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This Week's Citation Classic®

Harrison G G, Saunders S J, Biebuyck J F, Hickman R, Dent D M, Weaver V & Terblanche J. Anaesthetic-induced malignant hyperpyrexia and a method for its prediction. *Brit. J. Anaesth.* **41**:844-55, 1969.
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The clinical syndrome of anaesthetic-triggered malignant hyperpyrexia (MH) in pigs is described. It is considered to be the same as MH in humans and is likewise genetic in origin. Clinical features are accompanied by profound acidosis. Histological change is found in muscle only. *In vitro*, an abnormal depletion of muscle ATP is observed. Halothane, chloroform, and suxamethonium are identified as triggering agents. [The *SCI*® indicates that this paper has been cited in over 145 publications.]

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Of all the complications of general anaesthesia, perhaps the most dramatic, and indeed frightening, is that veritable metabolic storm that characterizes the unexpected, and in the past frequently fatal, syndrome of anaesthetic-induced malignant hyperthermia (MH). First described in 1960,[1] and definitively characterized through case reports over the next six years,[2] this syndrome became the nightmare of the anaesthetist. Rare and sporadic, its occurrence unpredictable, the syndrome boasted a mortality of 70-80 percent. Knowledge of the pathogenesis was lacking, and no specific therapy was available.

As on so many other occasions in the long history of medicine, serendipity now provided the *deus ex machina* that would ultimately help solve this dangerous clinical conundrum—in this case, the "Hot Pig." The authors of this paper, an interdisciplinary group that included surgeons, anaesthetists, physicians, and a laboratory technologist, all members of the Liver Research Group of the University of Cape Town, South Africa, were engaged in a program of experimental liver transplantation utilizing the pig (Landrace and Landrace X Large White) as the experimental model. The anaesthetic protocol was based on halothane.

To the surgeons' annoyance, the physicians' puzzlement, and the anaesthetists' embarrassment, one of the first animals anaesthetized became, for no apparent reason, cyanosed and extremely hot, its legs rigidly extended, and died before the surgical experimental protocol proper could be started. When, frustratingly, a further 5 of the first 34 animals anaesthetized displayed the selfsame reaction, we realized that the anaesthetist had no cause for embarrassment; we had stumbled on a specific syndrome.

Led through Hall's description (a year previous) of the identical reaction in littermate pigs in response to suxamethonium[3] to a consideration of the described syndrome of anaesthetic-induced malignant hyperpyrexia in human patients,[2] we came to the exciting conclusion that we had stumbled on a facsimile in pigs of the human condition. Here, indeed, was the animal experimental model of MH.

This discovery, reported first in a preliminary communication[4] and definitively thereafter in this paper, was seminal. Today, just less than 20 years later, though the minutiae of the pathogenesis of MH have yet to be elucidated, knowledge that has come from worldwide studies in MH swine has led not only to effective pharmacological control of the syndrome,[5] but also to valuable spin-offs in many biomedical areas, in particular those of muscle and membrane physiology, calcium transport, and kinetics, and in the meat industry.

A second reason for this paper's citation is that it carried, *inter alia*, the first report of an identifiable fundamental functional biochemical lesion in the muscle of animals susceptible to MH, i.e., a markedly increased rate of ATP depletion *in vitro*. We were led to investigate specifically the ATP content of muscle by the severity of the muscle rigor that characterizes the syndrome and that one of us (DD) insistently likened to rigor mortis setting in antemortem. Rigor mortis was already known to correlate with ATP depletion.

Further, this paper reported for the first time the laboratory *in vivo* identification of agents that trigger MH.

Though I earned no specific honour or award directly through this publication, it and the research that followed from it doubtless contributed to my later election as a Life Fellow of my university.

It is of some human interest that the authors of this paper (excepting the laboratory technologist) have all subsequently become professors and one has become a university vice chancellor. [For a recent review of the subject, see reference 6.]

1. **Denborough M A & Lovell R R H.** Anaesthetic deaths in a family. *Lancet* 2:45, 1960. (Cited 120 times.)
2. Malignant hyperpyrexia during general anaesthesia. *Can. Anaesth. Soc. J.* 13:415-48, 1966.
3. **Hall L W, Woolf N, Bradley J W P & Jolly D W.** Unusual reaction to suxamethonium chloride. *Brit. Med. J.* 2:1305, 1966. (Cited 105 times.)
4. **Harrison G G, Biebuyck J F, Terblanche J, Dent D M, Hickman R & Saunders S J.** Hyperpyrexia during anaesthesia. *Brit. Med. J.* 3:594-5, 1968. (Cited 55 times.)
5. **Harrison G G.** Control of the malignant hyperpyrexic syndrome in MHS swine by dantroline sodium. *Brit. J. Anaesth.* 47:62-5, 1975. (Cited 125 times.)
6. **Gronert G A.** Malignant hyperthermia. (Miller R D, ed.) *Anesthesia*. New York: Churchill Livingstone, 1986. p. 1971-94.

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