Thermal biology hyperthermia & ablation

Michael R. Horsman
Professor of Experimental Radiotherapy

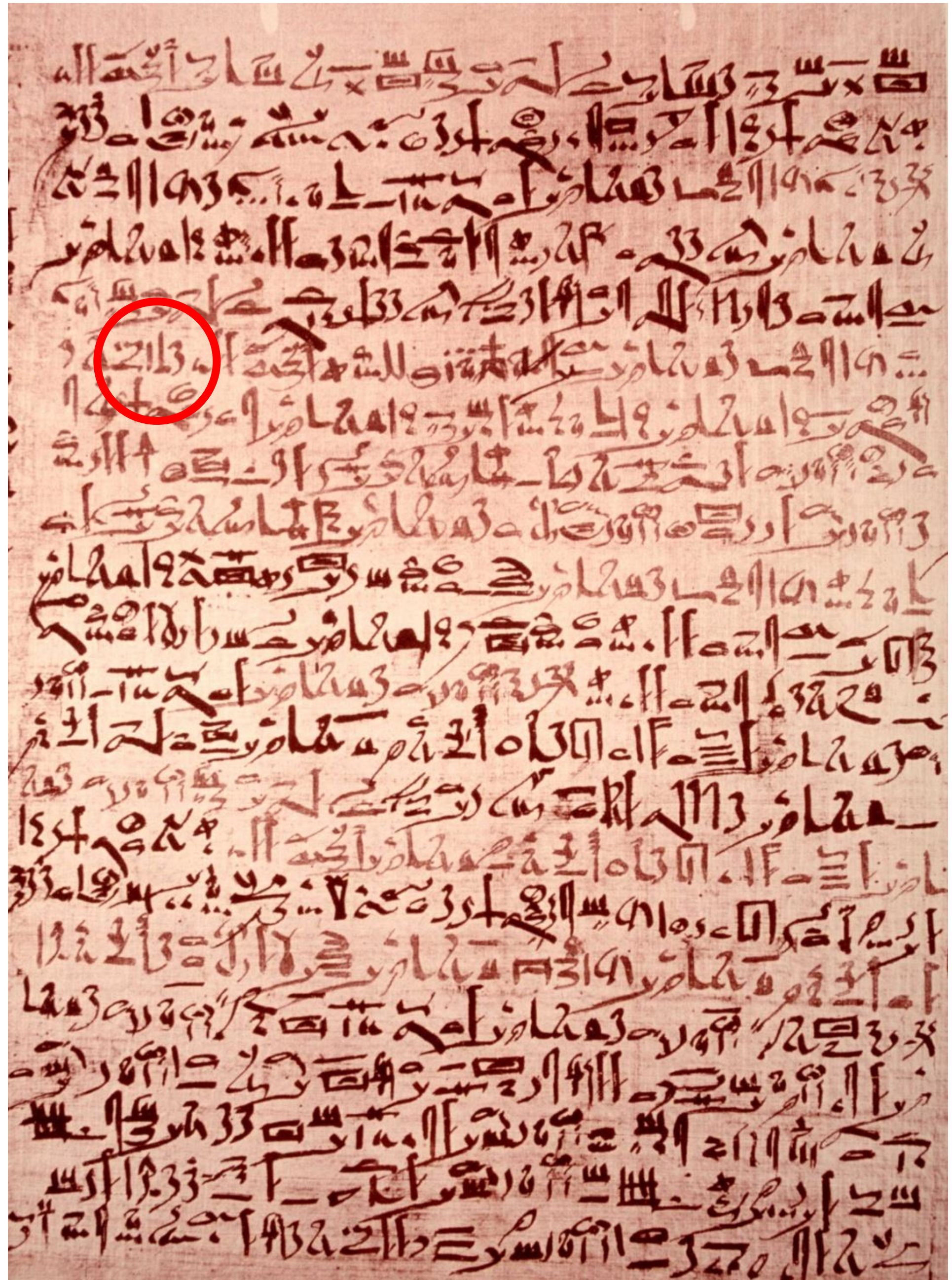
Experimental Clinical Oncology-Dept. Oncology
Aarhus University Hospital
Aarhus, Denmark.

Aarhus University

Aarhus University Hospital

Historical perspectives

- 3000 B.C. - Egypt (Edwin Smith Surgical Papyrus)
- 400 B.C. - Greece (Hippocrates)
- 200 A.D. - Rome (Galen)
- 17th Century - Reports of tumour regression in patients suffering with infectious fever
- 19th Century - Fever induced treatment to control tumour growth (Coley's toxin 1893)
  - Water circulating cisterns to treat carcinoma of the uterus with temperatures of 42-44 ^{O}C (F.Westermark 1898)
- 20th Century - Diathermy (Nagesschmidt 1926; N.Westermark 1927)
  - Dose-time thermal effects (Stevenson 1919; Rohdenburg & Prime 1921; Crile 1960s)



The Edwin Smith's Surgical Papyrus

Historical perspectives

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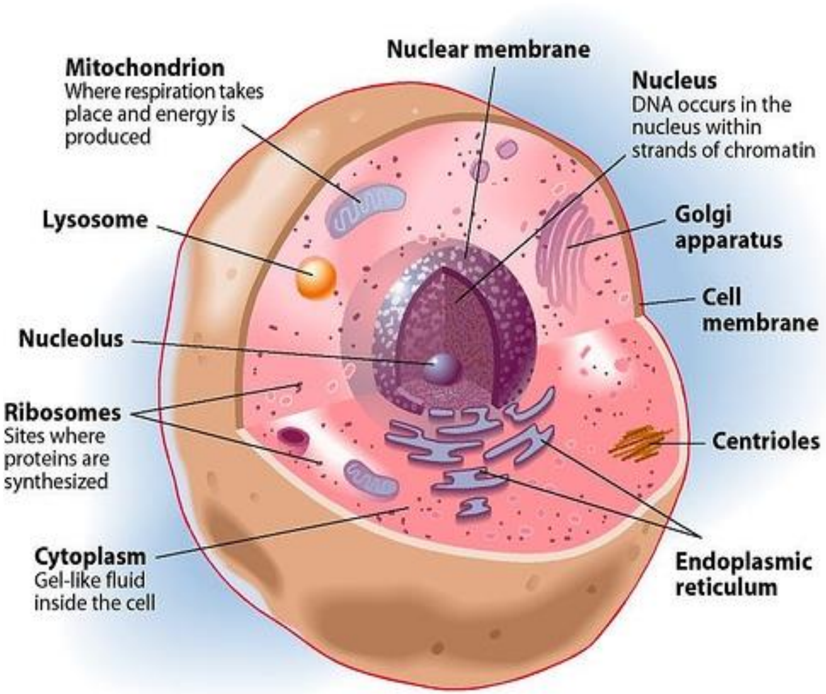
Heating Temperatures

- Fever range: 39-42 ^{O}C
- Hyperthermia: 40-45 ^{O}C
  (Mild temperature $\leq$ 42 ^{O}C)
- Thermal ablation: >45 ^{O}C

Targets for heat



- Membranes - lipids
  - proteins
- Cytoskeleton - microfilaments
  - microtubules
- Cytosol - mitochondria
  - lysosomes
  - respiration/glycolosis
  - protein synthesis
- Nucleus - DNA replication
  - RNA synthesis
  - chromosomal damage

Membrane transport

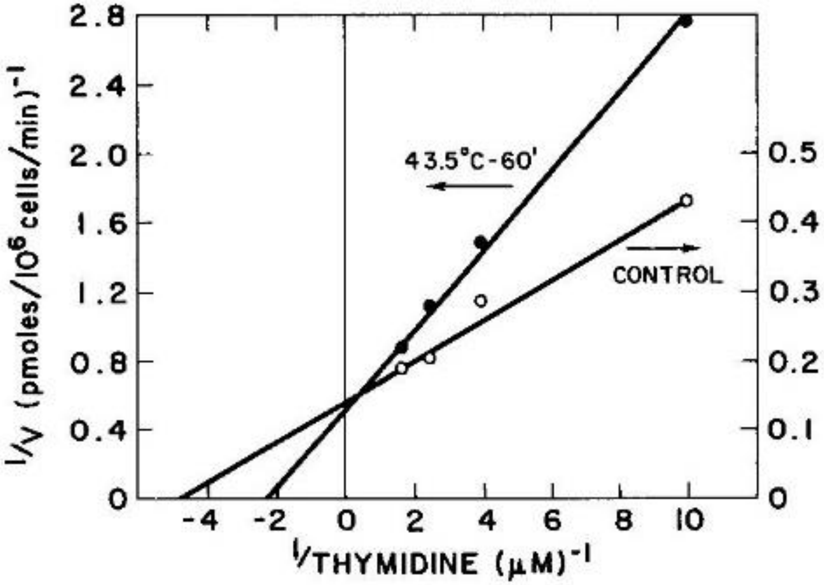


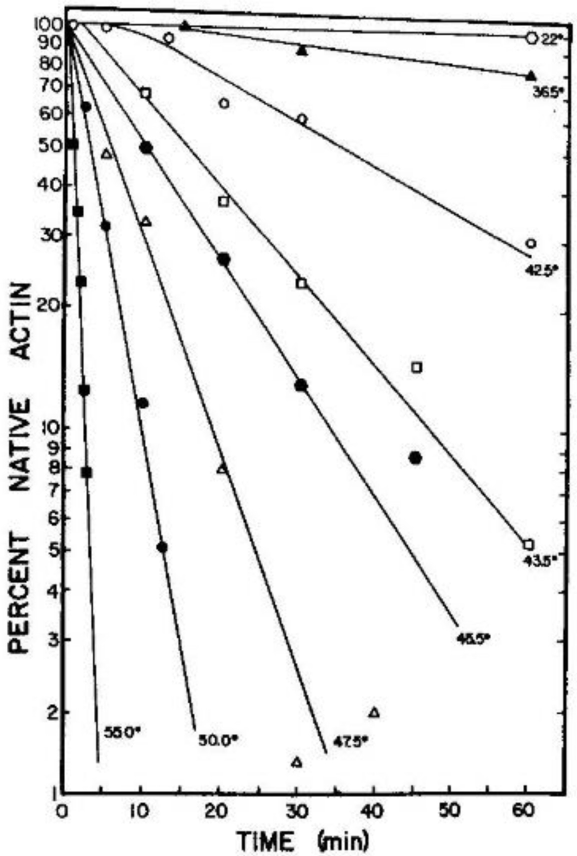
TABLE 1.—*Inhibition of dThd uptake by hyperthermia*[a]

Temperature, degrees C	Duration, min	Culture[b]	Postheating, min	V_{max} heated/control
43.5	60	M	20	0.43
43.5	60	M	20	0.59
			120	0.49
45.5	15	M	20	0.24
45.5	20	M	120	0.45
43.5	60	S	20	0.28
45.5	20	S	20	0.38
			180	0.14
			360	0.09

[a] Each temperature entry indicates a separate experiment in which V_{max} values were obtained from initial uptake rates or values.
[b] M = monolayer; S = suspension culture.

Slusser et al. (1982) JNCI 61:85-87

Protein inactivation



Heacock et al. (1982) JNCI 61:73-75

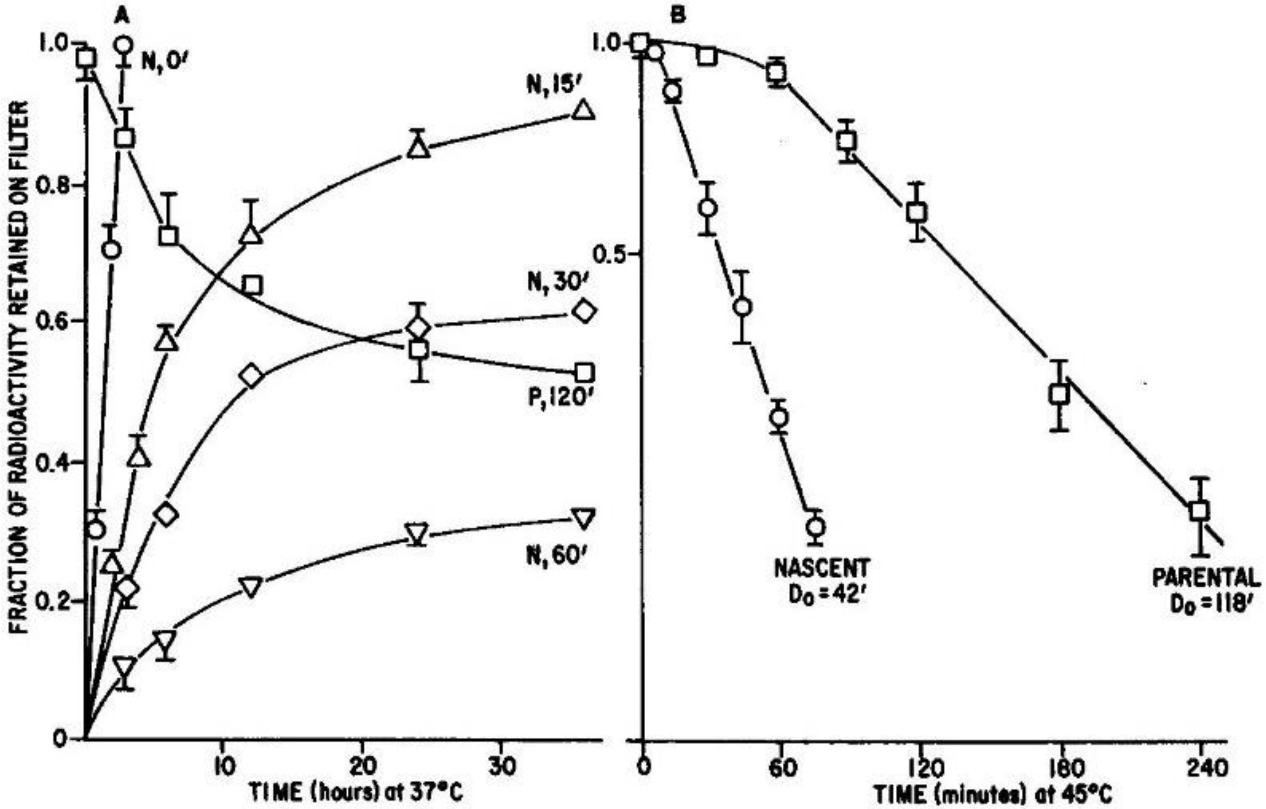
Cytoskeletal reorganization

Cell type	Stress-treatment	MF[a]	MT[b]	IF[c]
Rat hepatoma (H35)	30′, 43°C	X[e]	+[e]	+
Mouse neuroblastoma N2A	30′, 43°C	+	X	X
Mouse neuroblastoma N2A	60′, 100 μM arsenite	+	X	X
Mouse neuroblastoma N2A	30′, 45°C	+	+	+
C_3H-2K fibroblasts	30′, 43°C	X	nd[f]	nd
CHO cells	5′, 45°C	X	nd	nd
CHO cells G1,S	5–35′, 45°C	X	X	X
CHO cells G1	60–150′, 43°C	nd	X	nd
C3H 10T1/2 fibroblasts	30′, 45°C	X	X	+
3T3 fibroblasts	30′, 45°C	X	X	+
3T3 fibroblasts	30′, 43°C	nd	X	nd
Chicken embryo fibroblasts	3 h, 45°C	+	+	X
Chicken embryo fibroblasts	5′-1 h, 45°C	nd	nd	X
	3 h, 45°C	nd	nd	+
Mouse mammary epithelial cells	15′, 45°C	X	+	X
Normal human fibroblasts	30′, 45°C	X	+	+
Drosophila cells	10′, 37°C	nd	nd	X
HeLa cells	12 h, AzC[g]	+	+	X
Gerbil fibroma cells	16 h, AzC	≫[h]	+	X
Rat embryo fibroblasts	3 h, 43°C	≫	+	X
Rat embryo fibroblasts	5 mM, AzC	≫	+	X

[a]MF = microfilaments
[b]MT = microtubules
[c]IF = intermediate filaments.
[d]X = reorganization or 'destruction'
[e]+ = 'intact'
[f]nd = not done
[g]AzC = proline analog
[h] ≫ = increase in number (stress fibres)

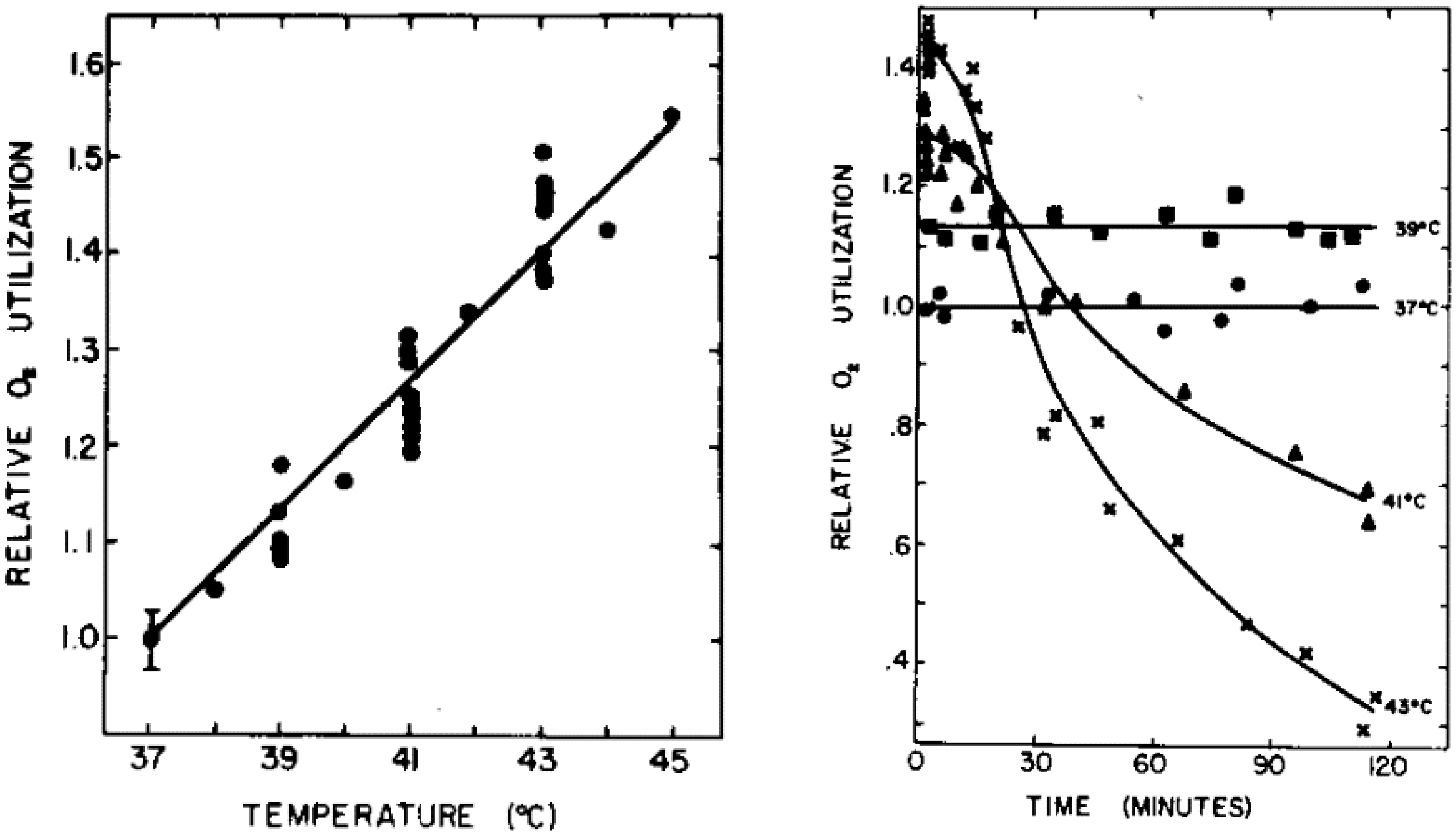
Coss & Linnemanns (1996) Int. J. Hyperthermia 12:173-196

DNA damage



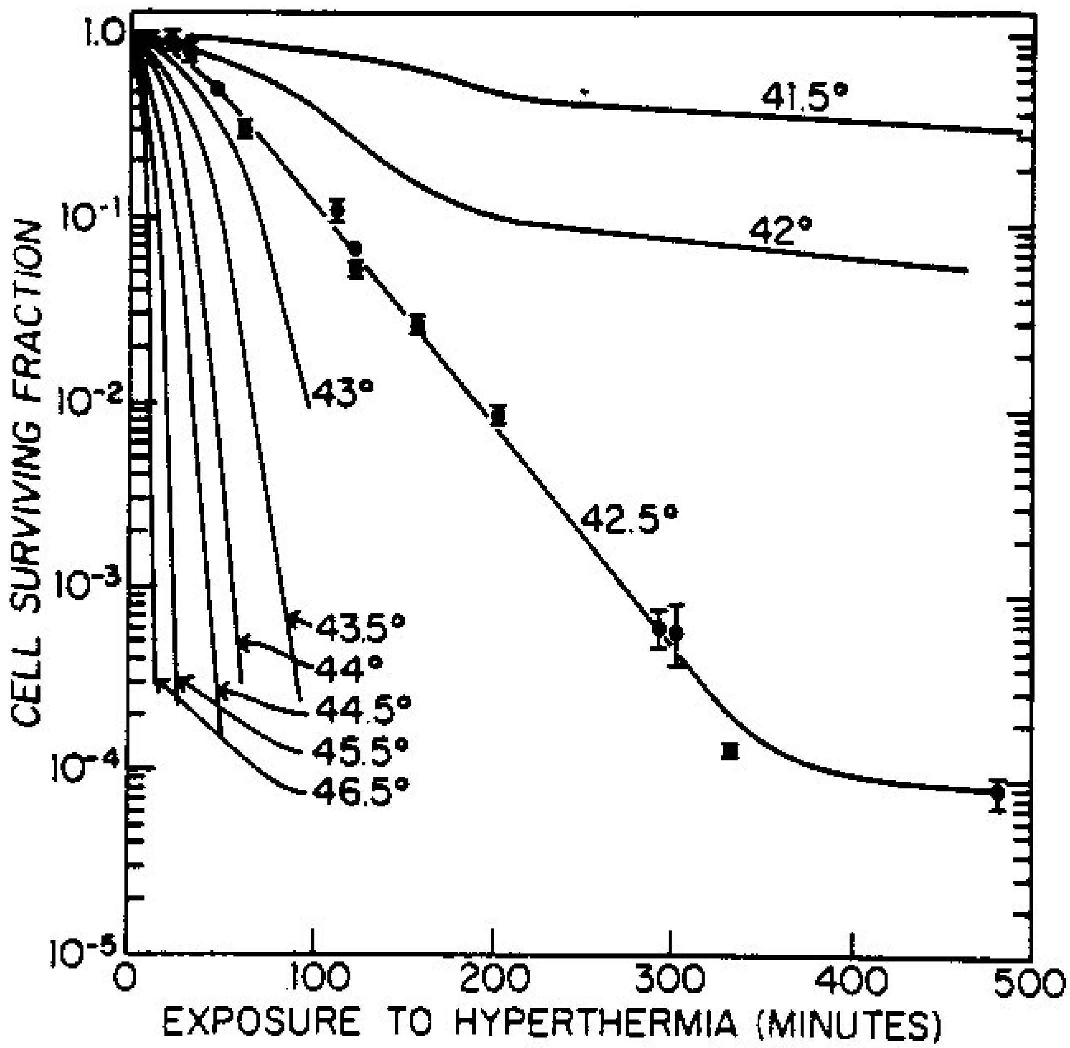
Warters (1982) JNCI 61:45-47

Oxygen consumption



Durand (1978) IJROBP 4:401-405

Cell killing by heat

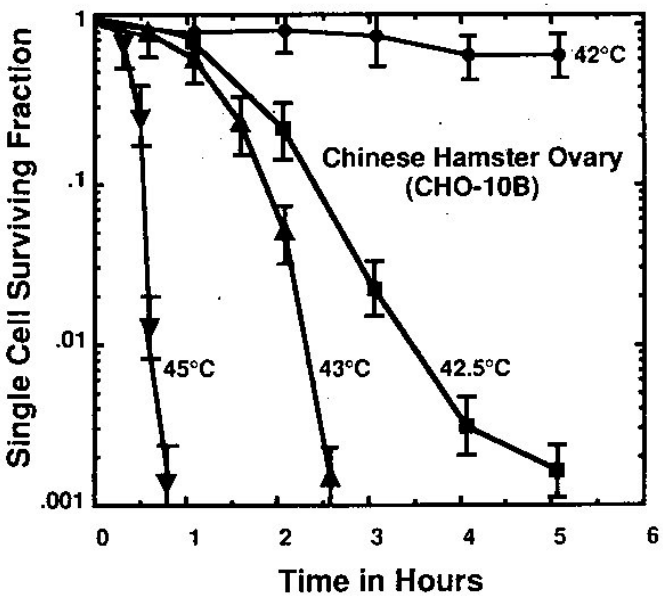


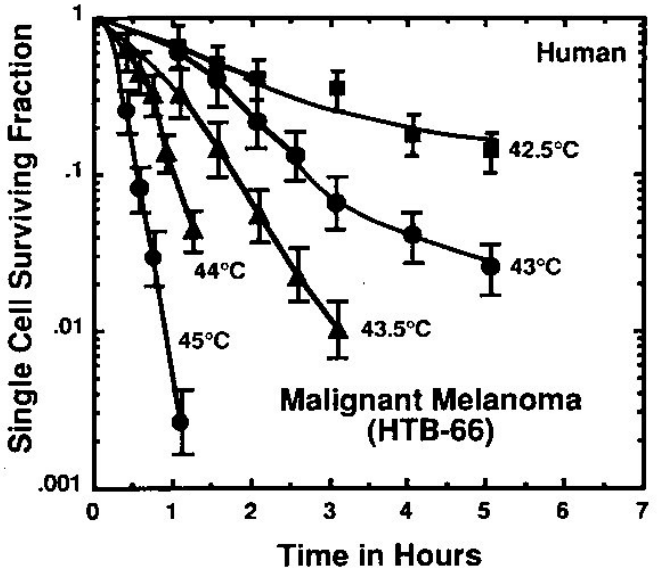
Dewey et al. (1977) Radiol. 123:463-474

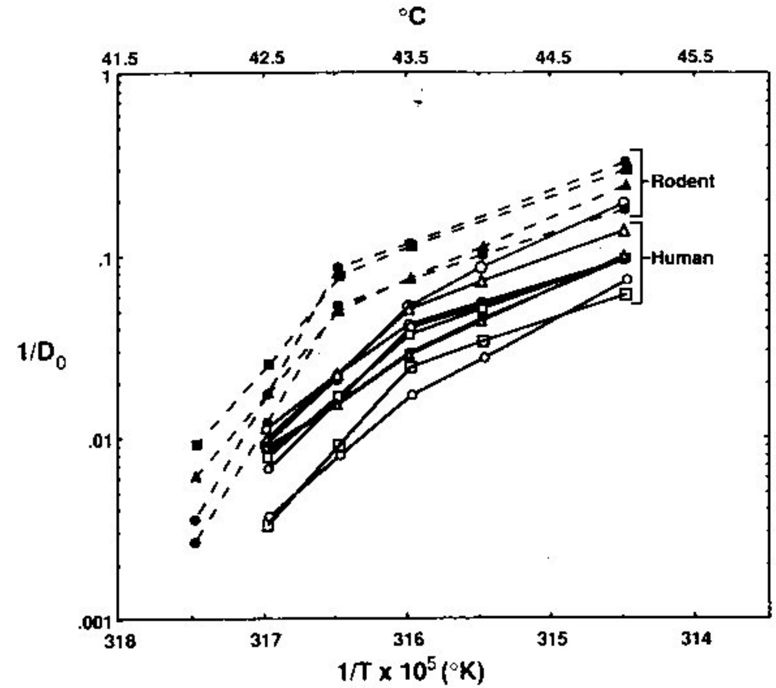
Factors influencing cell killing

- Cell type
- Cell cycle
- Hypoxia
- pH
- Metabolic status

Cell type

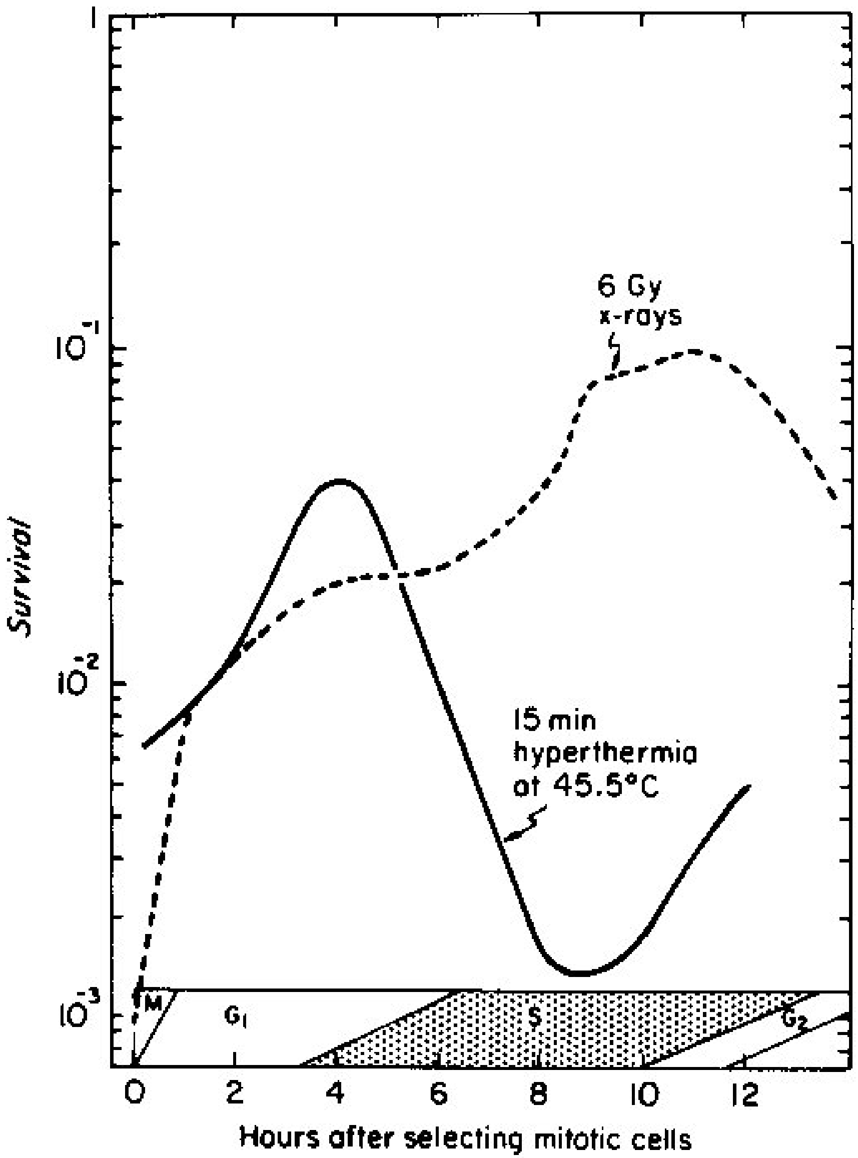






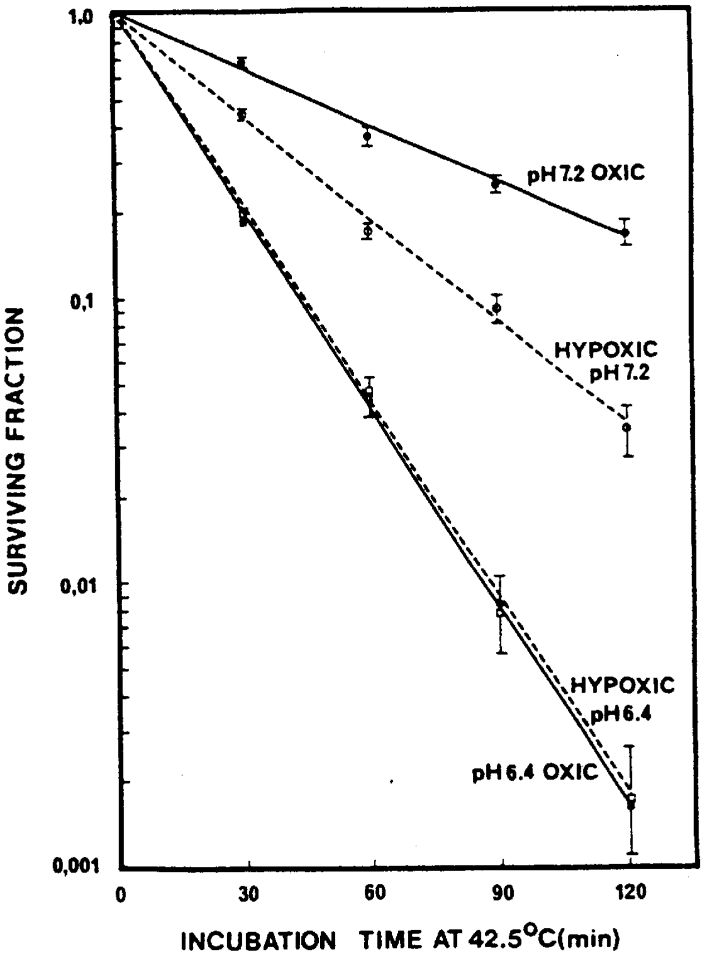
Roizin-Towle & Pirro (1991)
IJROBP 20:751-756

Cell cycle

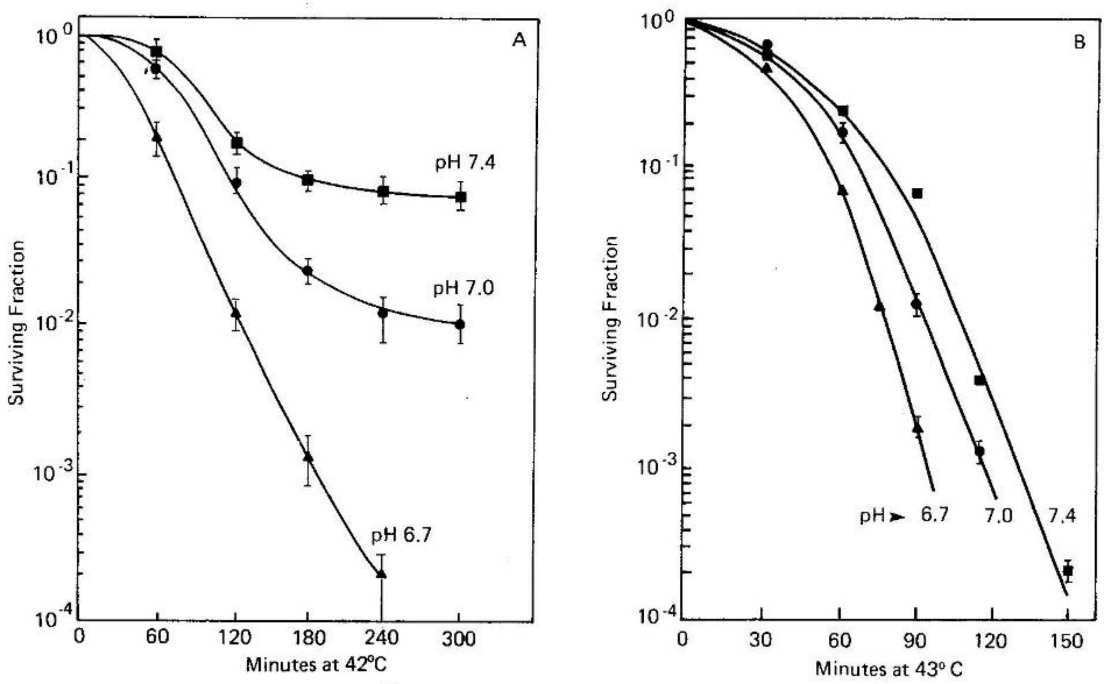


Dewey et al. (1977) Radiol. 123:463-474

Hypoxia and pH

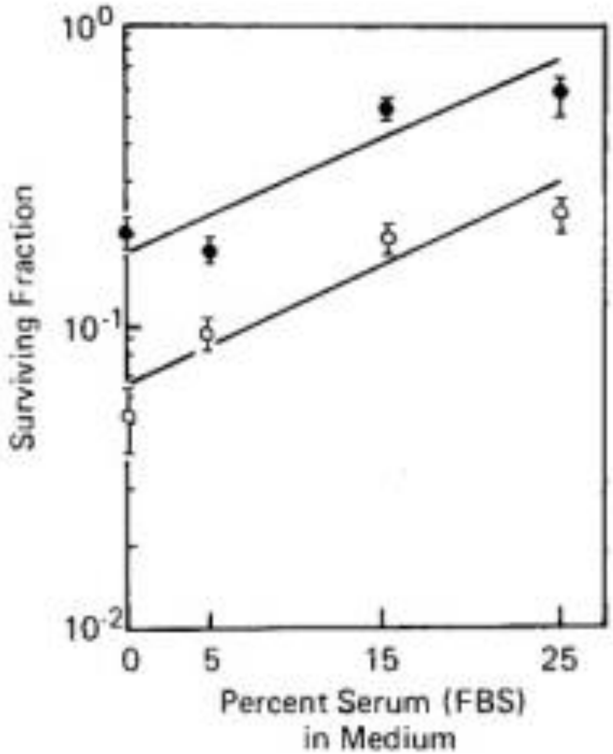


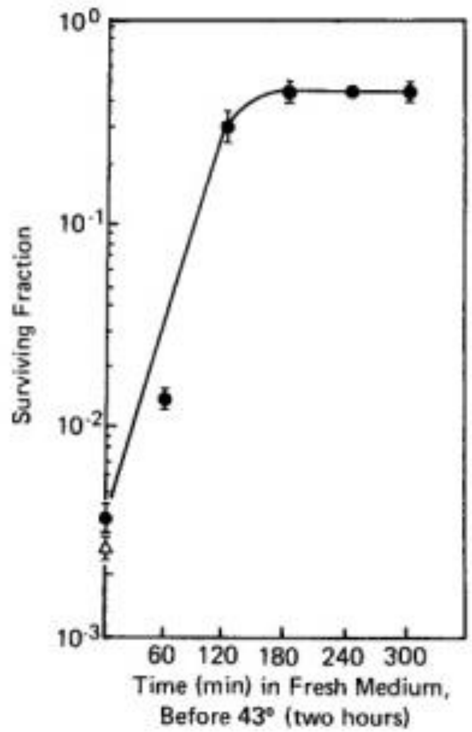
Overgaard & Bichel (1977)
Radiol. 123:511-514



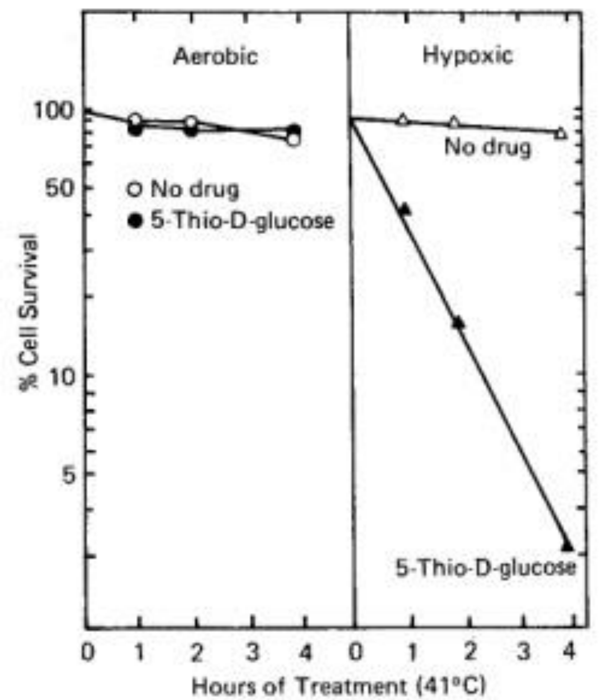
Gerweck (1977) Radiat. Res. 70:224-235

Metabolic status





Hahn (1974) Cancer Res. 34:3117-3123

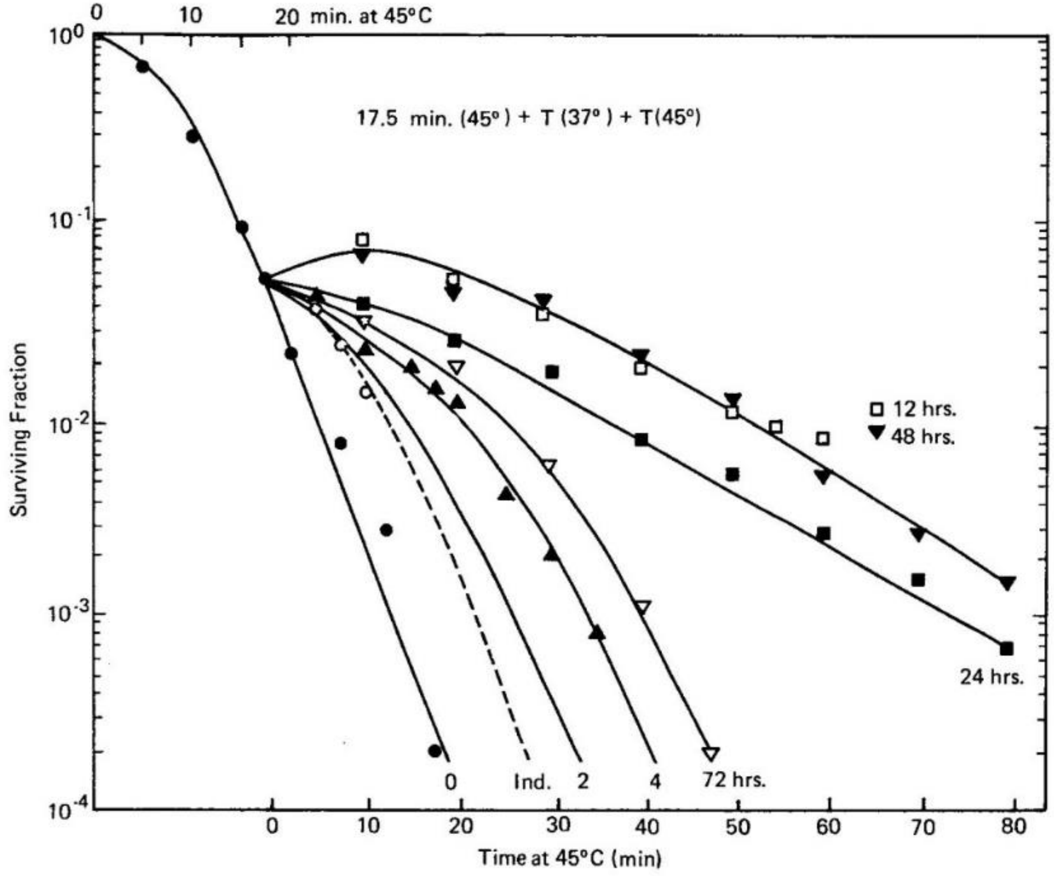


Kim et al. (1978) Cancer Res. 38:2935-2938

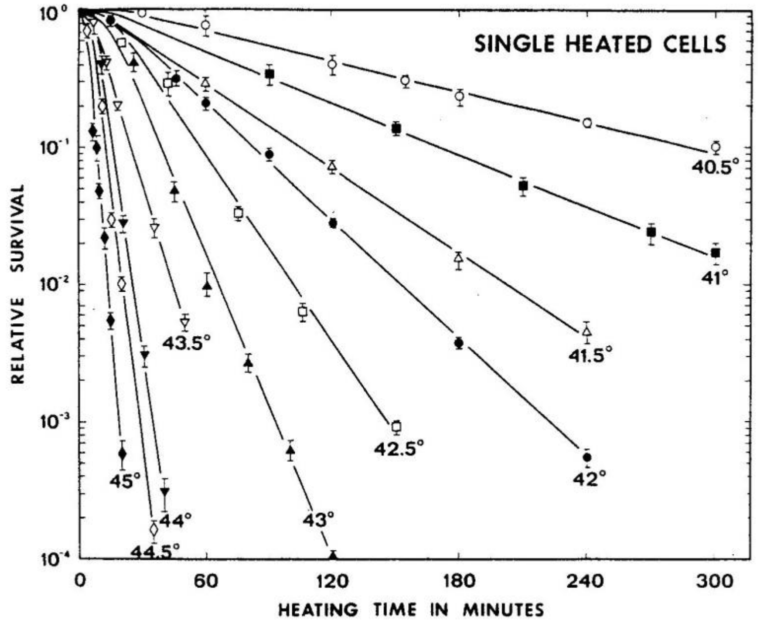
Additional factors influencing heat response

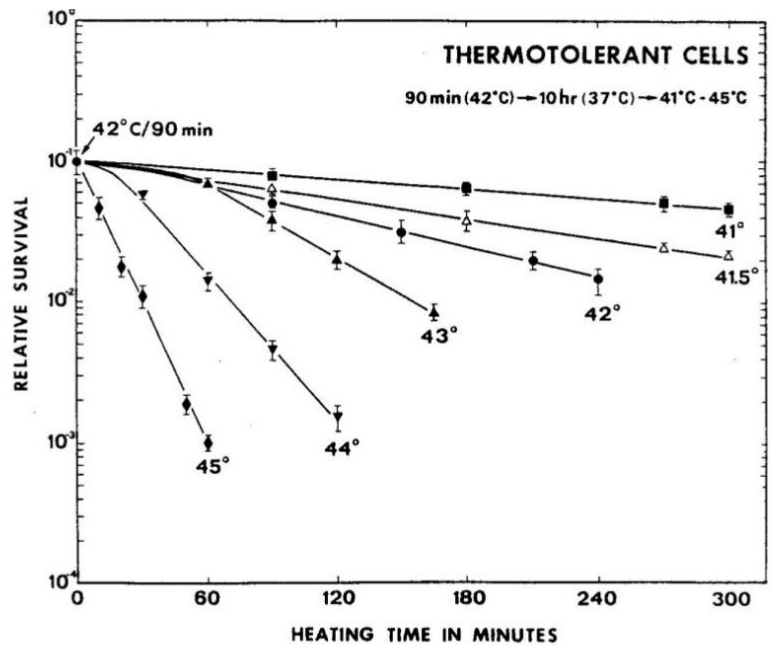
- Thermotolerance
- Step-up heating
- Step-down heating

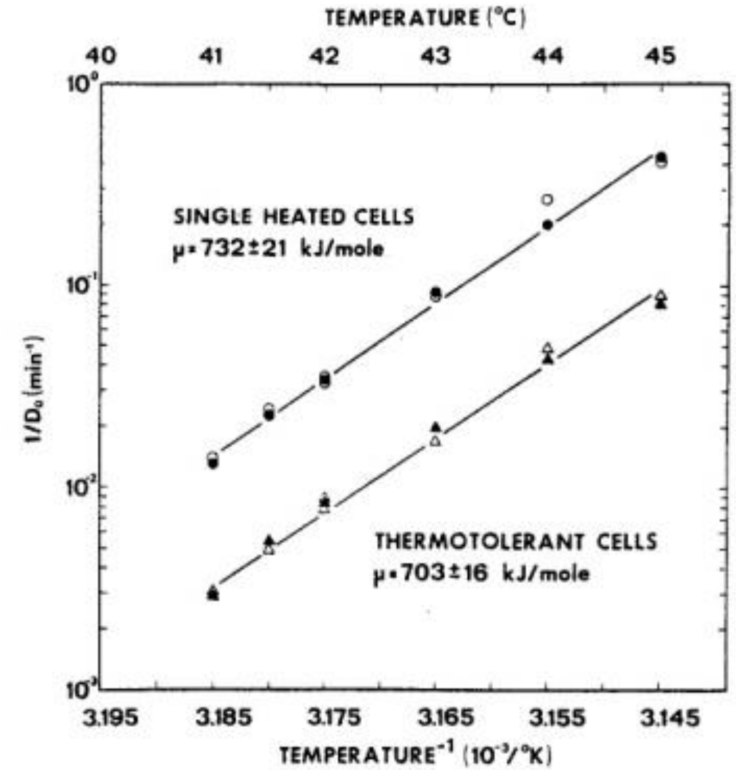
Thermotolerance



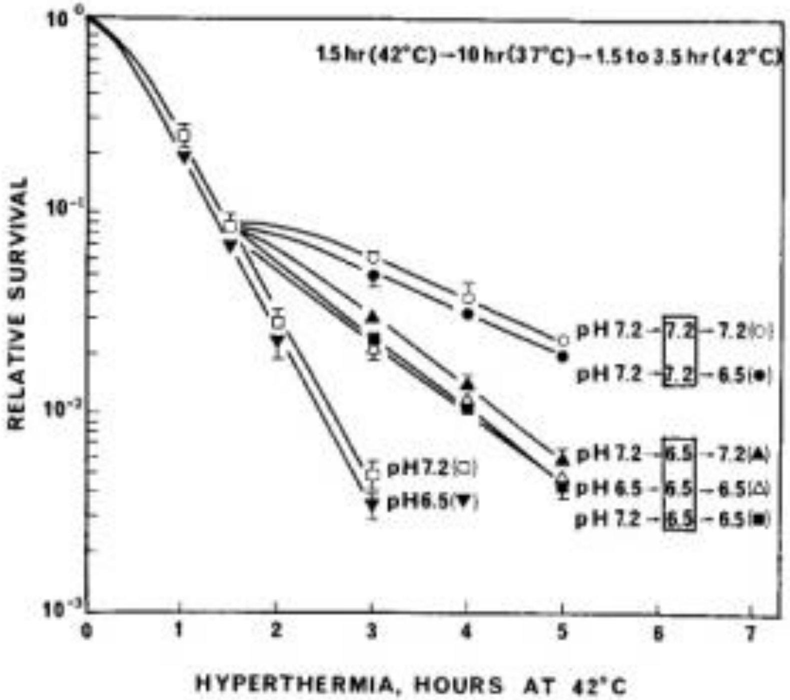
Henle & Leeper (1976) Radiat. Res. 66:505-518

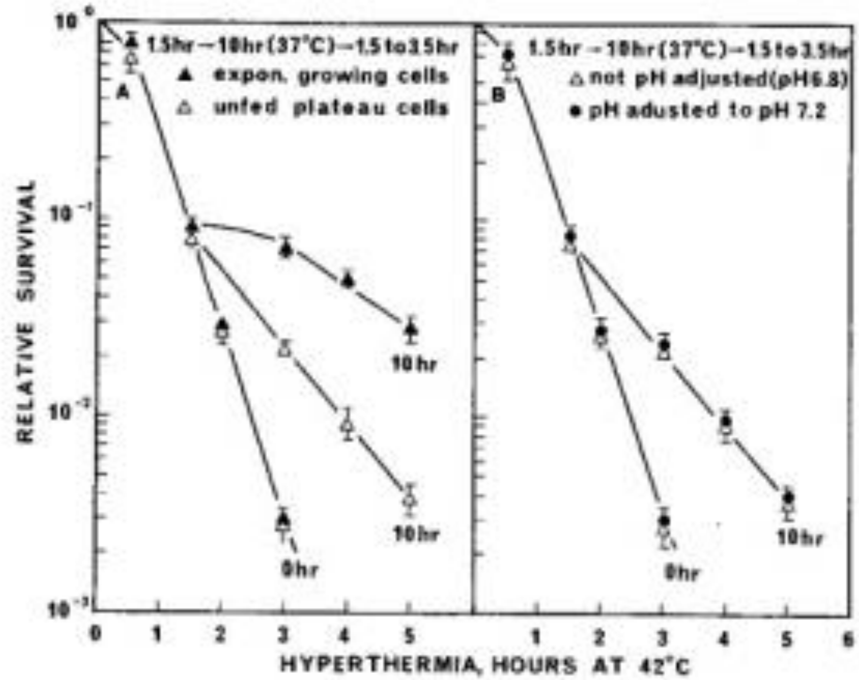






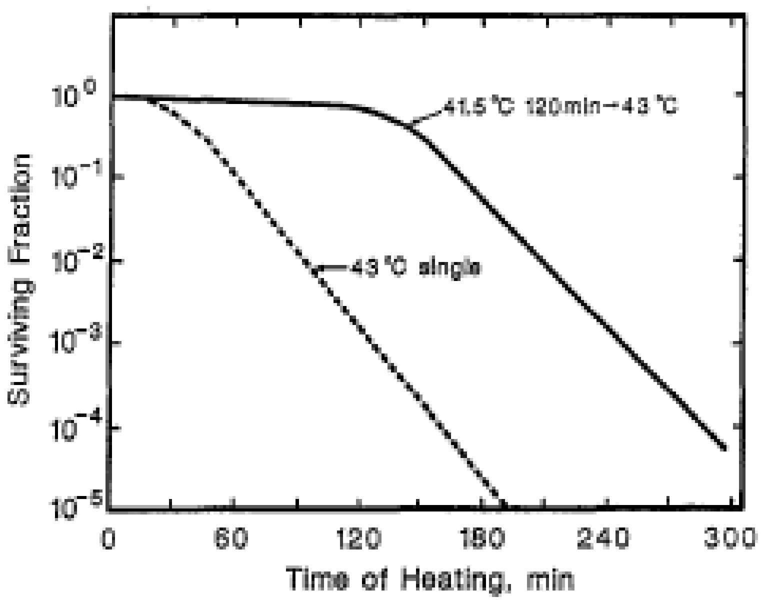
Nielsen et al. (1982)
Radiat. Res. 91:468-482



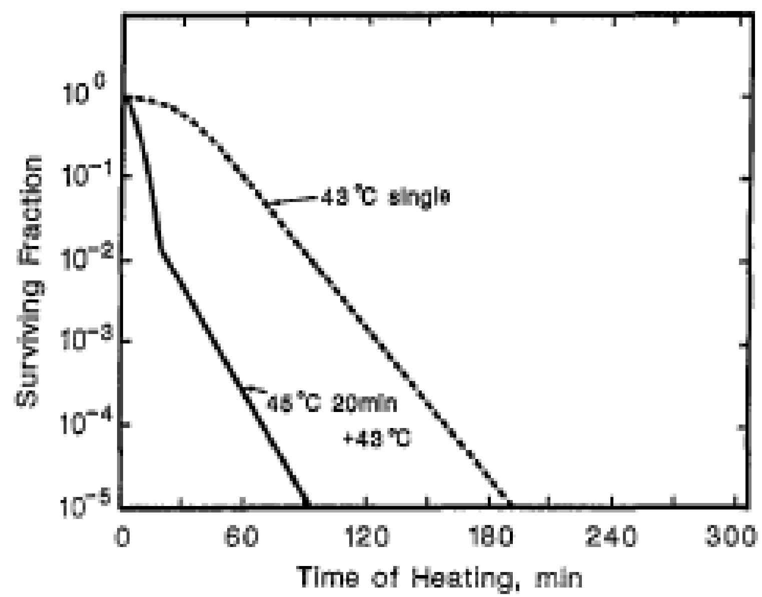


Nielsen & Overgaard (1982) JNCI 61:133-135

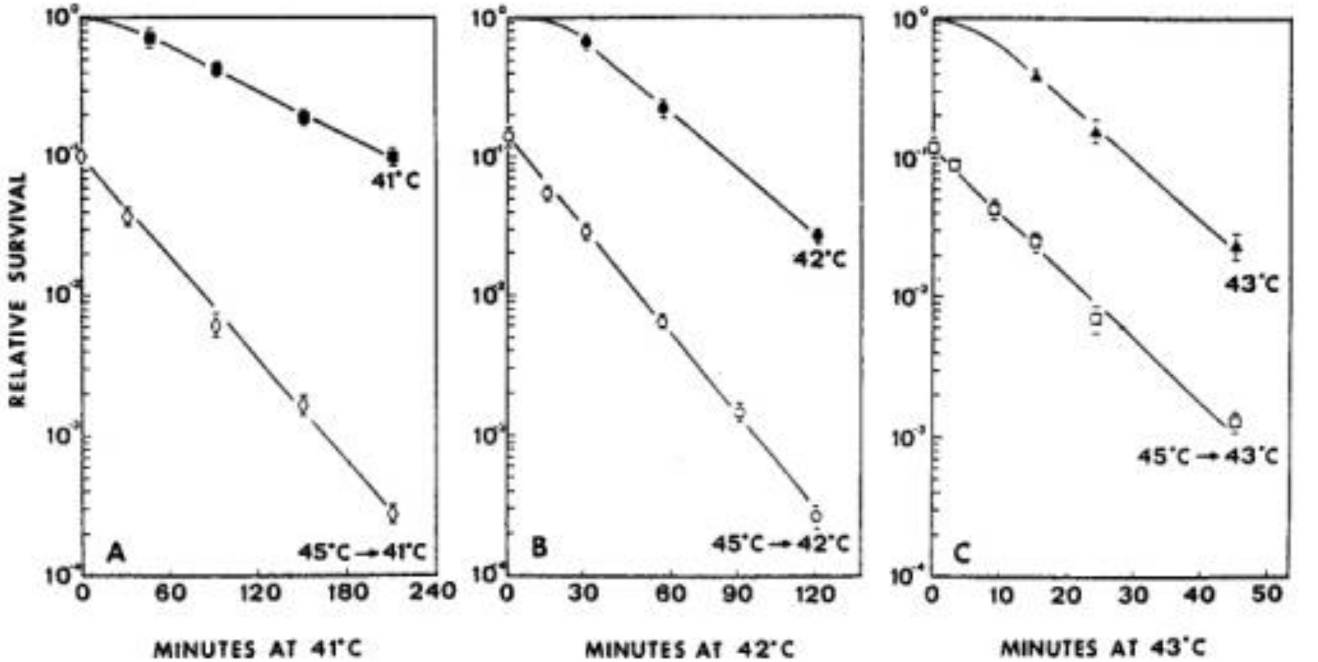
Step up heating

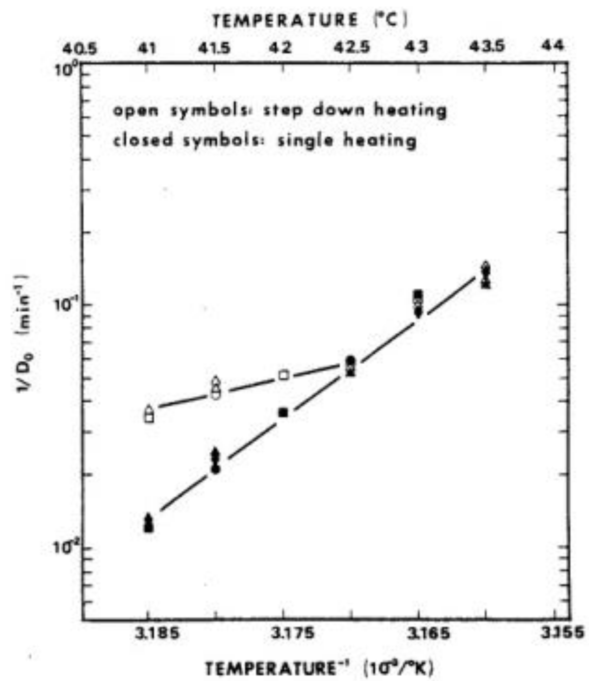


Step down heating



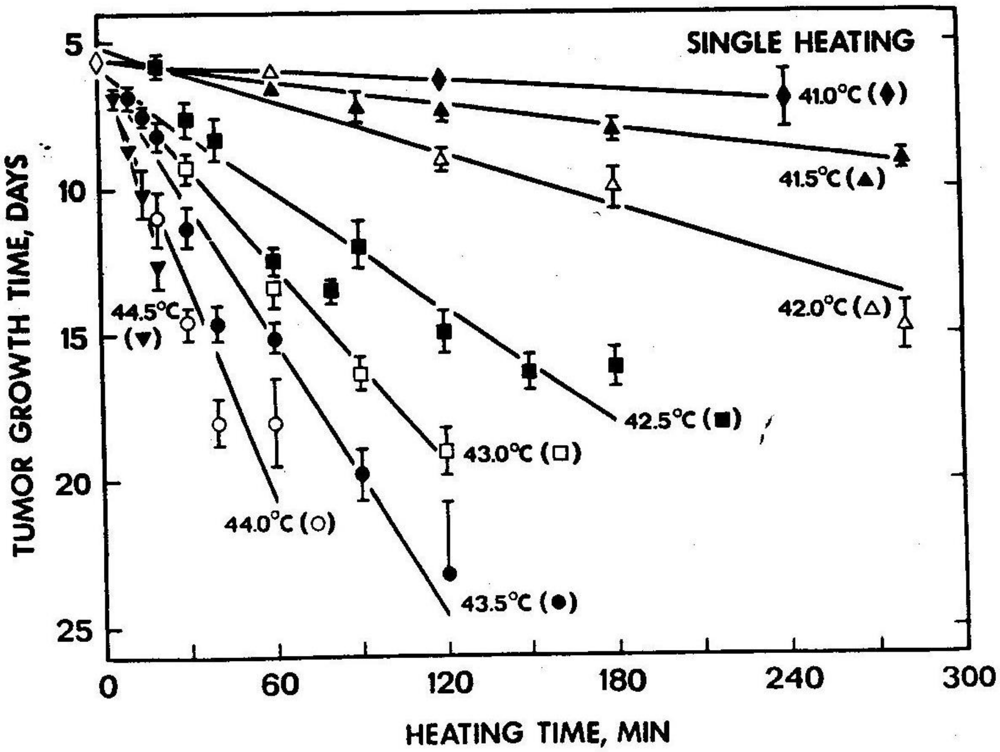
Kato et al. (1995) Med. Hypotheses 45:11

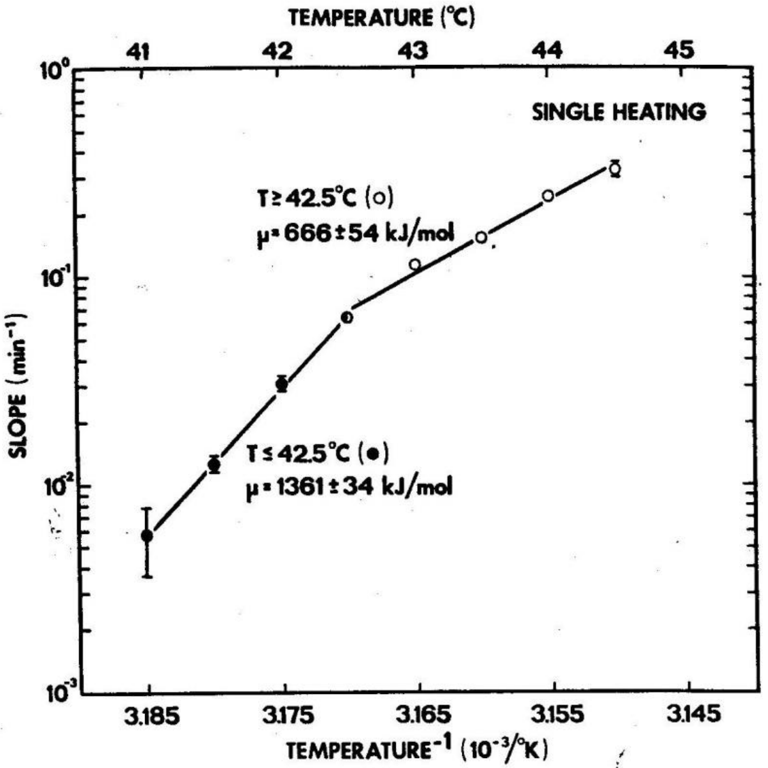




Nielsen et al. (1982)
Radiat. Res. 91:468-482

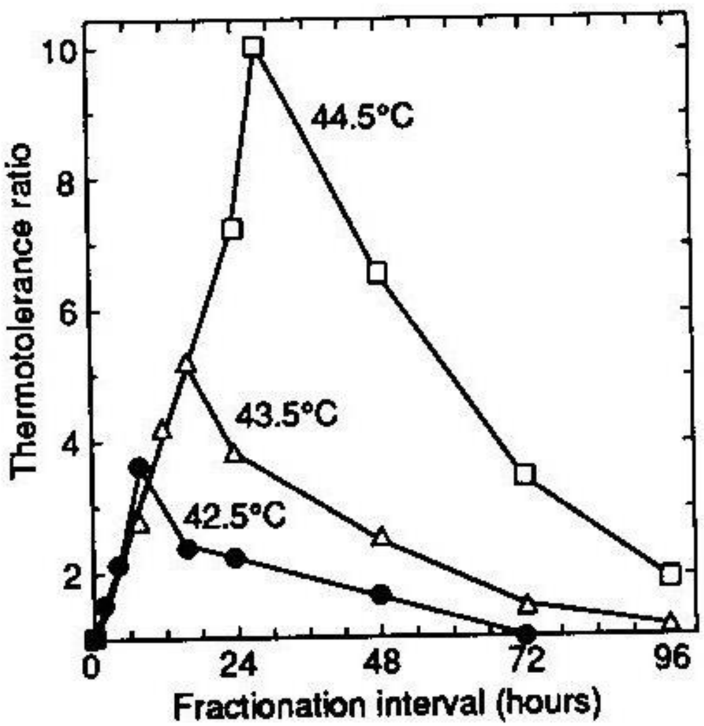
In vivo effects in tumors





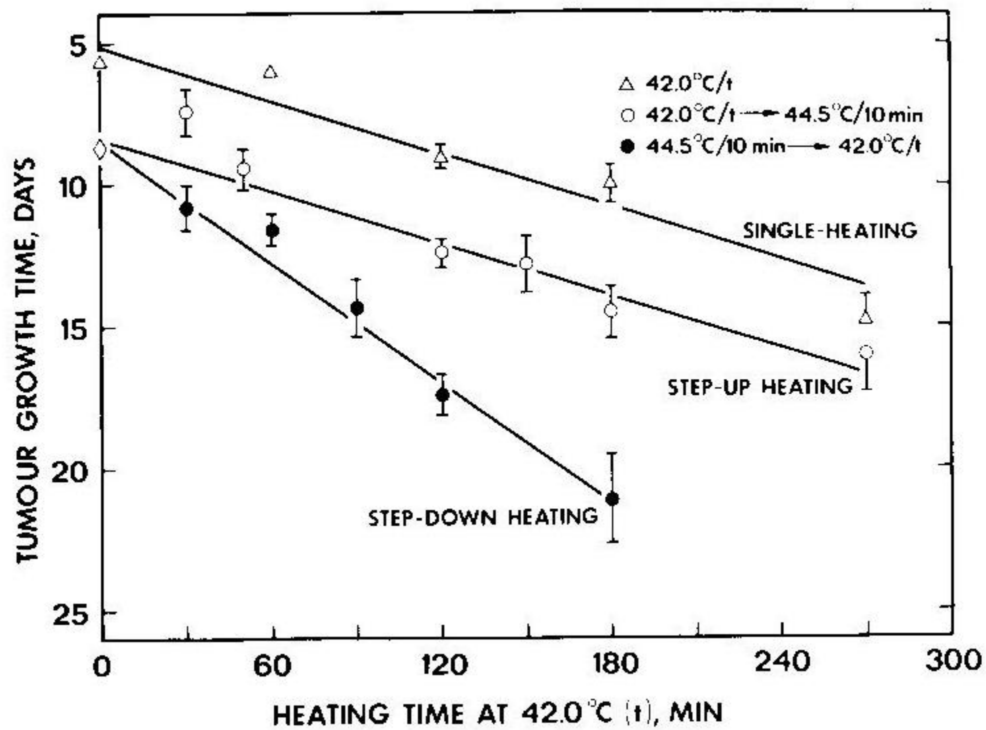
Lindegaard & Overgaard (1987) Int. J. Hyperthermia 3:79-81

Thermotolerance



Overgaard (1989)
IJROBP 16:535-543

Step-up/Step-down heating



Lindegaard & Overgaard (1987)
Int. J. Hyperthermia 3:79-81

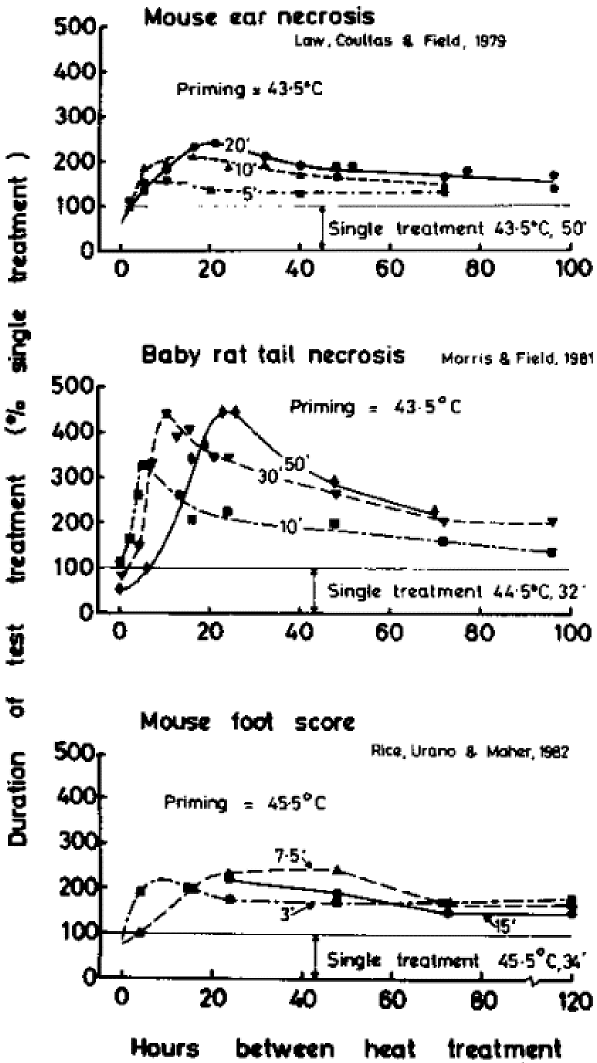
In vivo effects in normal tissues

Table 1.
Time–temperature relationships for thermal injury in normal tissues

Tissue	Endpoint	Temperature range (°C)	Transition temperature °C	Time factor for 1 °C		Temperature for 60 minutes °C	Authors
				Below 42.5 °C	Above 42.5 °C		
Testis of mouse	50 per cent weight loss	39.5–43.8	No transition	–	2.2	41.3	Hand *et al.* (1979)
Jejunum of mouse	50 per cent crypt loss	42.0–44.5	42.3	8	2.2	42.4	Hume *et al.* (1979a)
Jejunum of mouse	LD_{50}	43.0–46.0			2.0	42.4	Henle (1982)
Jejunum of hamster	LD_{50}	42.5–44.5			2.0	43.3	Milligan *et al.* (1984)
Tail of baby rat	Stunting in 5 per cent	42.0–46.0			2.0	43.3	Morris *et al.* (1977)
Pinna of mouse	Necrosis in 50 per cent	41.5–45.5	42.1	6	2.0	43.3	Law *et al.* (1978)
Skin of rat	Delay of hair growth	42.0–46.0			1.8	43.4	Okumura and Reinhold (1978)
Tail of baby rat	Necrosis in 50 per cent	41.8–46.0	42.8	6	1.8	43.4	Field and Morris (1983)
Foot of mouse	Loss of toe in 50 per cent	42.5–45.5			2.2	43.6	Overgaard and Suit (1979)
Foot of mouse	Loss of toe in 50 per cent	41.5–46.5	42.5	5	1.9	44.8	Urano *et al.* (1984)
Foot of mouse	Skin response in 50 per cent	43.5–45.0			2.0	44.8	Robinson *et al.* (1978)
Foot of mouse	Loss of feet in 50 per cent	43.0–49.0			2.0	45.7	Crile (1963)
Skin of pig and man	Threshold for necrosis	44.0–55.0			2.2	46.5	Moritz and Henriques (1947)

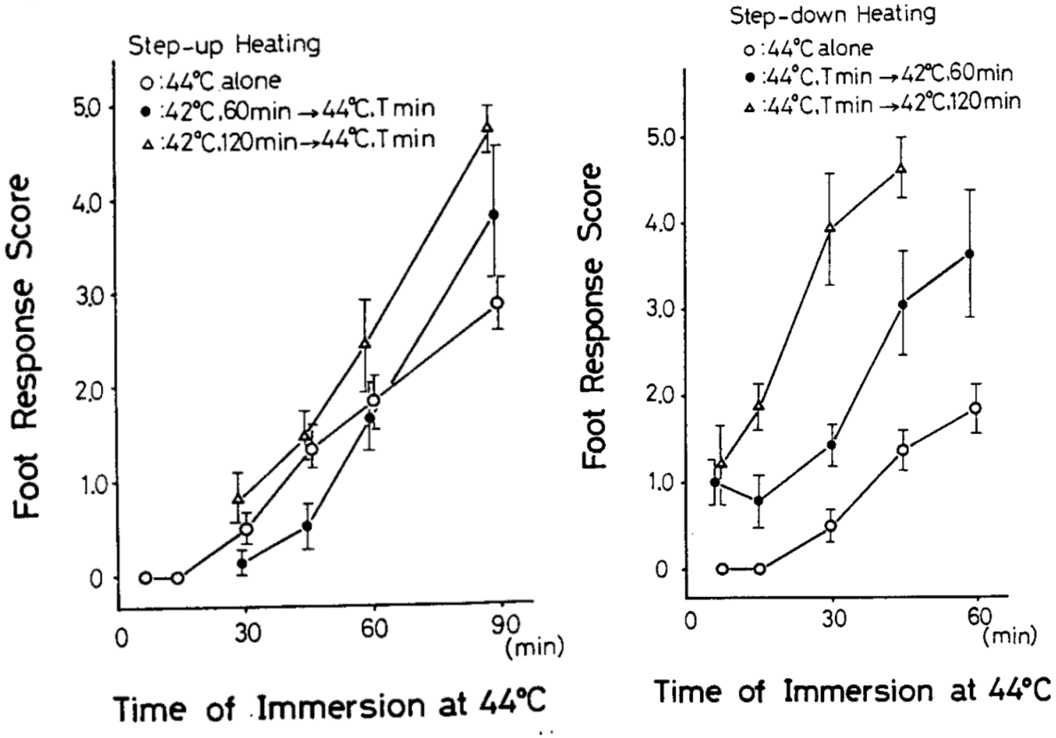
Law (1988) Hyperthermia & Oncology 1:121-159

Thermotolerance



Law (1988) Hyperthermia & Oncology 1:121-159

Step-up/down heating



Miyakoshi et al. (1983) IJROBP 9:1527-1532