Malignant Hyperthermia: The Genetic Disease is characterized by a runaway futile cycle operating at the acetylcholine (sodium channel) level

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Fall 1968

- Claude Taylor came to Enzyme Institute to discuss MH in Wisconsin.
- 2-weeks later UW Hospital had a 28 yr old patient who developed MH and died.
- Tim Galvez an anesthesia resident had given anesthetic for surgery ulcer project: pigs died
- Tim and CHW went to UW Arlington swine farm and tested a 40# pig with hernia and it developed MH with rectal temp of 109F

January 1969

- We returned to UW Arlington farm to check two litters of pigs that were closely related.

Saved 2 males and 3 females that were positive to halothane test for breeding stock.

The other pigs were used for experiments. Isolated muscle, liver, and heart mitochondria

For in vitro studies. Were not uncoupled!!!!!

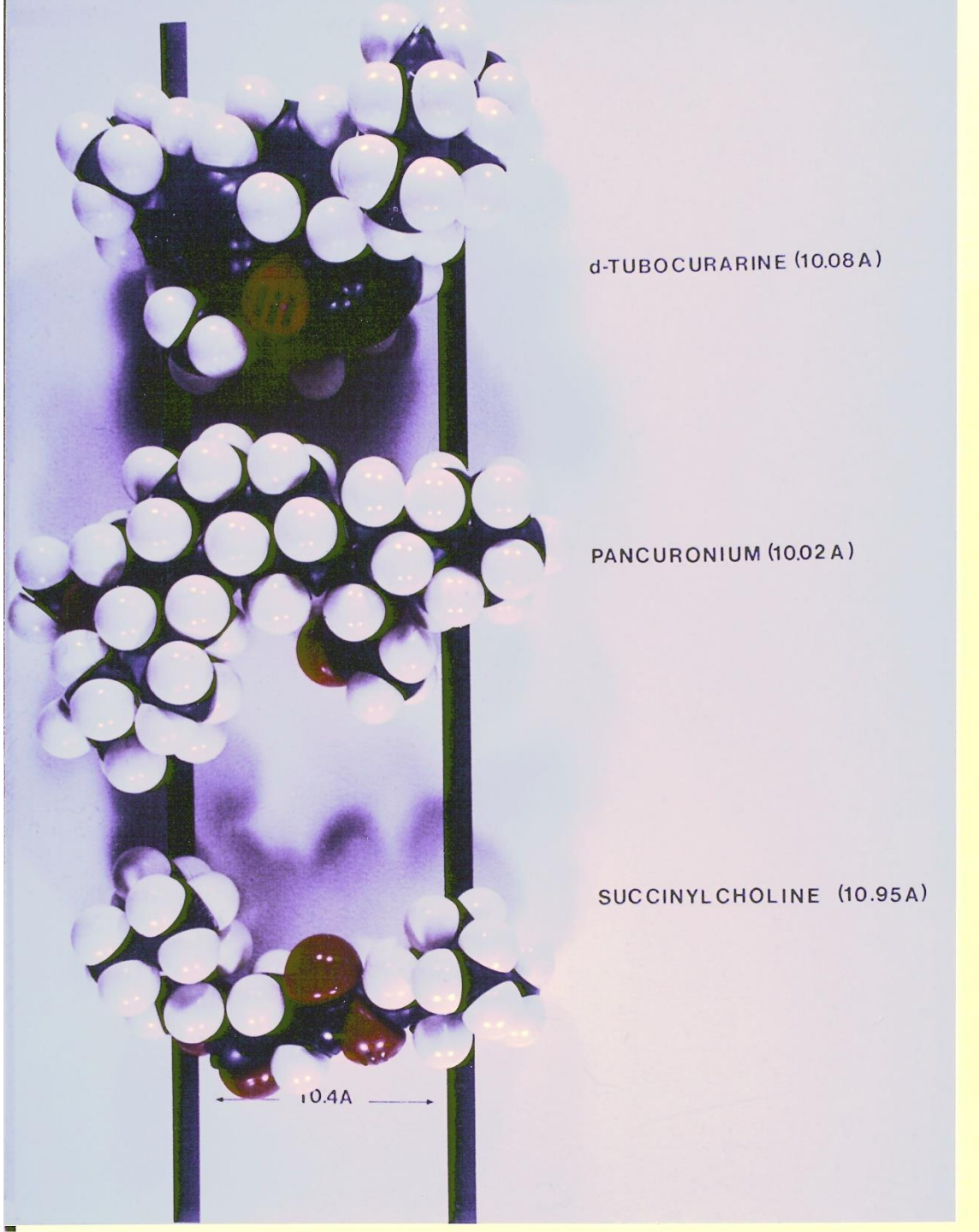


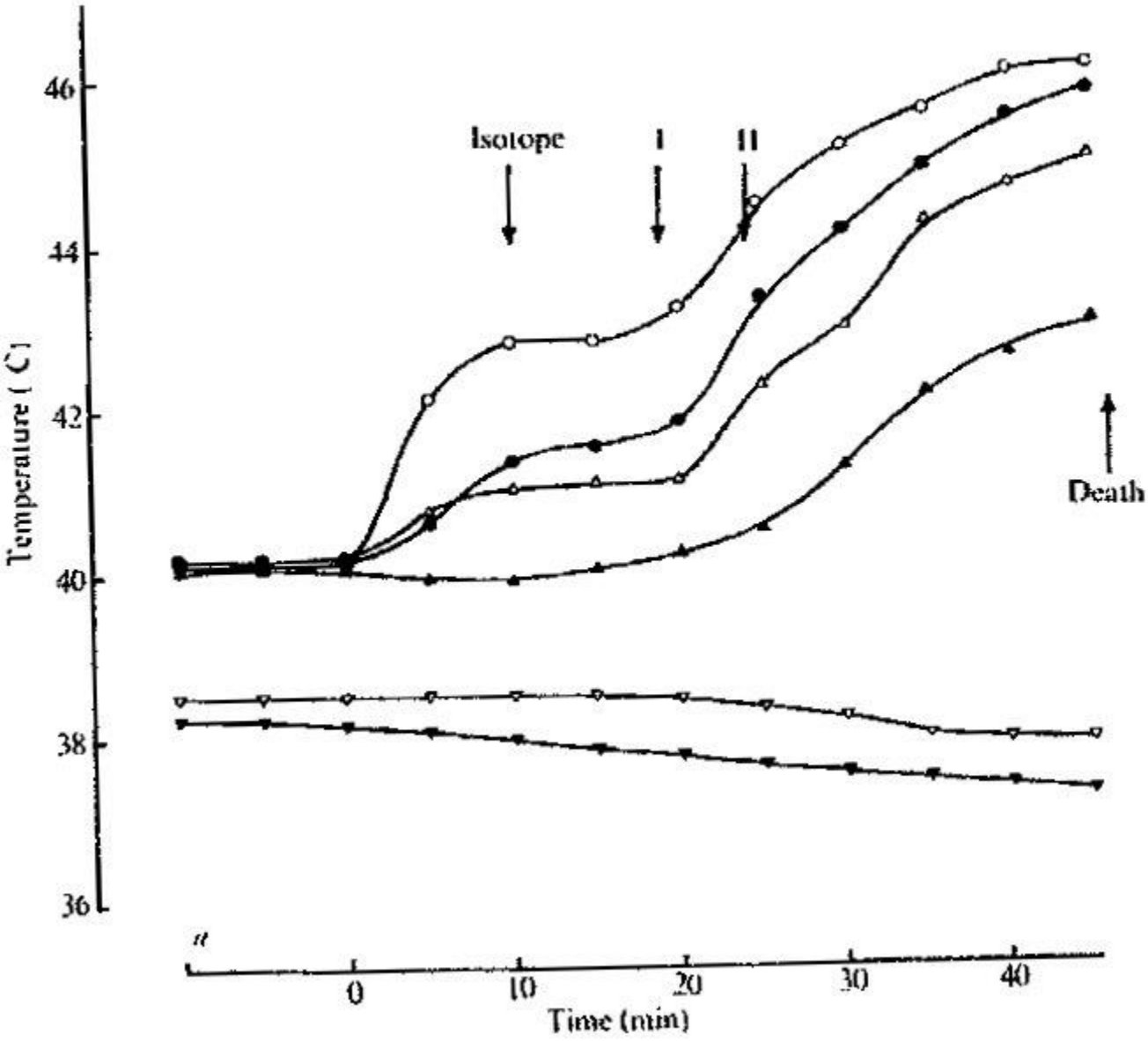
Slide from UW Arlington Farms



Economic Importance-1972

- Human MH cases: (1.2 M Malpracrice settlement)
- Porcine Stress Syndrome
- 1972-250-320 M
- PSE: 25% of carcasses in some packing plants
- Decreased feed efficiency
- Death losses at the farm
  - Baby pig mortality, transport deaths, heat stress.


d-TUBOCURARINE (10.08A)
PANCURONIUM (10.02A)
SUCCINYLCHOLINE (10.95A)
10.4A


Isotope
I
II
Death
Temperature (°C)
46
44
42
40
38
36
0
10
20
30
40
Time (min)

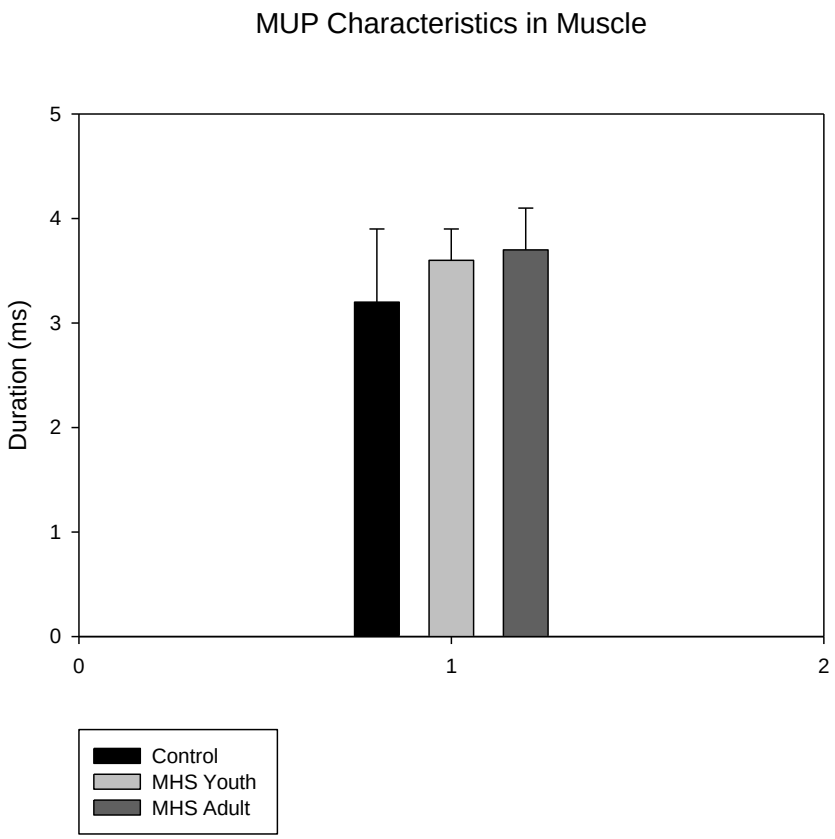
	220 ± 80	540 ± 50	2.8 ±
	(140 – 300)	(490 – 590)	(2.4 –
	300 ± 120	670 ± 40	3.3 ±
	(180 – 420)	(630 – 710)	(2.5 –
± SD	300 ± 160	550 ± 100	3.2 ±

essed as mean ± SD (min-max limits).

e MUP Characteristics of Muscles of Four

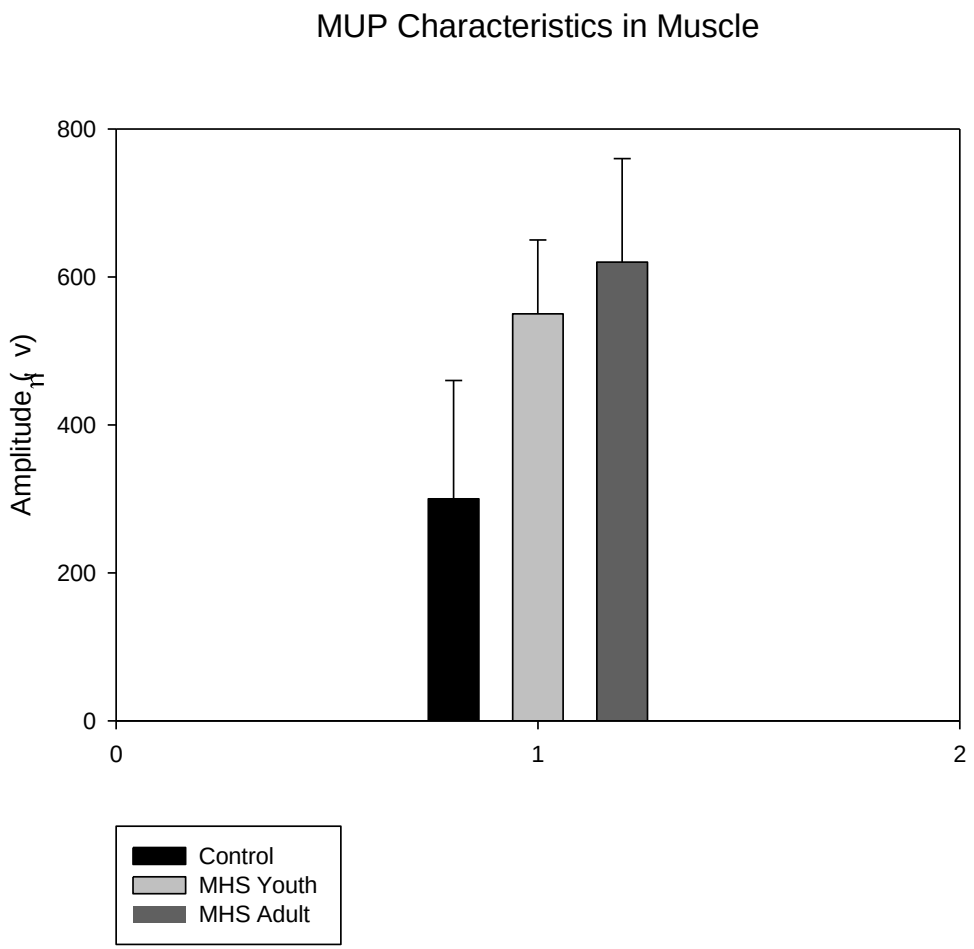
	Amplitude

MUP times



P<0.05

MUP amplitude



Malignant Hyperthermia in KC 1965-1985

- 2,038,200 anesthetics performed
- 38 cases of MH
- 1: 53, 636
- Succinylcholine was used in 87% of MH cases
- Halothane, enflurane, isoflurane was used in 84% of MH cases
- 4 MH deaths pre-dantrolene
- 0 deaths post-dantrolene

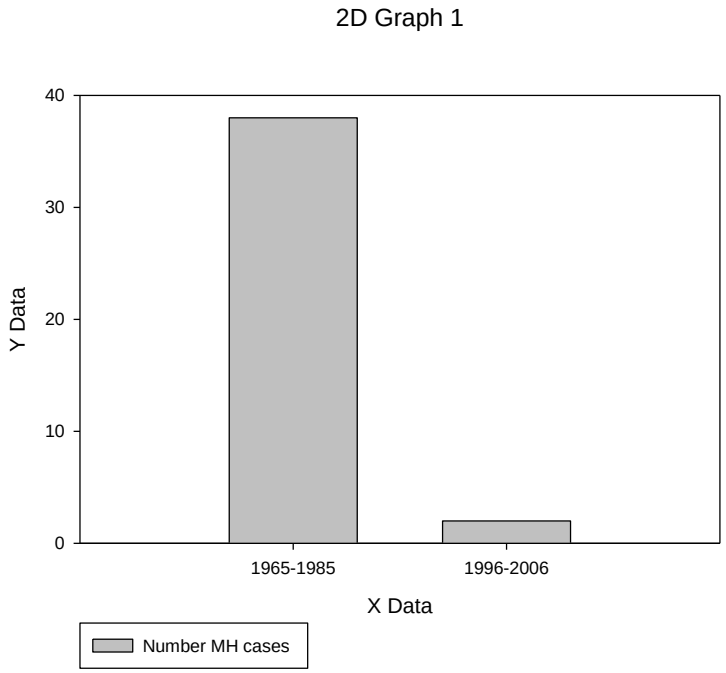
36
a
0
10
20
30
40
Time (min)
2
1
0
1
Muscle venous/arterial blood
temperature difference (°C)
b
0
10
20
30
40
Time (min)
6
4
denine nucleotides
eight of muscle)

Sevoflurane Development

- Sevoflurane synthesized at Baxter Labs-1971
- 1984-CHW contacted by Maruishi Pharm., Osaka, Japan
- Maruishi purchased Sevoflurane for $8,000,000
- ~1992 Abbott started selling Sevoflurane
- 2000- Court case in N. IL. Abbott selling $200 million per year of sevoflurane as Ultane

MH in KC 1996-2006

- 17/22 surgical-anesthesia units responded
- Total general inhalation anesthetics- 119,448 for 2006 x 10 = 1, 194, 480
- 2 MH cases = 1: 597,240
  - Diagnosed early
  - Treated with Dantrolene
  - Both cases survived

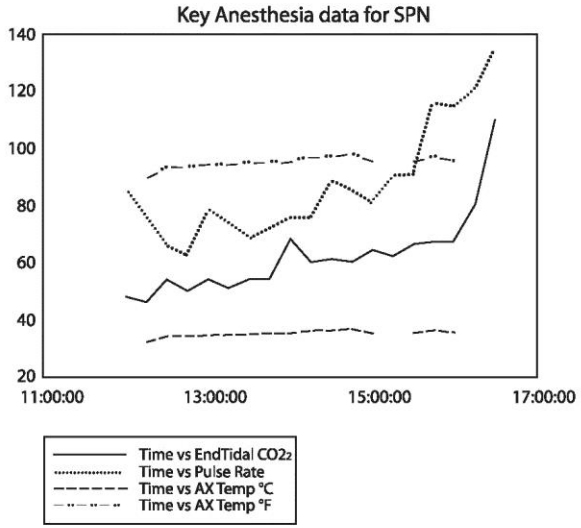

2D Graph 1
40
30
20
10
0
Y Data
1965-1985
1996-2006
X Data
Number MH cases

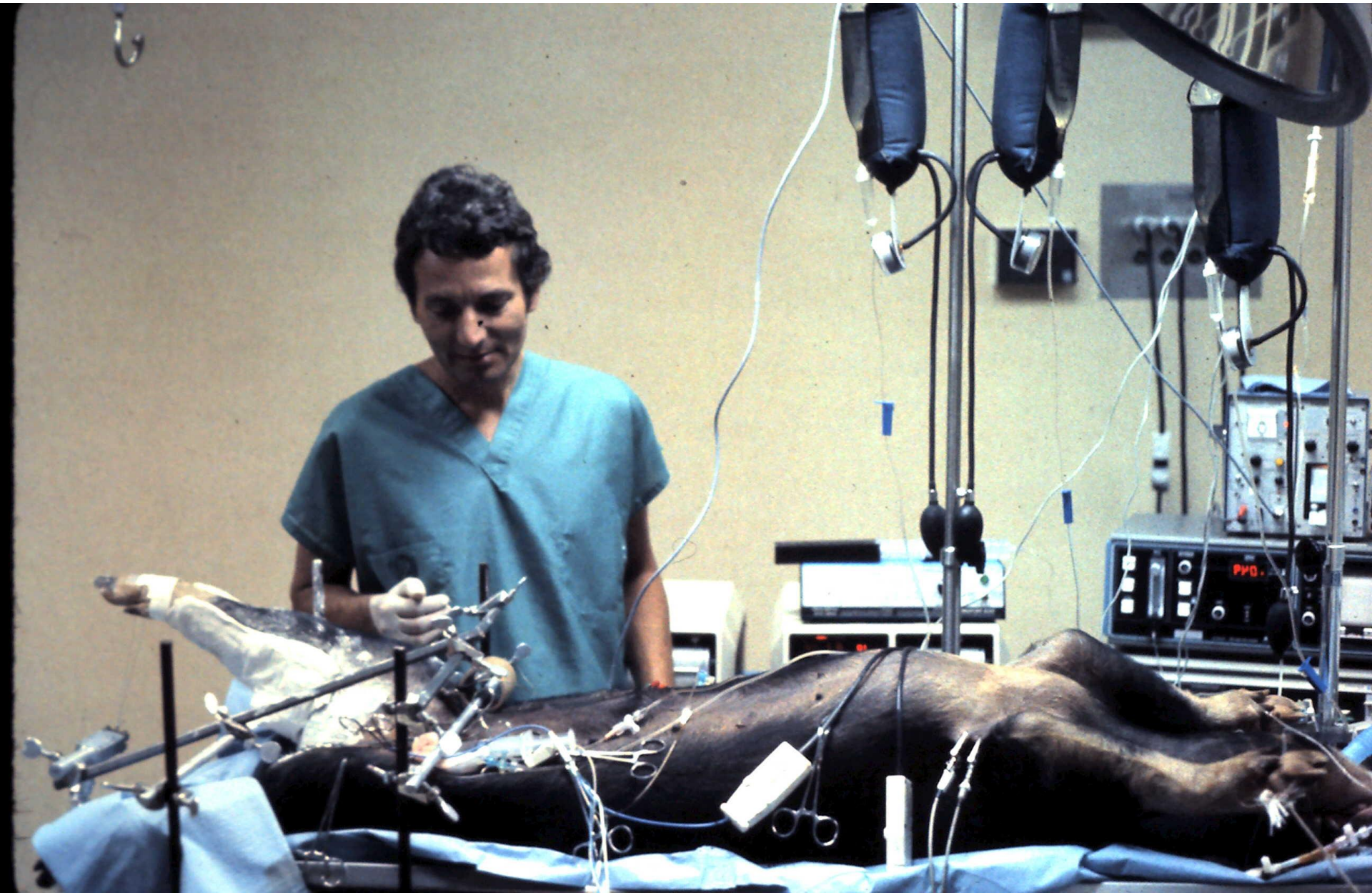
MH cases outside KC

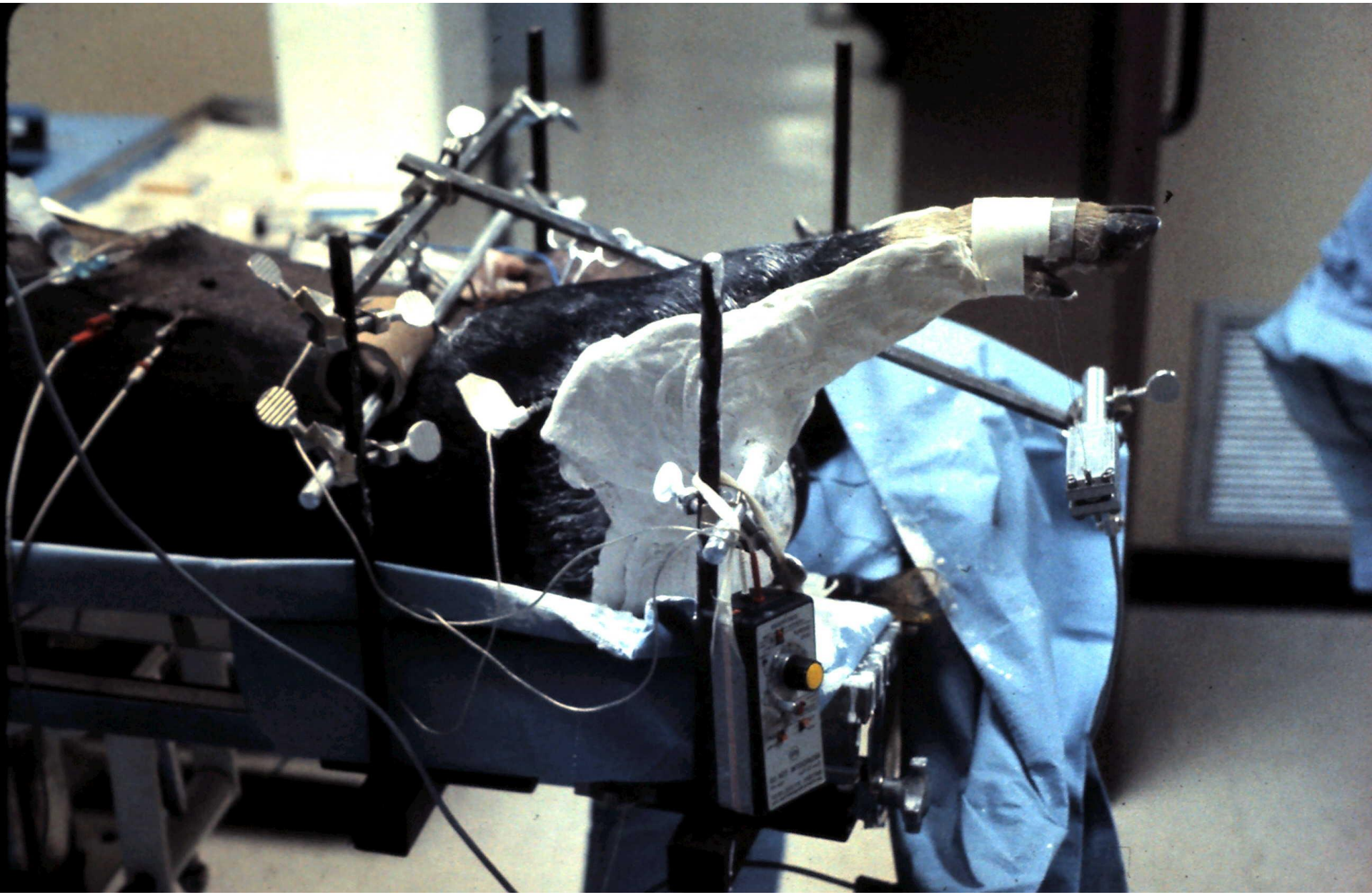
- Medline search- 29 cases MH with sevoflurane
  - All cases used succinylcholine as muscle relaxant
  - Dantrolene used in all cases and 100% survival

MH cases with Death

- SPN of Lacrosse, WI
  - Shoulder injury from skiing
- SJK of West Palm Beach, FL
  - Inverted nipple surgery


Key Anesthesia data for SPN
140
120
100
80
60
40
20
11:00:00
13:00:00
15:00:00
17:00:00
Time vs EndTidal CO2₂
Time vs Pulse Rate
Time vs AX Temp °C
Time vs AX Temp °F

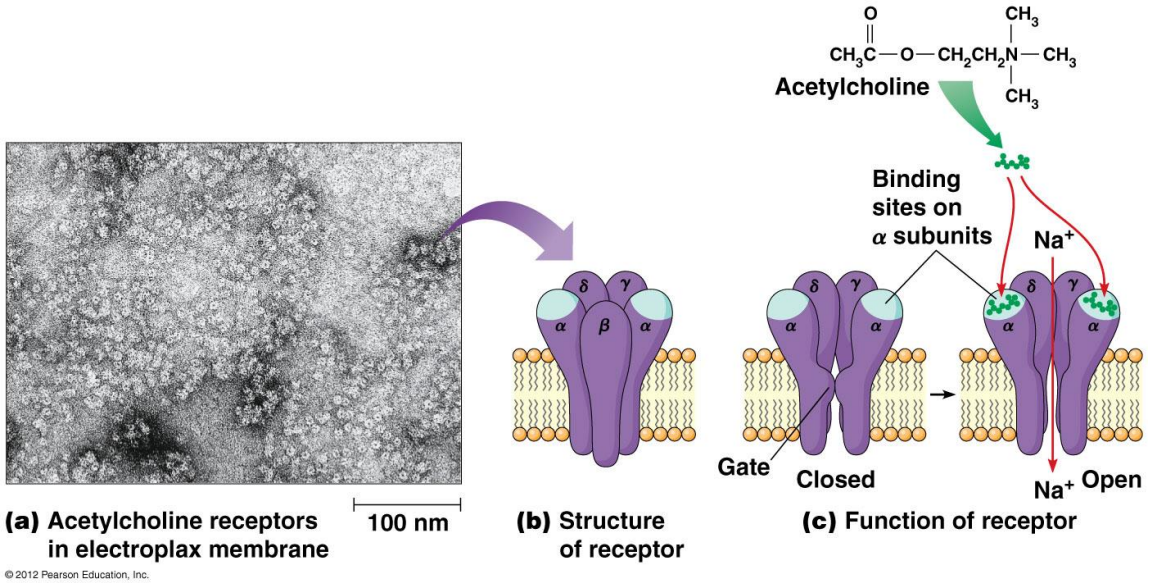




Safe Muscle Relaxants

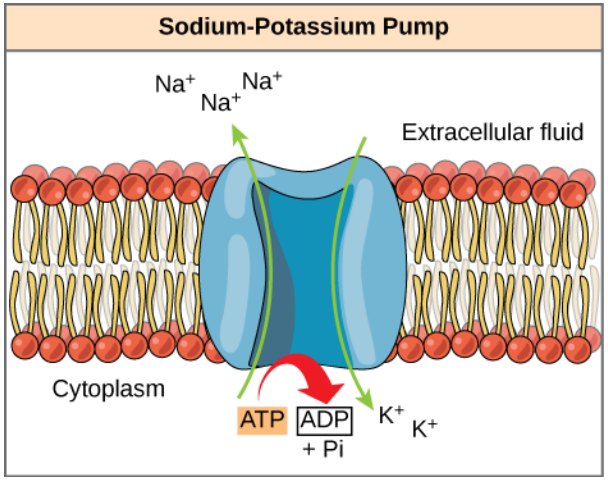
- Vecuronium
- Atracurium
- Organon 9426-Will actually prevent MH

Sodium channel structure

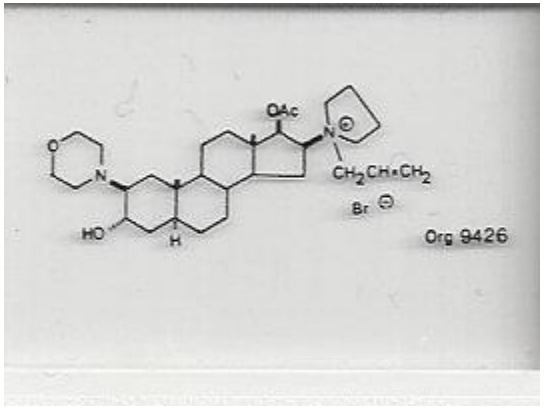


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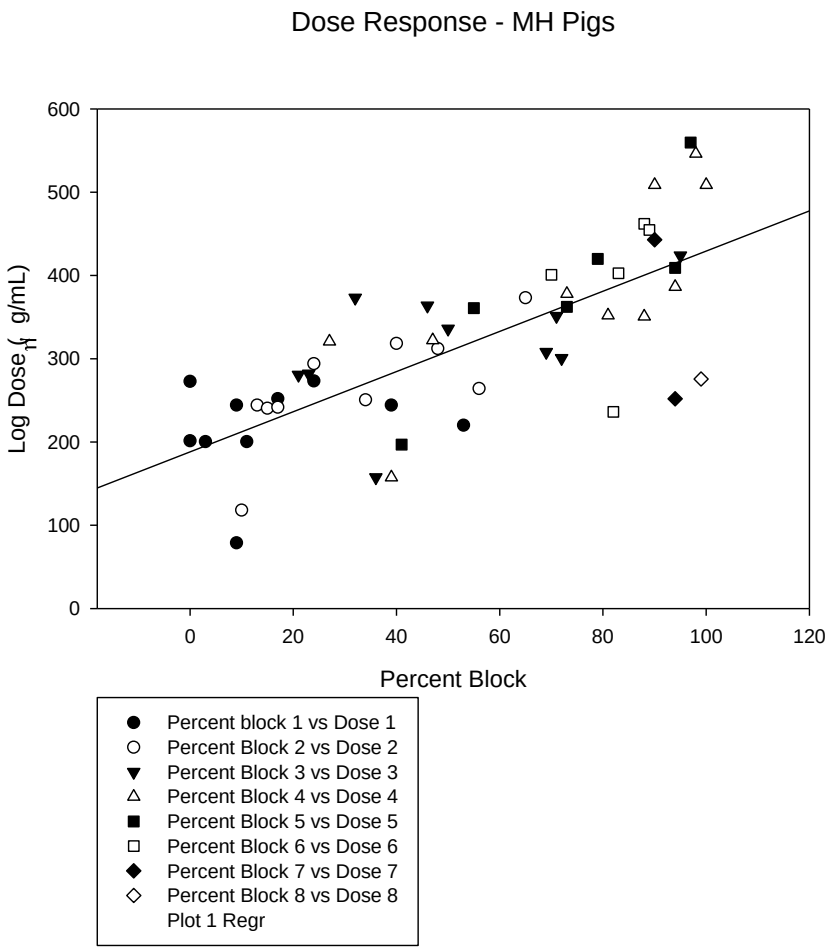
Sodium Potassium Pump



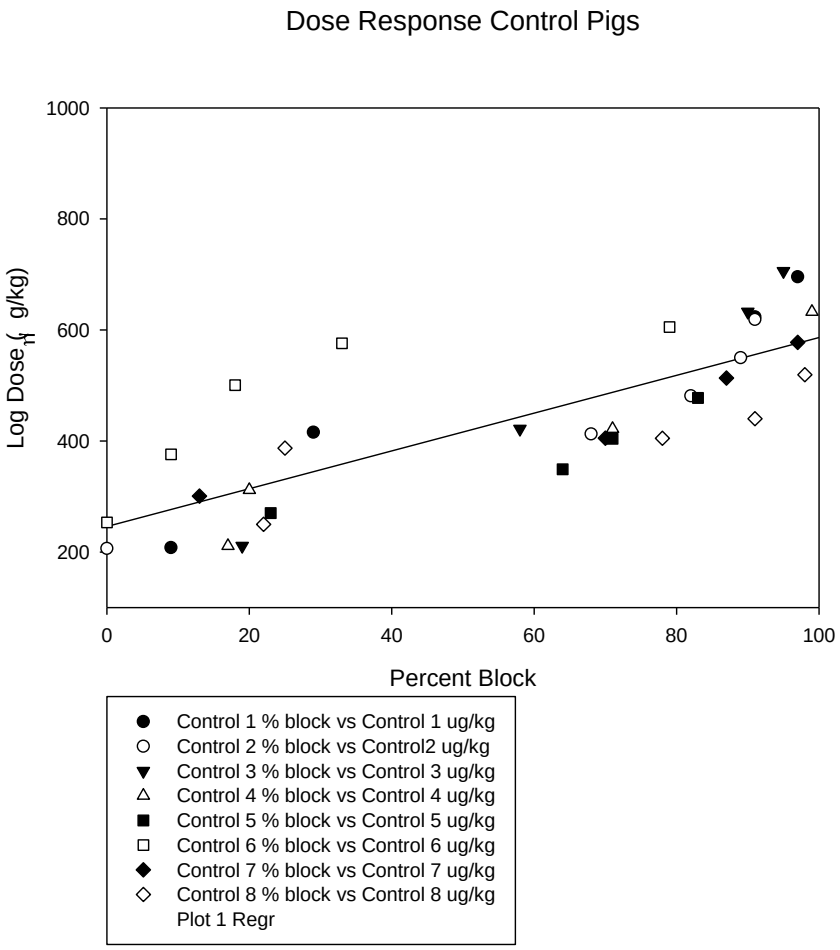
Organon 9426



Organon 9426



Organon 9426



Dose Response to 100% block

- Dose Response-ug/kg Org 9426
- Control pigs: 586.31
- MH pigs: 427.033
- 73% of the dose required by control pigs

Summary

- Fewer Na+ channels-30-35% decrease
- Total MH protection indicates an alosteric receptor site that regulates Na+ channel activity
- Succinylcholine holds open sodium channel
- Organon 9426 closes sodium channel to normal
- Genetic defect is a abnormal function at myonueral junction.