following surgical operation, and its cause was not proven to be septic. This well may represent a variant of the syndrome, more benign in nature and amenable to therapy.

The third, fourth, and fifth cases demonstrate an improvement in our recognition of and therapeutic measures in response to this serious complication. The third patient responded to succinylcholine with muscular rigidity and was vigorously treated postoperatively. The gentle slope of the temperature elevation and the ability to halt its rise suggest a variant of full-blown hyperthermia.

The fourth and fifth patients had abnormal responses to succinylcholine, followed by metabolic acidosis, hyperkalemia, and hyperthermia. The release of potassium, myoglobin and other cellular components into the blood stream is attributable to alterations in muscle cell membrane permeability and/or necrosis of muscle. Whether these products initiate the hyperpyrexic response via endogenous pyrogenic reactions or are only coincidental is unknown.

In further studies of the appearance of myoglobinemia during anesthesia and surgical operation we have not found a correlation between myoglobinemia and the subsequent development of acute hyperthermia.22 Approximately 3 per cent of our adult patients developed myoglobinemia after a single injection
of succinylcholine, whereas the incidence was 40 per cent in children receiving halothane and succinylcholine. None of the adults and only one child studied thus far developed hyperthermia. It is interesting to note that in the fifth patient myoglobinuria persisted for three days, whereas myoglobinemia was present for only a day. Probably the renal clearance of myoglobin is so rapid that its presence is more easily detected in urine than in blood.

Treatment of malignant hyperthermia entails correction of metabolic acidosis and effective cooling. Hyperkalemia as reflected by electrocardiographic changes should be verified by analysis of the blood. Catheterization of the urinary bladder allows estimation of urinary output and diagnosis of myoglobinuria if it is present. Surface cooling may be satisfactory in children if begun early. However, in adults and in some children, external cooling may be inadequate, as brachial arterial antecubital venous shunts have been. Cooling by extracorporeal circulation would be ideal theoretically. Practically, its use is limited to hospitals that have “pump teams,” by the immediate availability of personnel, and also by the time necessary to institute therapy.

The Wangensteen Gastric Hypothermia Unit affords a quick, simple and effective means of cooling during the period of tremendous heat production. This apparatus can be kept in the recovery room and needs only to be switched on to function. With direct esophagoscopy the balloon is easily passed through the esophagus and positioned in the stomach. The rapid flow of the hypothermia unit can provide efficient “core” cooling. The importance of a high-flow cooling system is borne out by the response of the fourth patient. The cold fluid, with a temperature of 2°C, was warmed to 20°C for about ten minutes until sufficient heat had been removed to lower the rectal temperature. The Wangensteen unit has a flow rate of 1 to 14 l/min and the ability to extract more than 1 kilocalorie of heat per minute.23

In the face of increased oxygen consumption it also appears desirable to supply supplemental glucose to provide substrate for metabolism. Since, in most cases, the body temperature rises rapidly, it is important to develop a protocol to be followed should hyperthermia occur. Most important, a high degree of suspicion should be present when any patient has: 1) unexplained tachycardia, and/or tachypnea without other obvious causes; 2) a history of muscular abnormality; 3) muscular rigidity following the administration of succinylcholine. We feel the occurrence of definite muscular rigidity after succinylcholine is sufficient grounds for canceling the operation. Perhaps temperature monitoring in all patients during anesthesia should be routine.

The low incidence of mortality in the above five cases may not have been due to alertness, preparedness, and vigorous therapy, but in some of the cases we feel it was mainly the result of the nature of the syndrome, i.e., the degree of biochemical aberration and the rapidity and severity of temperature elevation.

References


Obstetrics and Pediatrics

HYPOTHERMIA AND INSULIN RELEASE Plasma immunoreactive insulin and glucose levels were studied in 12 infants subjected to deep hypothermic cardiovascular surgery. In six infants receiving glucose infusion, temperature reductions to below 30°C were accompanied by marked hyperglycemia. Despite the development of hypoglycemia, plasma immunoreactive insulin levels decreased and remained low during cooling. Following rewarming, plasma insulin concentrations increased and glucose levels decreased despite continued glucose infusion. Plasma glucose and immunoreactive insulin levels remained relatively stable during cooling in three infants in whom infusions of saline rather than glucose solutions were used. In five of these patients, similar glucose infusions resulted in much smaller increases in plasma glucose despite increased insulin levels in the awake normo- thermal state. The studies indicate that a reduction in exogenous glucose uptake is associated with a reversible inhibition of insulin release of a significant degree in infants subjected to deep hypothermia during cardiovascular surgery. (Baum, D., Dillard, D. H., and Porte, D., Jr.: Inhibition of Insulin Release in Infants Undergoing Deep Hypothermic Cardiovascular Surgery, New Eng. J. Med. 179: 1309 (Dec.) 1968.)

PREGNANCY AND ALTITUDE Five pregnant sheep and one pregnant goat were exposed acutely to high altitude (10,000 and 15,000 feet) after femoral artery, uterine vein, umbilical vein and umbilical artery catheterization. High altitude produced a decrease in oxygen saturation in all vessels sampled. Oxygen tension decreased dramatically in maternal vessels, but there was little change in umbilical vessels. The arteriovenous difference of oxygen and the coefficient of oxygen utilization of the uterus showed little change. At high altitude, maternal Pco₂ decreased and pH increased slightly. The transplacental CO₂ tension difference was unchanged. The fetus possesses to some degree the capacity to regulate the rate at which oxygen reaches it, possibly by changes in uterine blood flow. (Blecher, J. N., and others: Observations on Pregnancy at Altitude. II. Transplacental Pressure Differences of Oxygen and Carbon Dioxide, Amer. J. Obstet. Gynec. 102: 794 (Nov.) 1968.)