

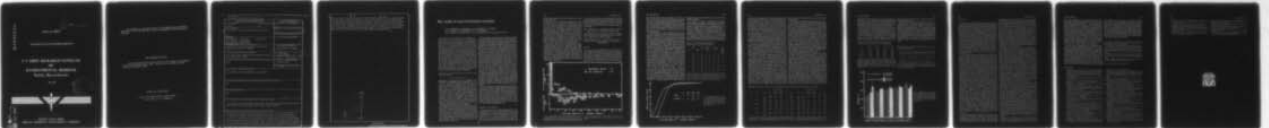
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A RAT MODEL OF ACUTE HEATSTROKE MORTALITY, (U)  
SEP 76 R W HUBBARD, W D BOWERS, W T MATTHEW  
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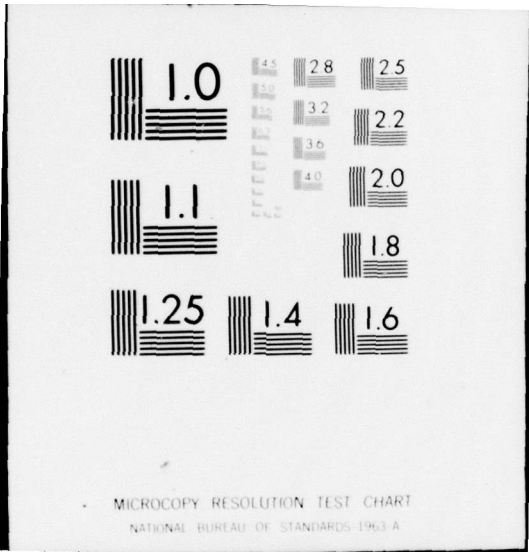
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RAT MODEL OF ACUTE HEATSTROKE MORTALITY

U S ARMY RESEARCH INSTITUTE  
OF  
ENVIRONMENTAL MEDICINE  
Natick, Massachusetts

July 1976

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| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number)<br>A total of 252 untrained, unacclimatized and unanesthetized laboratory rats<br>weighing between 485-545 g were fasted and either run to exhaustion at<br>5, 20, 23, or 26°C or were restrained and heated at an ambient temperature<br>of 41.5°C. The incidence of mortality associated with a wide range of work-<br>induced hyperthermias was compared to the lethality of equivalent heat loads<br>in the absence of physical effort. The severity of hyperthermia was calculated<br>in degree-minutes above a baseline core temperature of 40.4°C. The LD 25's |                       |                                                                                            |

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of run versus restrained rats were 16.8 and 30.1 degrees minutes, respectively. Survivors had a faster cooling rate than fatalities, but run survivors had a slower cooling rate than heated survivors. Results indicate that: 1) both the incidence of mortality and the survival time can be predicted from the severity of core heating, 2) work-related factors contribute to an increased rate of heatstroke death at low thermal loads, and 3) retrospectively, both heat-sensitive and heat-resistant individuals were identified.

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# Rat model of acute heatstroke mortality

R. W. HUBBARD, W. D. BOWERS, W. T. MATTHEW, F. C. CURTIS,  
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HUBBARD, R. W., W. D. BOWERS, W. T. MATTHEW, F. C. CURTIS, R. E. L. CRISS, G. M. SHELDON, AND J. W. RATTEREE. *Rat model of acute heatstroke mortality.* *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 42(6): 809-816, 1977. — A total of 252 untrained, unacclimatized, and unanesthetized laboratory rats weighing between 485 and 545 g were fasted and either run to exhaustion at 5, 20, 23, or 26°C or were restrained and heated at an ambient temperature of 41.5°C. The incidence of mortality associated with a wide range of work-induced hyperthermias was compared to the lethality of equivalent heat loads in the absence of physical effort. The severity of hyperthermia was calculated in degree-minutes above a base-line core temperature of 40.4°C. The LD<sub>50</sub>'s of run-exhausted versus restrained-heated rats were 16.8 and 30.1 deg-min, respectively. Survivors had a faster cooling rate than fatalities, but run-exhausted survivors had a slower cooling rate than restrained-heated survivors. Results indicate that 1) both the incidence of mortality and the survival time can be predicted from the severity of core heating, 2) work-related factors contribute to an increased rate of heatstroke death at low thermal loads, and 3) retrospectively, both heat-sensitive and heat-resistant groups were identified.

hyperthermia; heatstroke predisposition; heatstroke cooling rate; degree-minutes

HISTORICALLY, THERE HAVE BEEN two opposing views regarding the pathophysiology of heatstroke (2, 3, 10, 11, 15, 27, 35, 36). The classical work and concept is generally attributed to Malamud et al. (26) 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 (9, 12) have been attributed to both central and peripheral mechanisms. With either hypothesis, shock was the critical end point.

Although Malamud's attempts to demonstrate structural changes in the portions of the hypothalamus concerned with temperature regulation were unsuccessful, evidence of acute circulatory failure, such as hemorrhage, edema, and vascular engorgement, was observed in virtually all cases regardless of the duration of illness (26). Death within 24 h occurred in approximately 70% of the cases and the presence or absence of shock was the best prognostic index since the outcome usually depended on this factor (26).

The uncertainty surrounding the central or peripheral causes of heatstroke (neural versus cardiovascular) is evident in the following statement by Leithead and Lind (24): "The primary physiological failure in an unacclimatized man suddenly exposed to high heat stress probably lies in the failure of the sweating mechanism. But it is also true that in such conditions any heat disorder that develops is most frequently cardiovascular in origin." In a recent review, Knochel (18) has reemphasized the concept that hard work in a hot environment may lead to a serious deficit of effective arterial volume and profound shock would occur were it not for intense splanchnic vasoconstriction. Others have shown that cutaneous blood flow decreases drastically as exhaustion appears during exercise in the heat (6). The diminution of cutaneous blood flow with exhaustive exercise in the heat jeopardizes the ability to dissipate heat from the skin. For example, just prior to exhaustion, running rats display a drastic drop in tail temperature that coincides with an explosive rise in core temperature (17). A spiraling increase in rectal temperature during prolonged physical effort has been observed in humans with both high (19) and low (1) physical performance characteristics. This could be attributed largely to a marked reduction in cutaneous blood flow probably reflecting cardiovascular overload from the combined muscular and thermoregulatory blood flow demands, coupled with the effects of progressive dehydration.

However, the extent to which direct thermal injury to tissue and circulatory collapse combine to produce fatal heatstroke shock can be determined. If direct thermal injury to tissue is the primary factor in the pathogenesis of heatstroke shock, then the work-induced hyperthermia of running rats should *not* be more lethal than equivalent heat loads in the absence of physical effort. For this reason, the mortality associated with a wide range of thermal exposures, produced by either work at 20-26°C or sedentary exposure to 41.5°C, was measured in a large number of laboratory rats.

## MATERIALS AND METHODS

*Experimental animals.* Male Sprague-Dawley rats (Charles River CD strain) of equivalent ages were caged individually in an environmental chamber maintained at 26°C and 49 ± 17% relative humidity. The air in this chamber (13 x 11 x 6 ft) was replaced at a rate equivalent to 1.4 room volumes per hour. All rats were fed a diet of Purina chow and water ad libitum. Rats with

prefast body weights between 485 and 545 g were fasted 18–24 h before use.

**Experimental stress.** Animals were either exercised to exhaustion at one of four ambient temperatures (5, 20, 23, or 26°C) or were restrained in an appropriate sized wire cage which was placed in a small environmental chamber, set at 41.5°C ambient, until their core temperatures reached a preselected end point. The motor-driven treadmill was similar to the one described by Pattengale and Holloszy (28). Rats ran up a 6° incline at 11 m/min but were allowed a 2-min rest period after 20 and 40 min of work. Exhaustion was achieved under a shock-avoidance contingency. It was defined as that point at which rats could not keep pace, and when placed on their backs would not right themselves.

**Temperature measurement.** Core temperatures (rectal probe inserted 6.5 cm) were measured using copper/constantan thermocouples in conjunction with a thermocouple reference oven (Acromag model 340) and a 10-channel data acquisition system (Esterline-Angus model D-2020) with a teletype printout. After reaching exhaustion or a predetermined core temperature, all rats were monitored at 26°C ambient while resting in plastic cages lined with wood shavings. After recovery, animals were returned to their cages (26°C) and allowed water but no food for 24 h.

**Calculations.** The  $LD_{50}$  was estimated by the method of Reed and Muench (39) and the standard error by the procedure of Pizzi (39). Significance testing was carried out by using the Student *t*-test. *P* values >0.05 are omitted from the tables. Work done was calculated from the formula

$$\text{kg-m} = \text{body wt (kg)} \times \text{running time (min)} \times \text{treadmill speed (m/min)} \times \text{inclination of treadmill (sin)}$$

Core temperature was measured at 6 minute intervals and thermal area was calculated when core temperature exceeded 40.4°C using the formula

$$\text{thermal area (deg-min)} \approx \sum \text{time interval (min)} \times \frac{1}{2} [\text{°C above } 40.4\text{°C at start of interval} + \text{°C above } 40.4\text{°C at end of interval}]$$

## RESULTS

The severity of hyperthermia was calculated as an area in degree-minutes above a base-line core temperature of 40.4°C. This base line represents the minimum observed core temperature of exhausted rats which produced death within 24 h (16). The relationship between the severity of hyperthermia and rat survivability is depicted in Fig. 1. This histogram represents the results

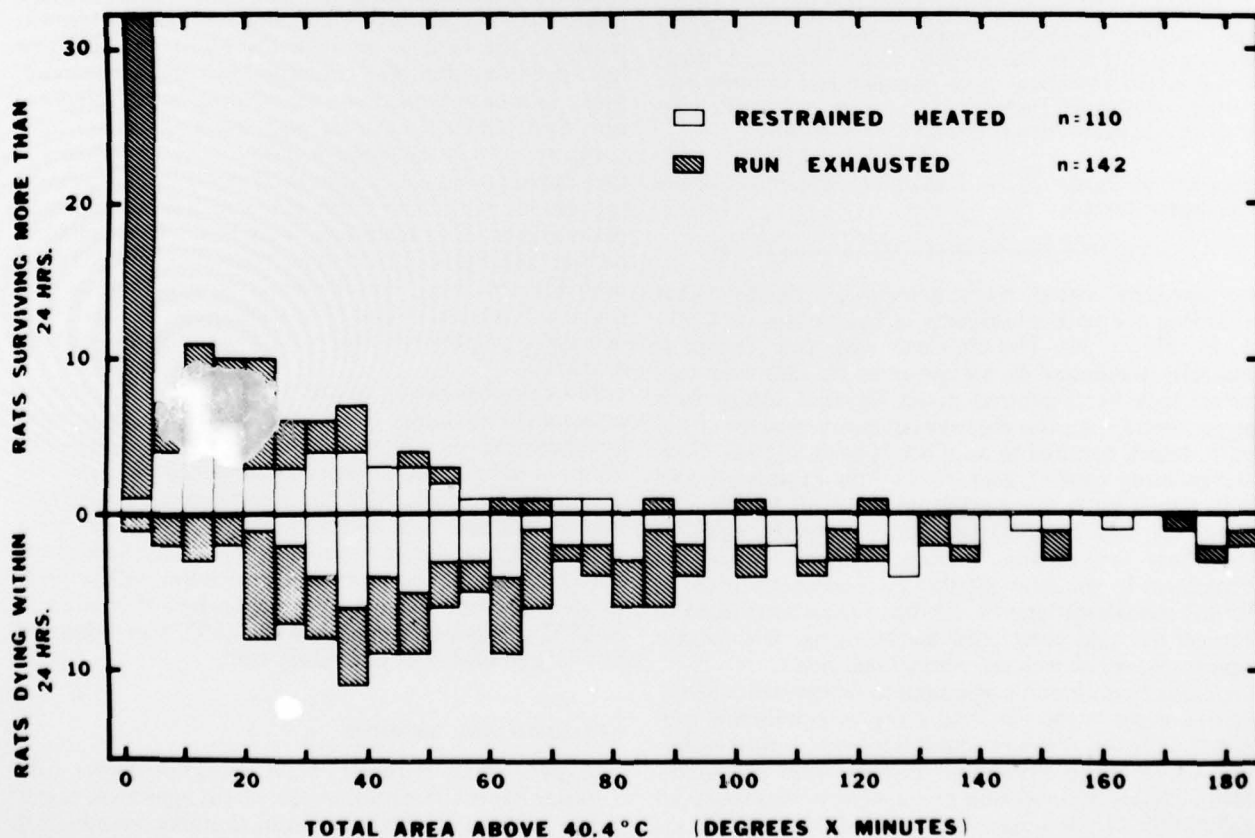


FIG. 1. Relationship between severity of hyperthermia measured in degree-minutes and rat survivability. Rats were either run to exhaustion at 5, 20, 23, or 26°C or passively heated while restrained at an ambient of 41.5°C. After running or heating, rats were removed

to a recovery chamber at 26°C ambient. Water, but not food, was supplied ad libitum after the core temperature returned to below 40.4°C.



from 252 rats either run to exhaustion at 5, 20, 23, or 26°C or passively heated while restrained at an ambient of 41.5°C. A number of observations should be noted: 1) mortalities occurred following exhaustive work over the entire range of individual hyperthermias from baseline levels to 185 deg-min, 2) with passive heating, mortalities were not observed below a thermal area of 20 deg-min, and 3) no rat enduring a thermal area above 125 deg-min survived.

The data from Fig. 1, when plotted as percent mortality versus hyperthermic area, generated the two dose-response curves seen in Fig. 2. These curves demonstrate a) a continuum of increasing incidence of death with increasing severity of hyperthermia, i.e., the existence within this population of both heat-sensitive and heat-resistant animals (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 (Fig. 1)); b) a dissociation of the effects of heat plus work from the effects of heat alone, i.e., an experimental demonstration that the hyperthermia induced by working to exhaustion can be lethal to some individuals while enduring an equivalent heat load at rest is not; and c) an objective method of classifying the severity of hyperthermia based upon the incidence of mortality within the total population. Thus, each animal was retrospectively assigned to one of five groups (Table 1) whose limits were described by intervals in degree-minutes along the dose-response curve: 1) LD<sub>0-25</sub>, 2) LD<sub>25-50</sub>, 3) LD<sub>50-75</sub>, 4) LD<sub>75-94</sub>, and 5) LD<sub>94-100</sub>. The LD<sub>94</sub> was chosen as a limit because it represents a) the point where the two dose-response curves converge (Fig. 2) and b) the approximate midpoint in the total range of thermal exposures. This classification makes it possible to compare 1) groups of run-exhausted and restrained-heated rats whose reaction to experimental treatment resulted in a similar probability of death and 2) to

compare survivors versus fatalities over a wide range of thermal exposures.

The results in Table 1 contrast the resolution achieved between groups by measuring either the intensity or duration of hyperthermia compared to the measurement of hyperthermic area in degree-minutes. As formerly reported (16), the significant differences between the temperatures at exhaustion of groups 1-5 reflect the continuum of increased mortality with increased core temperature at exhaustion. The average work done by the rats in groups 1-4 was similar and only slightly less than that achieved by group 5. The total work done by the run-exhausted rats is thus a constant contributing factor up to a 95% incidence of

TABLE 1. Comparison of heatstroke risk factors based on incidence of mortality

| Group | EOR T <sub>c</sub> , °C |       | Work Done, kg-m  | EOH T <sub>c</sub> , °C |                         | Total Time Above 40.4°C, min |   | Deg-Min above 40.4°C |  | Intervals in % Mortality* along D.R. Curves |
|-------|-------------------------|-------|------------------|-------------------------|-------------------------|------------------------------|---|----------------------|--|---------------------------------------------|
|       | R                       | H     |                  | R                       | H                       | R                            | H |                      |  |                                             |
| 1     | 41.1±0.4<br>(21)§       | 32±17 | 41.7±0.3<br>(29) | 20±12<br>34±18          | 7.2±6.0<br>17.4±6.6     | 0-25%                        |   |                      |  |                                             |
| 2     | 41.5±0.3<br>(16)        | 30±10 | 42.1±0.2<br>(15) | 50±28<br>50±38          | 21.5±1.8<br>35.2±3.1    | 25-50%                       |   |                      |  |                                             |
| 3     | 41.8±0.3<br>(19)        | 29±10 | 42.2±0.2<br>(18) | 48±9<br>55±22           | 31.2±3.8<br>44.5±3.6    | 50-75%                       |   |                      |  |                                             |
| 4     | 42.0±0.4<br>(22)        | 29±7  | 42.2±0.2<br>(14) | 50±14<br>62±35          | 48.8±8.4<br>56.6±3.9    | 75-94%                       |   |                      |  |                                             |
| 5     | 42.3±0.5<br>(40)        | 37±13 | 42.3±0.1<br>(34) | 87±39<br>99±46          | 97.2±33.6<br>110.8±33.0 | 95-100%                      |   |                      |  |                                             |

Values are means ± SD; no. of rats per group are given in parentheses. EOR T<sub>c</sub> and EOH T<sub>c</sub> = core temperature at end of running or heating, respectively. R = run-exhausted rats; H = restrained-heated rats. \*Run and heated groups were derived from corresponding segments of two dose-response curves of the percent mortality vs. thermal area. †P < 0.05; R vs. H ‡P < 0.05 between mean and mean above it §24 of the 142 run animals had total areas equal to 0 and were excluded from these groups.

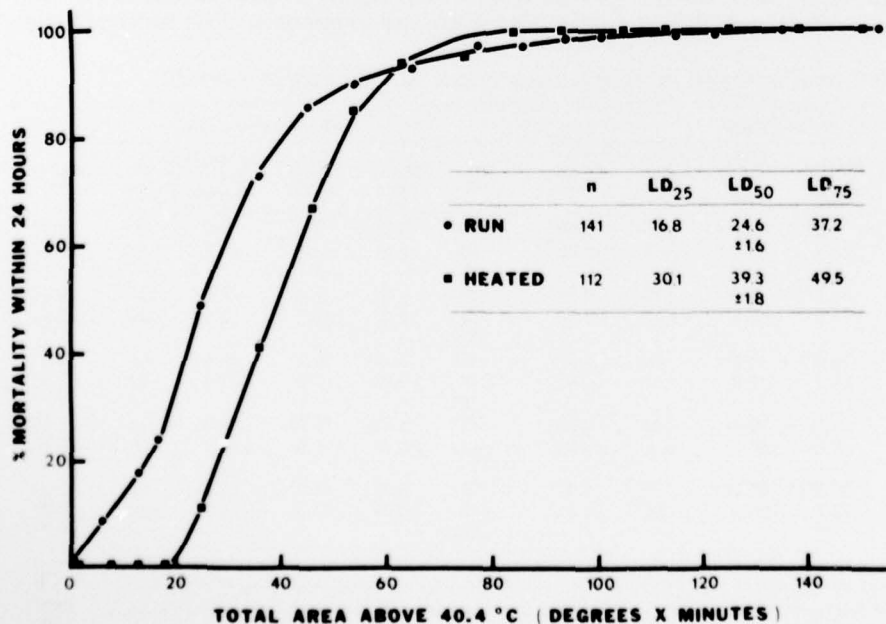


FIG. 2. Dose-response curves of percent mortality within 24 h versus the severity of core heating in degree-minutes. (Section of the curve from 160 to 185 degree-minutes not shown.) See legend Fig. 1. Values in insert represent mean ± SE.

mortality. In contrast to the run-exhausted animals, the lack of significant differences in core temperatures between heated groups 2 and 3, as well as groups 3 and 4, indicates the limited usefulness of this criterion for predicting the incidence of mortality with sedentary, heated animals. Furthermore, the total time the core temperature remains elevated above 40.4°C has even less usefulness in predicting death within 24 h. In only one case (group 1), does the duration of temperature elevation distinguish between run-exhausted and restrained-heated rats. In contrast to either the duration or intensity of body heating considered singly, the severity of core heating measured as a hyperthermic area in degree-minutes above a baseline core temperature of 40.4°C clearly defines the increased heat stress (group 1 vs. group 2, etc.) associated with the increased mortality in both run-exhausted and restrained-heated rats. Moreover, within each mortality range (groups 1 and 2, etc.), hyperthermic area analysis will differentiate between run-exhausted and restrained-heated rats. It should also be noted that both the run-exhausted and restrained-heated animals in group 5 were exposed to double the amount of body heating received by group 4.

In contrast to Table 1 which describes the entire heating and cooling curve, Table 2 contains the data separating the whole curve into two parts with the end of running (EOR) or heating (EOH) as the midpoints. The EOR represents the point of exhaustion and the EOH, the end of heating producing a range in core temperatures from 41.4 to 42.6°C. Within both run-exhausted and restrained-heated groups 1-4, the two halves of each area were nearly identical. In both run-exhausted and restrained-heated group 5, the cooling area was significantly greater than the heating area. In spite of this, the heating areas as a mean percentage of the total areas for run-exhausted or restrained-heated groups 1-5 were  $49 \pm 8$  and  $46 \pm 3\%$ , respectively. This indicates that a) in general, the heating and cooling portions of the total hyperthermic curve are nearly equal under these conditions and b) significant heat

injury can occur after exhaustion and/or withdrawal from the heat.

In both the running and heating experiments, groups 1 and 5 represent extreme positions along the continuum from low to high thermal exposures. By contrasting the restrained-heated groups 1-5, the following trends were evident: both the heating and cooling times were longer in groups with greater thermal area. As a result, heating and cooling rates were the slowest in the group with the highest thermal exposure (group 5). On the other hand, the individual variability in the shape of the heating curves for run-exhausted rats masked any trend in running time or heating rates with increased thermal area. Run-exhausted rats in group 5, however, had significantly longer cooling times and slower cooling rates than group 1. Both the run-exhausted and restrained-heated animals of group 5 had identical cooling times and rates. These groups, therefore, represent a point where the effects of high thermal stress appear to make the response of both run-exhausted and restrained-heated rats similar.

The relationship between core temperature, cooling rate and survival for the combined groups 1-5 is shown in Table 3. In confirmation of previous results (17), when all run-exhausted survivors and fatalities are separately pooled into two large groups which include a wide range of core temperatures, the fatalities have a higher core temperature at exhaustion than survivors. As indicated by Fig. 3, however, this distinction disappears when one compares the core temperatures of both survivors and fatalities within a narrow range of thermal exposure. In 9 of 10 cases within these prescribed intervals, neither the intensity of hyperthermia (Fig. 3) nor the hyperthermic area in degree-minutes (not shown) will distinguish between potential survivors and fatalities. These results appear in contradiction to the data in Table 3. However, there are two explanations for this: a) the means presented in Fig. 3 are isolated according to narrow ranges in thermal exposure (this eliminates the grosser comparison of all survivors with

TABLE 2. Comparison of heating and cooling times, rates and areas based on incidence of mortality

| Group | % Mortality | Run-Exhausted Rats |                |                               |                            |                        |                            | Restrained-Heated Rats         |                            |                             |                            |                        |                            |
|-------|-------------|--------------------|----------------|-------------------------------|----------------------------|------------------------|----------------------------|--------------------------------|----------------------------|-----------------------------|----------------------------|------------------------|----------------------------|
|       |             | RT, min            | HR, °C/min     | 40.4°C to EOR, deg-min        | EOR to 40.4°C, deg-min     | CT, min                | CR, °C/min                 | HT, min                        | HR, °C/min                 | 40.4°C to EOH, deg-min      | EOH to 40.4°C, deg-min     | CT, min                | CR, °C/min                 |
| 1     | 0-25        | 57*<br>±30<br>(21) | 0.07*<br>±0.04 | 4.0*<br>±3.9                  | 3.1*<br>±3.3               | 11*<br>±7              | 0.05*<br>±0.02             | 34<br>±10<br>(29)              | 0.14<br>±0.04              | 7.8<br>±4.1                 | 9.6<br>±4.2                | 20<br>±13              | 0.08<br>±0.04              |
| 2     | 25-50       | 58*<br>±19<br>(16) | 0.07*<br>±0.03 | 11.8* <sup>‡</sup><br>±3.0    | 9.8* <sup>‡</sup><br>±3.7  | 26 <sup>‡</sup><br>±31 | 0.05<br>±0.02              | 40<br>±8<br>(15)               | 0.12<br>±0.03              | 16.4 <sup>‡</sup><br>±5.1   | 18.8 <sup>‡</sup><br>±5.1  | 31<br>±38              | 0.06<br>±0.02              |
| 3     | 50-75       | 50<br>±16<br>(19)  | 0.08<br>±0.03  | 15.6* <sup>‡</sup><br>±5.9    | 15.6* <sup>‡</sup><br>±5.9 | 23 <sup>‡</sup><br>±7  | 0.06<br>±0.02              | 48 <sup>‡</sup><br>±14<br>(18) | 0.10 <sup>‡</sup><br>±0.03 | 22.1 <sup>‡</sup><br>±7.6   | 22.4 <sup>‡</sup><br>±7.4  | 31<br>±23              | 0.07<br>±0.03              |
| 4     | 75-94       | 50<br>±12<br>(22)  | 0.07*<br>±0.03 | 22.4 <sup>‡</sup><br>±9.8     | 26.4 <sup>‡</sup><br>±10.2 | 29 <sup>‡</sup><br>±12 | 0.05<br>±0.03              | 49 <sup>‡</sup><br>±14<br>(14) | 0.10 <sup>‡</sup><br>±0.03 | 27.8 <sup>‡</sup><br>±10.5  | 28.5 <sup>‡</sup><br>±10.1 | 31<br>±28              | 0.05 <sup>‡</sup><br>±0.03 |
| 5     | 94-100      | 65<br>±23<br>(40)  | 0.07<br>±0.03  | 35.3** <sup>‡‡</sup><br>±21.1 | 62.9 <sup>‡</sup><br>±29.2 | 51 <sup>‡</sup><br>±36 | 0.03 <sup>‡</sup><br>±0.03 | 77 <sup>‡</sup><br>±50<br>(34) | 0.09 <sup>‡</sup><br>±0.08 | 45.9 <sup>‡‡</sup><br>±27.9 | 71.4 <sup>‡</sup><br>±41.3 | 52 <sup>‡</sup><br>±36 | 0.03 <sup>‡</sup><br>±0.03 |

Values are means ± SD; no. of rats per group are given in parentheses. RT = running time; HT = heating time; CT = cooling time; CR = cooling rate at 26°C ambient measured during 30-min period post-EOR or -EOH. \*Values for run group significantly different from heated group,  $P < 0.05$ . <sup>‡</sup>Significantly different from group 1,  $P < 0.05$ . <sup>‡‡</sup>Heating area significantly different from cooling area,  $P < 0.05$ .

all fatalities which effectively masks the existence of both heat-sensitive and heat resistant individuals); and b) the dose-response curves of core temperature or hyperthermic area versus percent mortality indicate only the probability of death but not who will succumb.

The cooling rate, measured during the first 30 min of recovery, was more selective than core temperature (Table 3). Survivors, in restrained-heated groups 1-3 and in run-exhausted group 5, had significantly faster cooling rates than fatalities (not shown). The mean cooling rates for the survivors and fatalities in the combined groups 1-5 are shown in Table 3. Survivors, in general, had a faster cooling rate than fatalities; but run-ex-

hausted survivors had a slower cooling rate than restrained-heated survivors.

Finally, Table 4 indicates approximately when the animals died as the mortality rate increased with increasingly severe thermal exposures (groups 1-5). Within run-exhausted groups 1-4, less than 20% of the fatalities occurred before the core temperature returned to 40.4°C and the greater majority occurred overnight. In run-exhausted group 5, however, 70% of the animals died during prolonged or secondary hyperthermia and unassisted cooling at 26°C was completely ineffective. Essentially the same pattern was observed in restrained-heated rats with group 4 being a transitional stage.

TABLE 3. Relationship between core temperature, cooling rate, and survival of run and heated rats

| Group          | EOR T., °C              |                        | Cooling Rate, °C/min    |                         |
|----------------|-------------------------|------------------------|-------------------------|-------------------------|
|                | Run                     | Heated                 | Run                     | Heated                  |
| 1-5 Survivors  | 41.6*<br>± 0.6<br>(42)  | 41.8<br>± 0.4<br>(44)  | 0.06*<br>± 0.02<br>(36) | 0.08<br>± 0.02<br>(44)  |
| 1-5 Fatalities | 42.0*‡<br>± 0.6<br>(76) | 42.3‡<br>± 0.2<br>(66) | 0.04‡<br>± 0.03<br>(67) | 0.04‡<br>± 0.03<br>(64) |

Values are means ± SD; no. of rats per group are given in parentheses. EOR and EOH refer to end of running and end of heating, respectively. Cooling rate at 26°C ambient is measured during 30-min period post-EOR or -EOH. \*P < 0.05 for the Student t-test between mean of run vs. mean of heated rats. ‡P < 0.05 for the Student t-test between mean of survivors vs. mean of fatalities.

TABLE 4. Change in pattern of survival time with increasing thermal stress

| Group | Run,* deg-min | Total Fatalities, n | Died Pre-BL, % | Died Post-BL, % | Died Over-night, % | Heated,* deg-min | Total Fatalities, n | Died Pre-BL, % | Died Post-BL, % | Died Over-night, % |
|-------|---------------|---------------------|----------------|-----------------|--------------------|------------------|---------------------|----------------|-----------------|--------------------|
| 1     | 7             | 7                   | 14             | 57              | 29                 | 17               | 4                   | 25             | 0               | 75                 |
| 2     | 22            | 5                   | 20             | 20              | 60                 | 35               | 7                   | 0              | 29              | 71                 |
| 3     | 31            | 14                  | 14             | 36              | 50                 | 44               | 12                  | 0              | 33              | 67                 |
| 4     | 49            | 14                  | 14             | 14              | 72                 | 57               | 11                  | 27             | 36              | 37                 |
| 5     | 97            | 36                  | 66             | 17              | 17                 | 111              | 32                  | 66             | 25              | 9                  |

\*Hyperthermic area in degree-minutes above a core temperature of 40.4°C. †Percentage of fatalities dying before their core temperatures returned to base line (40.4°C). ‡Percentage of fatalities dying after their core temperatures returned to base line (40.4°C) during an observation period. §Percentage of fatalities dying overnight from 16 to 22 h after running or heating.

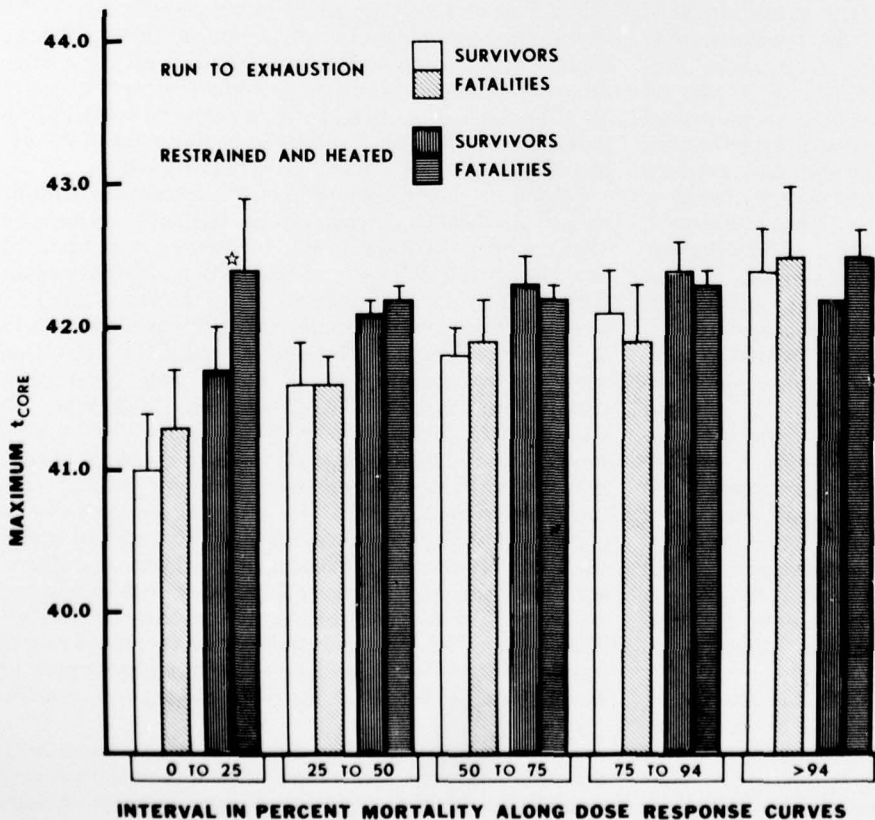


FIG. 3. Maximum core temperatures of groups of survivors and fatalities compared within intervals in percent mortality along dose-response curves. See legends of Figs. 1 and 2. P < 0.05 between survivors and fatalities indicated by star.



## DISCUSSION

The extent to which direct thermal injury and work-related factors combine to produce the pathophysiology of fatal heatstroke has not been experimentally defined due to the lack of an appropriate model. The widely held belief that cessation of sweating is a cardinal sign of heatstroke (22) 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, 5, 20, 23, 37), there are also numerous reports of heatstroke accompanied by profuse sweating (14, 26, 30-32, 38). The more general concept that either damage or overload to a heat dissipating mechanism can result in excessive body temperature and heatstroke (34) has resulted in the development of both rat and dog models (7, 17, 29). The purpose of this research has been to refine the use of the rat model as a research tool and to measure the extent to which work factors contribute to heatstroke death.

In their recent review on heatstroke (33), 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. (29) in developing a dog heatstroke model. Thermal load was measured as the area, in degree-minutes, of core heating above an assigned base line of 43°C. The choice of base line is determined by the minimum observed lethal temperature. In our experience, this temperature for rats is near 40.4°C. The superior resolution of this measurement over either the duration or the intensity of hyperpyrexia is seen in Table 1. These results provide experimental evidence that both the incidence of mortality as well as the survival time (Table 4) can be predicted from the severity of the heat stress measured in degree-minutes. Thus, 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 (40). However, Table 1 also shows a 10-fold difference in hyperthermic area between the run-exhausted rats of *group 1* and the run-exhausted rats of *group 5*. Obviously, certain animals can withstand tremendous heat stress before collapsing whereas others cannot. Since, in both cases, exhaustion is the end point, these results indicate why in some cases the most fit, highly motivated individuals often suffer the severest heat injury (18, 32). Under these circumstances, the point of collapse does not ensure similar chances of survival amongst different individuals. Furthermore, there is a small percentage of the population that will succumb to low heat loads (*group 1*) and, conversely, a small group that can withstand twice the thermal load that is lethal to 75% of the population (*group 5* vs. *group 4*).

In this regard, recent reviews (18, 33) have commented on the 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. For example, Carson and Webb

(8) described 14 cases of heat illness in fit, young English soldiers following sustained physical effort. Sweating was noted in nine patients, five were considered to have suffered heatstroke and yet the earliest recorded body temperatures averaged only  $39.8 \pm 1.3^\circ\text{C}$ . In the rat, as in man (25), a core temperature of 40.4°C or higher can be lethal to some individuals. Although in the run-exhausted animal there is good agreement between core temperature and mortality rates, this is a special case. In the sedentary-heated condition, it is only the amount of body heating in degree-minutes that defines the incidence of mortality. Thus, in reality, elevated core temperatures only describe a zone of potential danger and surely, ignoring cases of borderline hyperpyrexia, will result in unexpected deaths. This is especially true if the duration of the hyperthermia is unknown and work is a factor.

The ability to compare individual susceptibility to heat-induced mortality based on the degree and duration of hyperthermia has produced two new insights. First, examination of Fig. 3 emphasizes the existence of both heat-sensitive and heat-resistant animals over the entire range of comparable thermal exposures. These data and the pattern in survival times described in Table 3 suggest that the pathophysiology of fatalities in *group 1* might be different from that in *group 5*. Furthermore, by this method of retrospective analysis and by comparing *group 1* and *group 5* survivors, it should be possible to determine which noncritical biochemical or physiological factors increase with thermal load independently of mortality rates. Conversely, by examining *group 1* mortalities, it should be possible to determine which vital biochemical or physiological factors change rapidly in some susceptible individuals with a low thermal load. Thus, it should be possible to carry the analysis of heatstroke beyond the dose-response relationship indicating "how many" could die to the point of resolving for the clinician "who" could die and why.

Second, as recently reviewed (33), temperatures sufficient to produce heatstroke can be reached 1) actively by physical exercise; 2) passively, by gaining heat from the environment; 3) following deterioration of heat dissipation; or 4) by a combination of these. However, as presented in the introduction, when the reactive hyperemia of work is added to the burden of superficial dilatation provoked by hyperthermia, an intense splanchnic vasoconstriction must occur or shock would intervene. As shown by the mortality data in Fig. 2 and Table 1, this combination of heat plus work is much more dangerous at low, comparable thermal loads than is acute exposure to excessive heat at rest. The proposed series of events leading to profound peripheral vascular collapse under these conditions has been described by Daily and Harrison (9). In this regard, the cooling rate of run-exhausted survivors (Table 3) is significantly less than restrained-heated survivors. This may indicate an increased rate of heat production or, more likely, serious impairment of cardiovascular function in heat dissipation mechanisms.

Additionally, with this model it seems possible to evaluate the work component of heat illness in a way consistent with the hyperthermic area concept of ther-

mal stress. The difference in thermal areas (40.4°C to EOH or EOR, Table 2) in degree-minutes (heated minus run) within each group of Table 2 is an estimate of the thermal equivalency of work stress. Since no fatalities occurred below a core temperature at exhaustion of 40.4°C, only work done above this threshold core temperature should be relevant to the calculation of a degree-minute per kilogram-meter factor. The value of this ratio under these experimental conditions was calculated to be  $0.44 \pm 0.11$  deg-min/kg-m of work above a core temperature of 40.4°C. The use of this factor may allow the direct addition of work stress, expressed in degree-minutes, to the thermal stress in order to predict and test their combined effects on mortality rates or tissue injury in various experimental paradigms.

Finally, caution demands that this experimental attempt to quantitate and define the cause of heartstroke death must be regarded, simultaneously, as a toxicological approach to the lethal interactions of multiple environmental and physiological stressors. In reality, these dose-response curves represent a hierarchy of stress effects combining electrical stimulation, exercise to exhaustion and hyperthermia on the one hand, and restraint and hyperthermia on the other. Although it is recognized that restraint, per se, is a stressor (13, 21), we have never observed death within 24 h as a result of short-term restraint alone. Likewise, animals exercised

to exhaustion at 5°C; all survive, run longer, do more work (+85%), and presumably receive more electrical stimuli than animals exhausted at or near room temperature (16, 17). Therefore, we suggest a) the convergence of the two dose-response curves indicates that hyperthermia is the predominant forcing function, but b) at low, comparable thermal loads, work plus hyperthermia is more lethal than hyperthermia alone. These suggestions do not preclude the possibility that measurements other than the incidence of mortality would be more stress specific than stress related.

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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.

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