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REFERENCES

1. Gronert GA, Milde JH, Theye RA: Role of sympathetic activity in porcine malignant hyperthermia. ANESTHESIOLOGY 47:411–415, 1977
2. Gronert GA, Milde JH, Theye RA: Dantrolene in porcine malignant hyperthermia. ANESTHESIOLOGY 44:488–495, 1976
3. Gronert GA, Milde JH, Theye RA: Halothane-induced porcine malignant hyperthermia. ANESTHESIOLOGY 44: 36–43, 1976
4. Gronert GA, Milde JH, Theye RA: Porcine malignant hyperthermia induced by halothane and succinylcholine. ANESTHESIOLOGY 44:124–132, 1976
5. Williams CH: Some observations on the etiology of the fulminant hyperthermia stress syndrome. Perspect Biol Med 20:120–130, 1976
6. Williams CH, Houchins C, Shanklin MD: Energy metabolism in pigs susceptible to the fulminant hyperthermia stress syndrome. Br Med J 3:411–413, 1976; Br Med J 1:724, 1977 (correction)
7. Williams CH, Stubbs DH, Payne CG, et al: Role of hypertension in fulminant hyperthermia–stress syndrome. Br Med J 1:628, 1976
8a. Williams CH: The development of an animal model for the fulminant hyperthermia–porcine stress syndrome, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 117–140
8b. Williams CH, Lasley JF: The mode of inheritance of the fulminant hyperthermia–stress syndrome in swine, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 141–148
8c. Williams CH, Shanklin MD, Houchins C: Energy metabolism in fulminant hyperthermia–stress syndrome in swine, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 149–156
9. Fuchs F: Thermal inactivation of the calcium regulatory mechanism of human skeletal muscle actomyosin. ANESTHESIOLOGY 42:584–589, 1975
10. Westfall TC: Local regulation of adrenergic neurotransmission. Physiol Rev 57:659–712, 1977
11. Davis TP, Gehrke CW Jr, Gehrke CW, et al: A sensitive flourometric assay of biogenic amines by reverse phase high pressure liquid chromatography. Fed Proc 36:734, 1977
12. Davis TP, Gehrke CW Jr, Williams CH, et al: The fulminant hyperthermia–stress syndrome: Biogenic amine levels in the blood of susceptible and normal pigs (abstr). Second International Symposium on Malignant Hyperthermia, Denver, 1977
13. Wingard D: Malignant hyperthermia—Acute stress syndrome of man?, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 79–95
14. Williams CH, Roberts JT, Hoech GP Jr, et al: The fulminant hyperthermia–stress syndrome: Total neuromuscular blockade with dimethyl curare prevents the development of the syndrome in susceptible pigs, Strategies in Cold: Natural Torpidity and Thermogenesis, Jasper, Canada, 1977. Cryobiology, February 1978 (abstr)
15. Williams CH, Stubbs DH: Drugs, Biogenic Amines and Body Temperature. Edited by Lomax P, Schonbaum E. Basel, Karger, 1976, pp 233–234
16. Williams CH, Shanklin MD, Hedrick HB, et al: Proceedings of Second International Symposium on Malignant Hyperthermia, Denver. Edited by Aldrete AJ, et al. New York, Grune and Stratton, 1978
17. Williams CH, Davis TP, Gehrke CW Jr, et al: The fulminant hyperthermia–stress syndrome: biogenic amine levels in the blood of susceptible and normal pigs (manuscript submitted to ANESTHESIOLOGY)
18. Eighmy JJ, Williams CH, Anderson RR: Proceedings of Second International Symposium on Malignant Hyperthermia, Denver. Edited by Aldrete AJ, et al. New York, Grune and Stratton, 1978
19. Eighmy JJ, Williams CH, Anderson RR: Plasma thyroxine changes in normal pigs and those susceptible to fulminant hyperthermia (abstr) 69th Annual Meeting, American Society of Animal Science, Madison, 1977, p 154
20. Williams CH, Shanklin MD, Hedrick HB, et al: The fulminant hyperthermia–stress syndrome: Energy metabolism in susceptible and normal pigs (abstr). 69th Annual Meeting, American Society of Animal Science, Madison, 1977, p 219

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In reply:—First, we purchase swine from several regional Poland China breeders who each have a minimum of 30 years' experience with their registered herds and who inbreed for greater muscle mass. Obviously, however, inbred homozygotic Poland China swine may not have inbred susceptibility to malignant hyperthermia. Susceptibility, as Williams *et al.* recommend,[1] is best evaluated by a halothane challenge. They define susceptibility as the appearance of rigidity and fever within 20 min of exposure to halothane, and report an incidence of 55–57 per cent.[1] At the time of purchase, we discard any animal in which these changes do not develop within 5 min, and find an incidence of about 50 per cent, suggesting that we have comparable inbreeding for malignant hyperthermia.

Their fivefold increased "basal" metabolic rates were determined by placing awake pigs into a calorimeter.[2] But instead of reporting mean group values, they report values from individual animals, wherein

biological variation makes comparison with other data difficult. In the above letter they interpret the results as increased basal levels, while elsewhere they refer to the same results as malignant hyperthermia triggered awake,[1,2] which seems more likely. Measured blood pressures again are values from single animals and are higher than our mean (and most individual) values.[3]

Second, our starting temperatures did vary in different studies, but all animals had control measurements relating to metabolism, circulation, and acid–base balance that were within the normal ranges for non-susceptible Poland China swine. Studies were not started unless all measurements were stable; we had indisputable evidence that malignant hyperthermia had not started in any pig during the control period. Despite these differences in starting temperatures, the changes in metabolism, circulation and acid–base balance were remarkably consistent.

Third, while our mean norepinephrine levels were significantly increased after 30–40 min, metabolic and acid–base mean values had increased after 10–30 min. Williams *et al.* explain this time difference as a delayed increase in blood norepinephrine levels due to local uptake and saturation of enzyme systems, referring to Westfall.[4] However, Westfall states that norepinephrine uptake and degradation are slow, and that with increased release of norepinephrine, these are easily swamped, resulting in overflow of excess norepinephrine into venous blood. Thus, our data do not support their hypothesis.

The authors do not reference their estimates of "enzyme complement" or "enzymatic capability," and I found no evidence in their published studies to support these estimates. Their assumptions of 50–75 per cent and 1–25 per cent appear meaningless, ill-founded and without distinction. The authors' other comments do not apply directly to our differences.

The authors have not addressed the key question raised by our data: does sympathetic blockade caused by total spinal anesthesia prevent *any* sympathetic activation, or is there perhaps enough to initiate malignant hyperthermia without resulting in detectable blood levels of catecholamines? There are several reasons why I favor our prior conclusion, which is that the sympathetic activation seen during porcine malignant hyperthermia is an expected adrenergic response to major stress. First, norepinephrine release is related to sympathetic nervous impulses.[4] Second, pigs with both cord section and adrenalectomy can still develop malignant hyperthermia in the denervated area (unpublished data). Third, dantrolene completely halts porcine malignant hyperthermia.[5] If the response were mediated by the sympathetic nervous system, catecholamines should continue to increase after dantrolene, but do not.

While it thus appears that the sympathetic nervous system is a secondary though unneeded contributor to malignant hyperthermia, it undoubtedly does play an integrated role in the progression of malignant hyperthermia, whether it is initiated in the awake subject or during anesthesia. Wingard's data imply that awake episodes are more subtle in man than in swine,[6] but subtle or not, the sympathetic hyperactivity probably accelerates the reaction. Conversely, the reaction itself may intensify the sympathetic response. We found that malignant hyperthermia is associated with an increase in whole-blood ionized calcium, and increases in extracellular fluid ionized calcium have been shown to increase the amount of catecholamines released per nerve impulse.[4]

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REFERENCES

1a. Williams CH: The development of an animal model for the fulminant hyperthermia–porcine stress syndrome, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 117–140
1b. Williams CH, Lasley JF: The mode of inheritance of the fulminant hyperthermia–stress syndrome in swine, Malignant Hyperthermia: Current Concepts. Edited By Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 141–148
1c. Williams CH, Shanklin MD, Houchins C: Energy metabolism in fulminant hyperthermia–stress syndrome in swine, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 149–156
2. Williams CH, Houchins C, Shanklin MD: Energy metabolism in pigs susceptible to the fulminant hyperthermia–stress syndrome. Br Med J 3:411–413, 1976
3. Williams CH, Stubbs DH, Payne CF, et al: Role of hypertension in fulminant hyperthermia–stress syndrome. Br Med J 1:628, 1976
4. Westfall TC: Local regulation of adrenergic neurotransmission. Physiol Rev 57:659–712, 1977
5. Gronert GA, Milde JH, Theye RA: Dantrolene in porcine malignant hyperthermia. ANESTHESIOLOGY 44:488–495, 1976
6. Wingard D: Malignant hyperthermia—Acute stress syndrome of man?, Malignant Hyperthermia: Current Concepts. Edited by Henschel EO. New York, Appleton-Century-Crofts, 1977, pp 79–95

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