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EFFECTS OF EXERCISE IN THE HEAT ON PREDISPOSITION TO HEATSTROKE--ETC(U)
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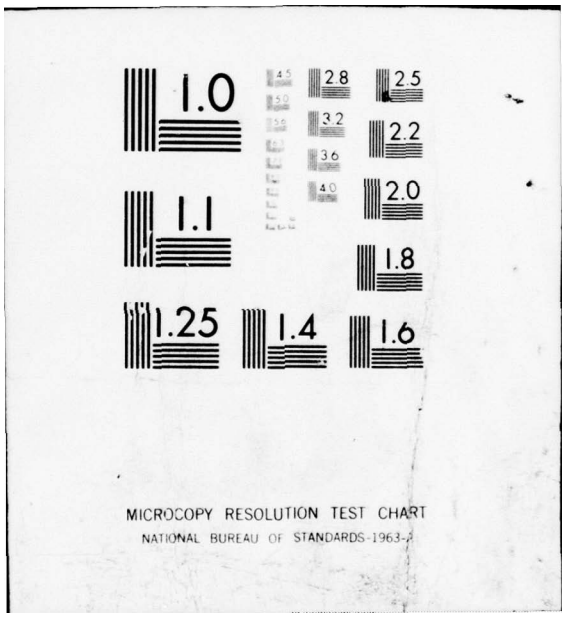
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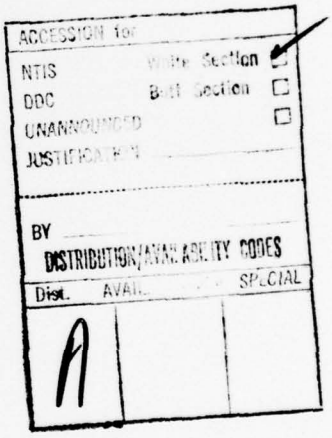

Effects of Exercise in the Heat on Predisposition to Heatstroke

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Although it has long been known that work and external heat supplement one another in producing heatstroke, the extent to which direct thermal injury and work related factors combine to produce the pathophysiology of fatal heatstroke has not been experimentally defined. Two factors have apparently retarded the study of the pathophysiology of heatstroke through controlled experimentation: 1) the high risk of mortality precludes its purposeful induction in man, and 2) the widely held belief that cessation of sweating is a cardinal sign of heatstoke has a priori prevented the use of non-sweating animal models. Although there is considerable evidence that a breakdown of heat dissipating mechanisms and a lack of sweating may precipitate heatstroke (4,6,30,32,49), there have been numerous reports, more recently from Israel, of heatstroke accompanied by profuse sweating (17,37,43-45,48,50). Instead of being an uncommon variant or occurrence (34), these observations may reflect both the Israeli military practice of drinking by command in the absence of thirst as well as the role of physical effort in precipitating heatstroke (21,45). These conflicting observations have been synthesized into a more general concept that heatstroke develops when excessive body temperature, itself, becomes a noxious agent. Adherance to this concept has resulted in the recent development of both dog and rat heatstroke models (8,20,21,41). A number of observations drawn from the existing literature indicated that the laboratory rat would be a suitable animal for heatstroke research. Adolph (1) pointed out that the rat does not pant or sweat and, as a result, exposure to dry heat produces relatively less dehydration than in the dog or man. However, Lewis et al. (35) demonstrated conditions under which rapid dehydration of rats occurred in spite of lack of panting. The major route of water loss appeared related to the continuous licking

and wetting of the body that occurs in the heat. The average weight loss for a 1 h exposure to ambient temperatures between 39 and 45°C was equivalent to 30 g/kg body weight (35). This rate of body weight loss is similar to the rate of sweat loss in unacclimatized men in the heat (29). Subsequently, Hainsworth (18) has shown that there are two components necessary for the survival of rats at high ambient temperatures: physiological secretion of saliva in response to hyperthermia and appropriate behavioral utilization of the saliva for cooling. By working the rats on a treadmill at or near room temperature or by restraining them in the heat, we hoped to achieve both dehydration and rapid hyperthermia through limiting the grooming behavior. The use of the treadmill was suggested by the observation that heatstroke often occurs in highly motivated individuals such as athletes and soldiers engaged in some form of programmed work and, at times, on relatively cool days (26°C) (45,47). By running rats in the cold, we hoped to assess any lethal cardiovascular or shocklike effects of work independent of hyperthermia. A 24 h survival period was suggested by the observations of Malamud et al. (37). In this classic description of 125 heatstroke fatalities in military recruits, death occured in less than 24 h in approximately 70% of the cases. In a large percentage of these, the men were relatively unacclimatized and overweight which suggested the use of large, untrained and unacclimatized rats. Since heavier rats have a lower surface area-to-mass ratio and must do more work at any given speed and incline, they should produce and store more heat.

In contrast to earlier experiments determining the tolerance time or time until death of rats continuously exposed to heat (15) or heat plus work (40), the degree of hyperthermia achieved in these experiments was a variable related to both the run time to exhaustion and the given ambient temperature. The effect of exhaustive exercise at different ambient temperatures on rat core temperature and

subsequent survival is depicted in Fig. 1. All rats ran 11 m/min up a 6° grade until exhausted and then were removed to a recovery chamber at 26°C ambient. This histogram represents the results from 123 animals run to exhaustion at ambient temperatures of 5, 20, 23, and 26°C. A number of observations should be noted; 1) rats forced to run at different ambient temperatures displayed a range of overlapping core temperatures at exhaustion, 2) all rats run at 5°C, ran 85% longer, did proportionately more work and all survived for 24 h, and 3) with increasing core temperatures at exhaustion (0.5°C - increments above 40.0°C), the percentage of rats dying within 24 increased (0, 10, 48, 74 and 88% mortality at 42.5°C).

The data from Fig. 1, when plotted as percent mortality versus core temperature at exhaustion, generated the dose-response curve shown in Fig. 2. A core temperature of 40.4°C represented a threshold hyperthermia above which mortalities occurred in exhausted animals. The LT50 and standard error were equivalent to a core temperature at exhaustion of 41.5 ± 0.1°C. Thus, the probability of death in exhausted rats resting at 26°C appeared directly realted to the core temperature at collapse. This trend toward increasing core temperatures and death with exercise to exhaustion at increasing ambient temperatures supports the contention of Gilat et al. (17) that work and external heat are to be considered as collaborators, supplementing one another in producing heatstroke. Although the rats run at 5°C ran 85% longer, and did proportionately more work without fatalities, these results still left unanswered to what degree did work, per se, contribute to heatstroke death.

In their recent review on heatstroke (46), Shibolet et al. have emphasized that the effect of heat, like other physical agents, is determined by both its intensity and duration. This concept was employed by Shapiro et al. (41) in developing a dog heatstroke model. Thermal load, as shown in the next figure, Fig. 3, was measured

as the area, in degree-minutes of core heating above an assigned baseline. The choice of baseline is determined by the minimum lethal temperature. In our experience, this temperature for rats is near 40.4°C which is close to the apparent threshold levels of body temperature (40.6°C) for heatstroke in man estimated by Leithead and Lind (33). The rat, like man, elevates its core temperature above basal levels when exercising. After five to ten minutes of work, there is a sudden increase of tail skin temperature reflecting the onset of vasodilation. Just prior to exhaustion, there is a characteristic divergence between core and tail temperature. Since this jeopardizes the ability to dissipate heat from the skin, this may account for the simultaneous rise in core temperature. The hyperthermic area is then calculated under both the heating and cooling portions of the curve to estimate the intensity and duration of thermal load. Thus, theoretically, any attempt to limit either the intensity or duration of the hyperthermia should reduce the death rate. This has been clearly demonstrated in South Africa, where the incidence of fatal heatstroke was reduced by the early application of therapeutic cooling (53).

Prior to 1967, no prognostic or diagnostic significance was attached to the rise in serum enzymes noted in heatstroke (25). For example, in 1964 Leithead and Lind (34), while expressing dissatisfaction with the distinction, suggested that heat hyperpyrexia differs from heatstroke in that the patient is conscious and rational and sweating may be present. However, in 1967, both Kew et al. (25) and Shibolet et al. (43) reported on the diagnostic and prognostic value of measuring the serum transaminases (SGOT and SGPT) in suspected heatstroke cases. In fact, both groups agreed that elevations in SGOT in excess of 1000 units indicated both severe heatstroke and possibly a poor prognosis (25,43). These results were supported by two assumptions: one, that heatstroke is accompanied or preceded by widespread cellular injury; and two, that heat injury will result in the release into the

circulation of the transaminase enzymes found in high concentrations in heart, and skeletal muscle, brain, liver, and kidney tissues (5).

That the degree and/or intensity of hyperthermia is related to the incidence of cellular injury is shown in the following table taken from Hubbard et al. (24). A total of 57 non-run, restrained-heated survivors were divided into three groups based on the range of SGPT activity at 24 h (time of peak activity): Group 1, 0-50 IU/L; Group 2, 50–500 IU/L; Group 3, > 500 IU/L. Fractional increases in either the hyperthermic [illegible] (degree-minutes) or the Tc max resulted in exponential increases in enzyme activities of both SGPT and SGOT, but not CPK. The data in this table indicates that the greater the intensity and duration of hyperthermia, the more intense is the transaminase release and inferred tissue damage. It should be noted, however, that CPK is not elevated to heatstroke levels in the most severe cases (Group 3). This is consistent with the observation that evidence for muscle damage and severe elevations in CPK in human heatstroke in the absence of work in lacking. By the same token, the liver is invariably damaged in both human (27) and rat (9) heatstroke but CPK is not present in this organ (28). These results, therefore, emphasize the importance of measuring the serum transaminases when heatstroke uncomplicated by work has occurred (12).

The purpose of the next experiment was to verify the elevation of serum transaminase to heatstoke levels (> 1000 IU/L) in this rat heatstroke model, and to determine if the incidence of cellular injury, as reflected by these enzymes, were higher with work-induced hyperthermia than with equivalent heat loads in the absence of physical effort. A total of 171 untrained, unacclimatized and unanesthetized laboratory rats weighing between 485 and 545 g were fasted and either run to exhaustion at 5°C (n=13), at 20, 26 or 30°C (n=57), immobilized in a restraining cage and heated at an ambient of 41.5°C (n=81), or served as controls

(n=20). In the next figure (Fig. 4) are shown dose-response curves of the percentage of surviving rats with serum GOT levels in excess of 1000 IU/L versus the maximum core temperatures after running or heating. Values in the insert represent mean ± S.E. of core temperatures at the indicated percentages. The CT50 for run rats was significantly different from the CT50 for heated rats ($p < .025$). There is good evidence to support the concept that elevations in SGOT reflect generalized cell damage. It was first found useful in diagnosing myocardial infarction (31) and hepatitis (52) and more recently, cellular injury due to prolonged exercise (42), muscle stimulation and hypoxia (36), hyperthermia and hypoxia (39), as well as acute heatstroke (22,25,43). Thus, it is not surprising that heatstroke elevations in SGOT occurred in a small percentage of exhausted-normothermic rats which can be attributed primarily to exercise induced cellular injury. Further increases in the incidences of elevated SGOT above 40.5°C appear due to the combined effects of heat plus work. In contrast, with hyperthermia alone there are no heatstroke elevations in SGOT until a core temperature of 41.5°C is reached. These results indicate that the incidence of cellular injury as reflected by the release of SGOT, is higher with work-induced hyperthermia than with equivalent heat loads in the absence of physical effort.

If, in fact, heatstroke is accompanied or preceded by widespread cellular injury, then the dose-response curves for heatstroke mortality should be similar to those reflecting heatstroke injury. On the other hand, if direct thermal injury to a target tissue, such as the thermoregulatory centers of the brain, is the primary factor in the pathogenesis of heatstroke, then the work-induced hyperthermia of running rats should <u>not</u> be more lethal than equivalent heat loads in the absence of physical effort. A total of 252 rats were either run to exhaustion at 5, 20, 23, or 26°C or passively heated while restrained at an ambient of 41.5°C. The severity of

hyperthermia was calculated as an area in degree-minutes above a baseline core temperature of 40.4°C. As shown in Fig. 5, mortalities occurred following exhaustive work over the entire range of individual hyperthermias from 5 to 185 deg-min. With passive heating, mortalities were not observed below a thermal area of 20 deg-min. No rat enduring a thermal area above 125 deg-min. survived. These curves demonstrate three important concepts: 1) within each population there are both heat-sensitive and heat-resistant individuals. For example, there is an apparent 14-fold difference in heat tolerance between an exhausted animal that succumbs to a 5 deg-min. exposure and one that survives over 120 deg-min. of hyperthermia, 2) the convergence of the two dose-response curves indicates that, at some point, hyperthermia is the predominant forcing function, and 3) at low, comparable thermal loads, work plus hyperthermia is more lethal than hyperthermia alone (approximately 30% at 20 deg-min.).

In an attempt to draw examples of this phenomenon from the existing human literature, we have recalculated data from two series of heatstroke cases where both core temperature on admission and subsequent mortality were available (14,16). The report by Gauss and Meyer (16) in 1917 on 158 cases of heatstroke from Cook County, Chicago indicates that 96 percent were males, 80% were 30 to 50 years old, and over 65% were manual laborers. In contrast, Ferris et al. (14) described 44 cases of heatstroke occurring in Cincinnati during two severe heat waves in 1936. In this series, 61% were males, 73% were over 50 years old and only 9 (20%) were doing work which at most required moderate exercise at the time of or preceding their collapse. The majority of these patients presented clinical evidence of degenerative vascular disease. If hyperthermia alone were the predominant cause of heatstroke mortality, then one might have expected a slightly higher mortality at equivalent core temperatures in the older population with

cardiovascular disease. As shown in the next figure, Fig. 6, it was not the case. Approximately 30% of the heatstoke deaths occurred in younger and presumably healthier laborers with temperatures on admission below 106°F (41.1°C). In contrast, there were no deaths (at temperatures below (107°F) in the older, sedentary population. These results appear in reasonable agreement with both the rat model and with those of Malamud on military recruits (37) where 22% of heatstroke fatalities were characterized by temperatures below 106°F (41.1°C) on admission.

Heatstroke is a complex disorder with a well-described symptomatology and pathology (37). Despite the wealth of observations, however, there is still difficulty in defining exactly when body temperature is "too high," what degree and duration of hyperthermia produces injury, and, by inference, what is the associated risk (21,46). In fact, the primary physiological failure in human heatstroke is still uncertain (21). This is especially true since one or more of the classic symptoms (coma, anhidrosis and a fever over 106°F (41.1°C)) may be lacking. For example, Shibolet et al. (43) reported that 28 of 29 cases observed at the time of collapse were sweating actively, if not profusely. If a patient is still sweating, he may be both conscious and rational when seen by a physician. Because of the many host and environmental factors interacting to produce hyperthermia during military training, sports, certain occupations and living conditions, it is doubtful whether total prevention is possible (7) and, thus, there is concern that under-diagnosis is itself a risk (46).

Historically, there have been two opposing views regarding the pathophysiology of heatstroke and their origins can be traced to the observations of Andral (3), Wood (51), Osler (38), Haldane (19), Adolph and Fulton (2), Fantus (13) and Drinker (11) during the 100 year period between 1838 and 1936. The classical concept is generally attributed to Malamud et al. (37) who suggested that heat

induced direct thermal injury to a target tissue, i.e. the thermoregulatory centers of the brain, which resulted in a failure of sweating and thermoregulatory control and shock. This hypothesis was at variance with the earlier proposal of Adolph and Fulton (2), who believed heatstroke to be the result of circulatory failure also leading to shock. Thus, the breakdown in the heat regulatory mechanism and the clinical manifestations (10,14) have been attributed to both central and peripheral mechanisms. With either hypothesis, shock was the critical end point.

The concept that hard work in a hot environment can predispose to a serious deficit of effective arterial volume and shock (11,13,29) combined with both human and rat experimental data that indicates that working to exhausiton results in an increased rate of cellular injury and heatstroke mortality at low thermal loads appears to lend renewed support for a cardiovascular origin of heatstroke pathophysiology. These results appear to confirm that strenuous physical effort, even when the external heat load is moderate, can contribute more to the pathophysiology of heatstroke than an increased metabolic heat load. Taken in the general context of a model for heatstroke shock, these results would predict certain anomolous physiological and metabolic events in susceptible individuals such as: inappropriate increases in serum lactate, normal arterial PO_2 and at some point, decreased total body oxygen consumption during progressive exertion-induced hyperthermia. At least two experimental approaches can be tested to explain the basis for this pathophysiological process: (1) the development of relative ischemia progressing to stagnant anoxia in the viscera due to inappropriate shifts in cardiac output and fluid volume or (2) a disruption in the steady state flux of energy transduction mechanisms such that the loss of function, as in sweat glands, might be seen as the effect of an underlying cellular disorder as well as a contributor to the pan-systemic failure in heatstroke. Under different circumstances, perhaps when strenuous exercise is or is not a factor, one mechanism or

the other may predominate. The points being made, however, are: (1) that the mechanism is not exclusively neural and anhidrotic and, (2) work, per se, may contribute to an increased rate of heatstroke mortality and injury at low thermal loads.

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In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences - National Research Council.

The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Figure Legends

Fig. 1 Effect of exhaustive exercise at different ambient temperatures on core temperature and subsequent mortality of 123 rats. From Hubbard et al. (20).

Fig. 2 Dose-response curve of percent mortality within 24h vs. core temperature at exhaustion. All rats recovered at 26°C with water supplied ad libitum. From Hubbard et al. (20).

Fig. 3 The core and tail skin temperature of a rat exercising to exhaustion at an ambient temperature of 26°C. The rat ran 11 m/min up a 6° incline until the end of run (EOR). All rats exercised in these experiments were allowed 2 min rests at 20 and 40 min. Hyperthermic area was calculated by the formula in the insert. (See Hubbard et al. (21).

Fig. 4 Dose-response curves of the percentage of surviving rats with serum GOT levels in excess of 1000 IU/L versus the maximum core temperatures of run-exhausted or restrained-heated rats. Values in insert represent mean ± SE of core temperatures at the indicated percentages. The CT 50 for run rats was significantly different from the CT 50 for heated rats ($P < .025$). From Hubbard et al. (23).

Fig. 5 Dose-response curves of percent mortality within 24h versus the severity of core heating in degree-minutes (Section of the curve from 160 to 185 degree-minutes not shown). See text for details. From Hubbard et al. (21).

Fig. 6 Dose-response curves of percent mortality versus temperature on admission in human heat stroke patients. Data was recalculated by the method of Reed and Muench from the sources indicated in the insert. See text for details. From Hubbard et al. (23).

TABLE 1 - ELEVATIONS IN SERUM ENZYME ACTIVITY OF RESTRAINED-HEATED RATS

GROUP[a]	N	Tre MAX (°C)	HYPERTHERMIC AREA[b] (DEG-MIN)	ENZYME ACTIVITY POST-STRESS (IU/L) 30' CPK	24 H SGPT	24 H SGOT
# 1 SGPT LEVELS 0-50 IU/L	18	41.7 ± 0.3	27.3 ± 9.1	141 ± 105	31 ± 5	134 ± 42
# 2 SGPT LEVELS 50-500 IU/L	15	41.9* ± 0.3	33.9* ± 10.4	161 ± 102	170* ± 142	409* ± 328
# 3 SGPT LEVELS > 500 IU/L	24	42.3* ± 0.2	47.1* ± 9.8	355 ± 628	3635* ± 2942 (23)	6881* ± 5882 (21)

[a] THE SURVIVING RATS WERE ASSIGNED TO ONE OF THREE DATA GROUPS BASED ON THE VALUE OF THE 24 H SGPT.

[b] AREA $\propto \Sigma$TIME INTERVAL (2 to 6 MIN) X 1/2 [°C ABOVE 40.4°C AT START OF INTERVAL + °C ABOVE 40.4°C AT END OF INTERVAL].

[c] NUMBERS IN PARENTHESES = N RATS.

* $P < 0.05$ BETWEEN MEAN AND MEAN ABOVE IT.

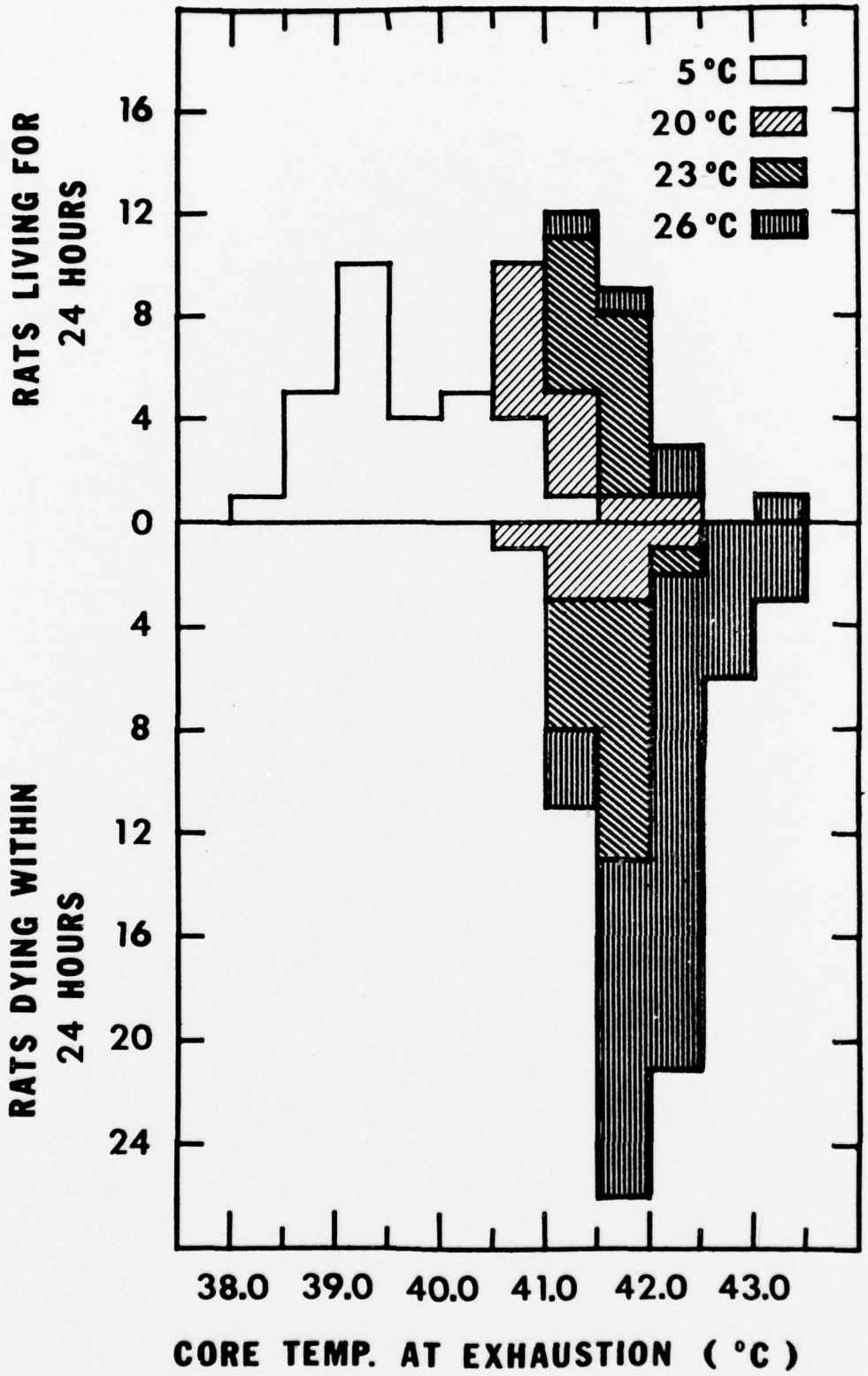

5 °C
20 °C
23 °C
26 °C
RATS LIVING FOR 24 HOURS
RATS DYING WITHIN 24 HOURS
16
12
8
4
0
4
8
12
16
20
24
38.0
39.0
40.0
41.0
42.0
43.0
CORE TEMP. AT EXHAUSTION (°C)

Fig 1

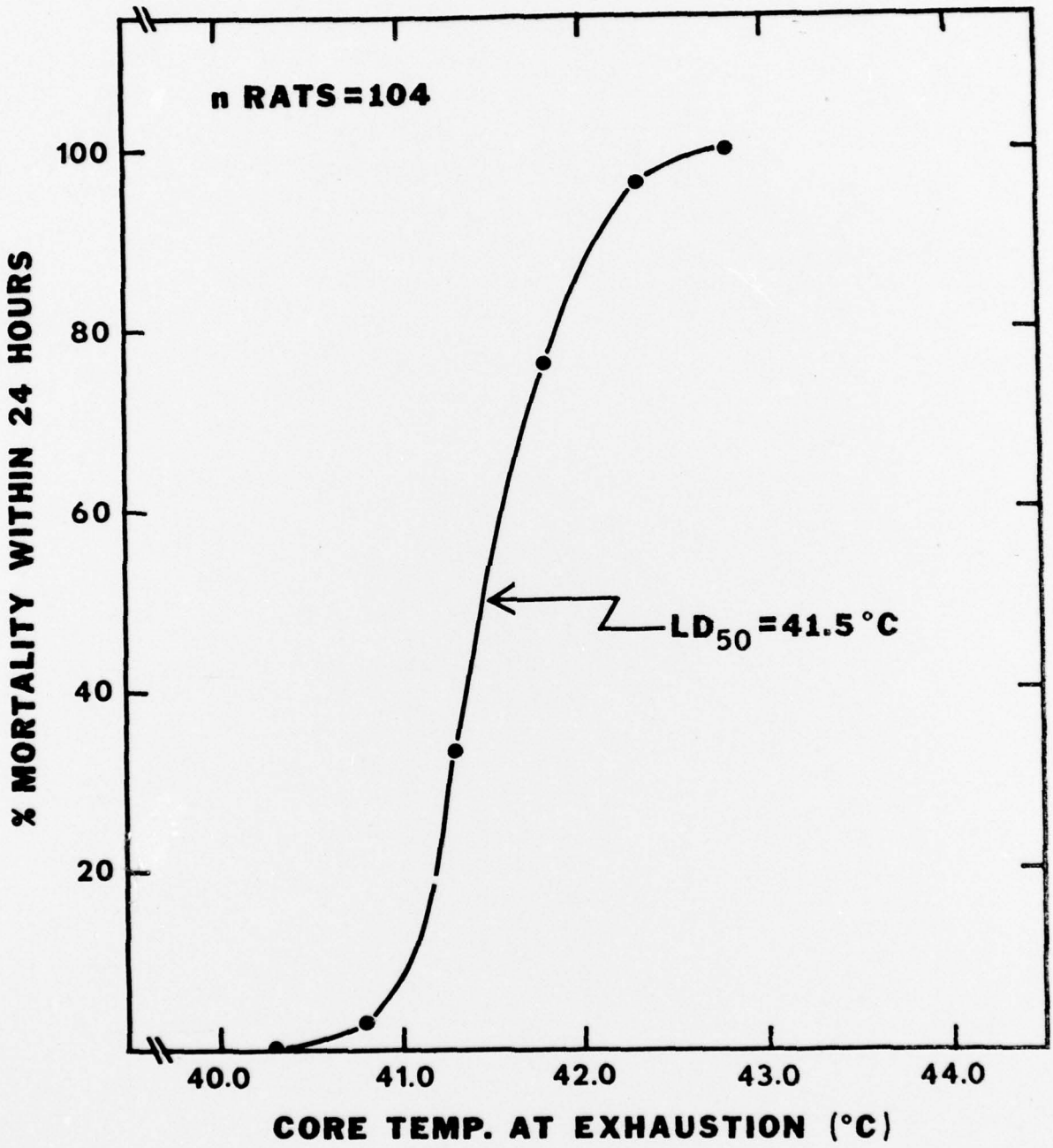
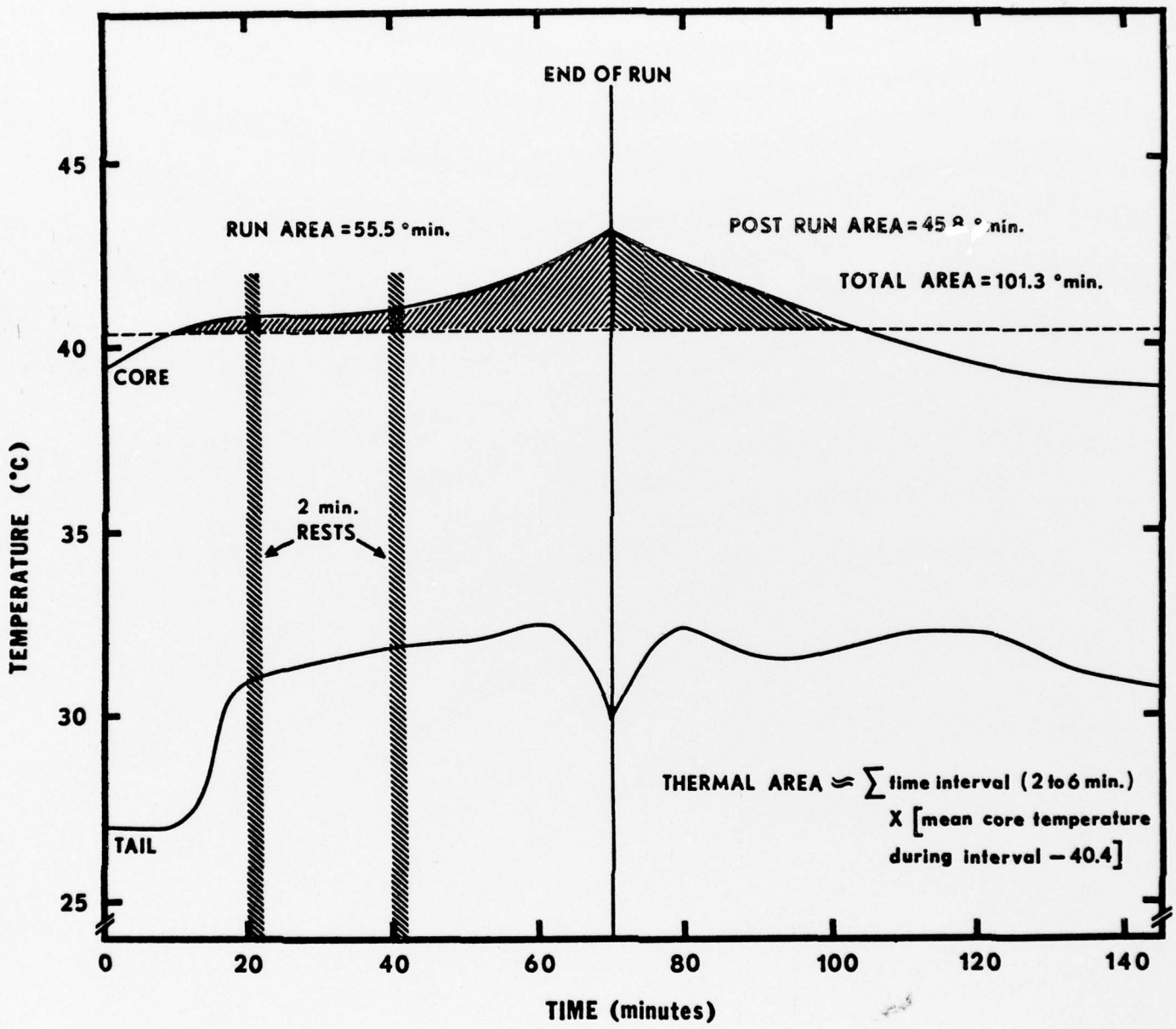
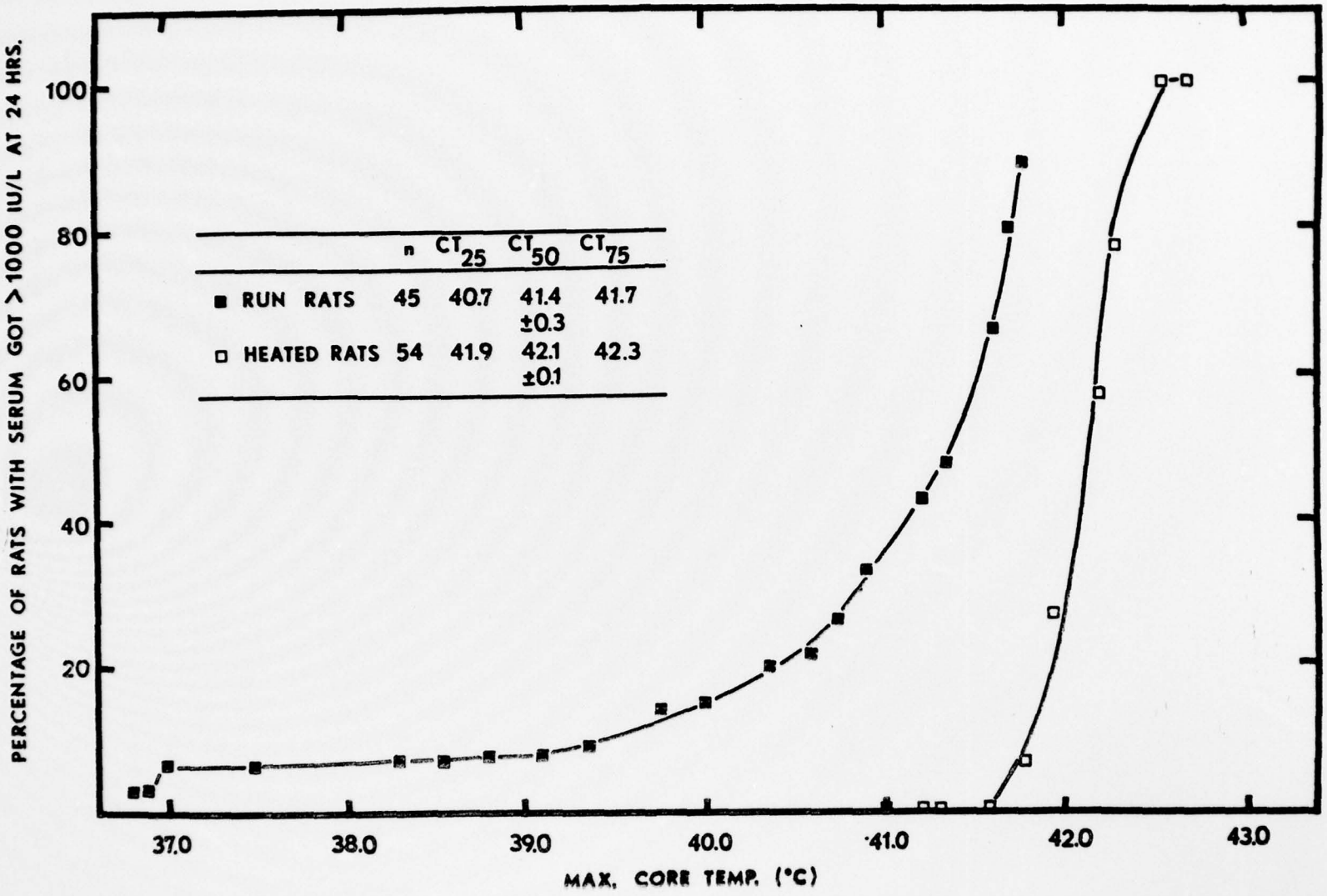
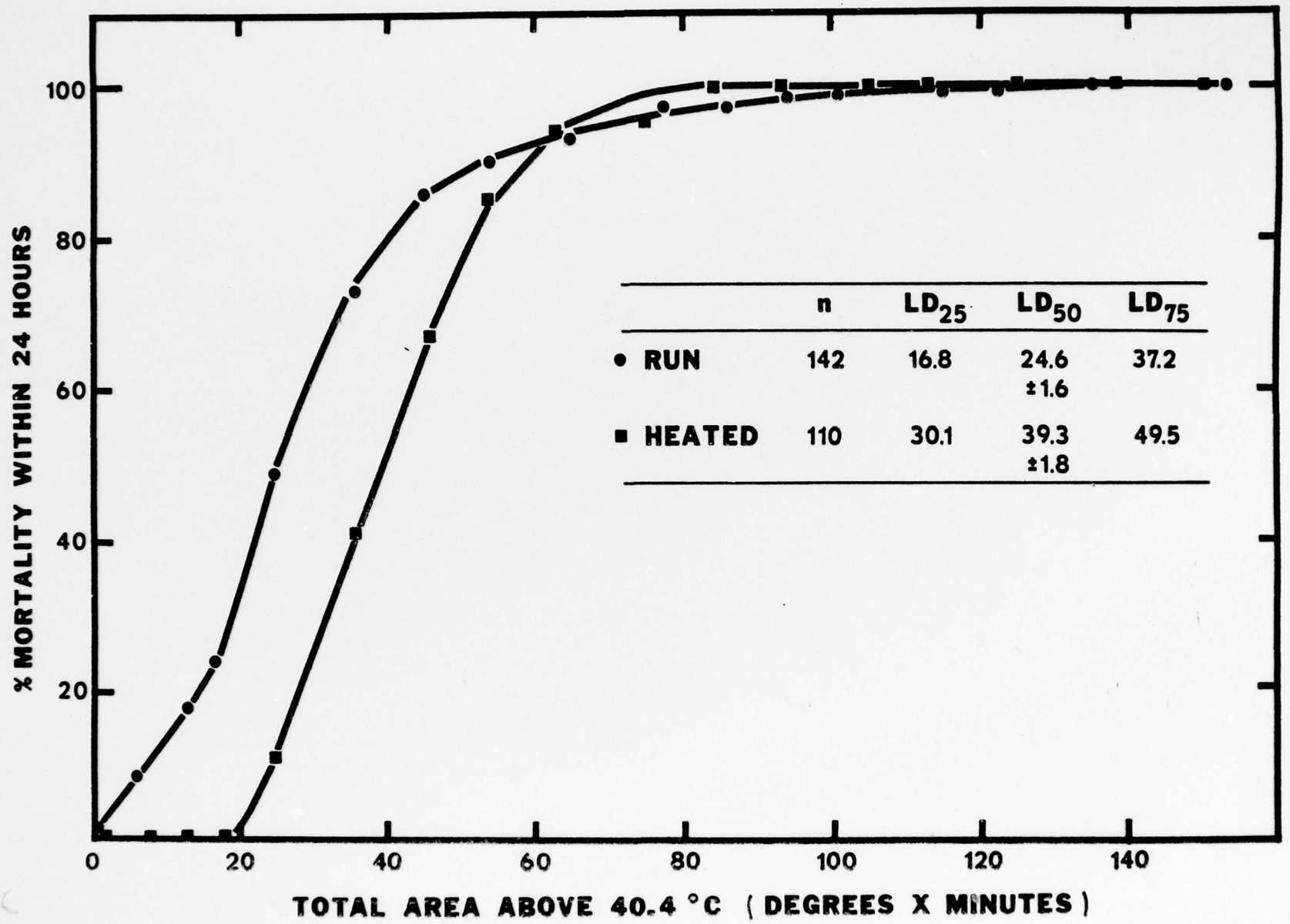
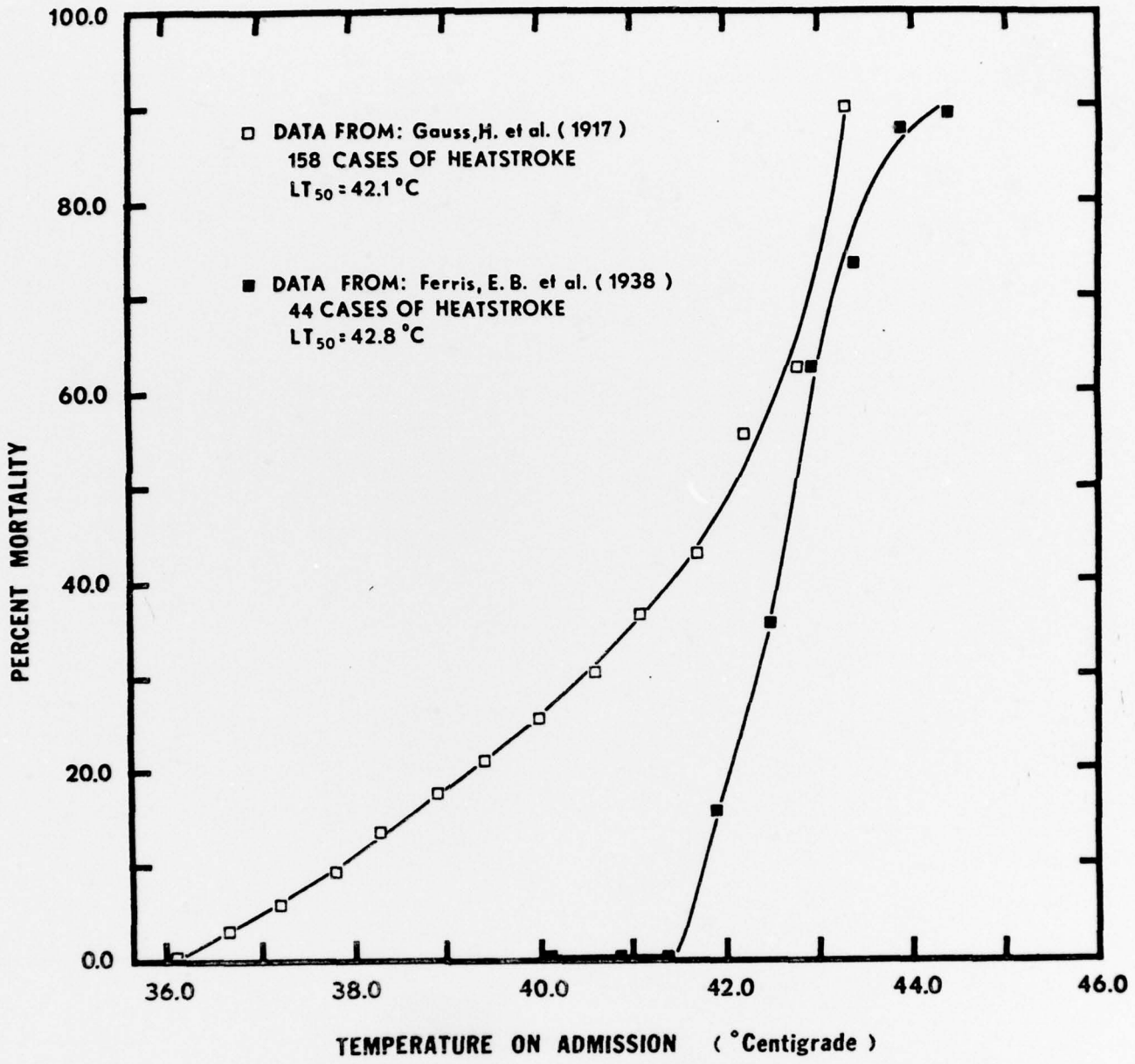

n RATS=104
100
80
60
40
20
% MORTALITY WITHIN 24 HOURS
LD50=41.5 °C
40.0
41.0
42.0
43.0
44.0
CORE TEMP. AT EXHAUSTION (°C)

fig 2


END OF RUN
RUN AREA = 55.5 °min.
POST RUN AREA = 45.8 °min.
TOTAL AREA = 101.3 °min.
CORE
2 min.
RESTS
TAIL
THERMAL AREA ≈ ∑ time interval (2 to 6 min.)
X [mean core temperature
during interval − 40.4]
TEMPERATURE (°C)
45
40
35
30
25
0
20
40
60
80
100
120
140
TIME (minutes)


PERCENTAGE OF RATS WITH SERUM GOT >1000 IU/L AT 24 HRS.
100
80
60
40
20
37.0
38.0
39.0
40.0
41.0
42.0
43.0
MAX. CORE TEMP. (°C)
n CT25 CT50 CT75
■ RUN RATS 45 40.7 41.4 ±0.3 41.7
□ HEATED RATS 54 41.9 42.1 ±0.1 42.3


% MORTALITY WITHIN 24 HOURS
100
80
60
40
20
0
20
40
60
80
100
120
140
TOTAL AREA ABOVE 40.4 °C (DEGREES X MINUTES)
n
LD25
LD50
LD75
● RUN
142
16.8
24.6 ±1.6
37.2
■ HEATED
110
30.1
39.3 ±1.8
49.5


100.0
80.0
60.0
40.0
20.0
0.0
PERCENT MORTALITY
□ DATA FROM: Gauss, H. et al. (1917)
158 CASES OF HEATSTROKE
LT_{50} = 42.1 °C
■ DATA FROM: Ferris, E. B. et al. (1938)
44 CASES OF HEATSTROKE
LT_{50} = 42.8 °C
36.0
38.0
40.0
42.0
44.0
46.0
TEMPERATURE ON ADMISSION (°Centigrade)