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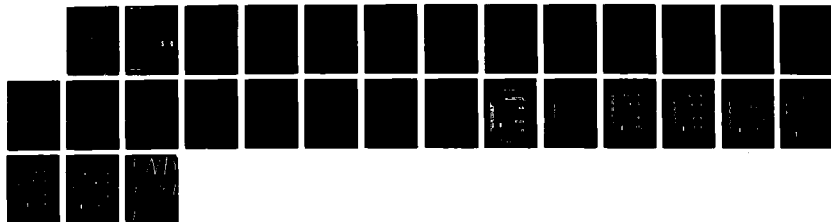
EXERCISE IN THE HEAT: EFFECTS OF DINITROPHENOL
ADMINISTRATION(U) ARMY RESEARCH INST OF ENVIRONMENTAL
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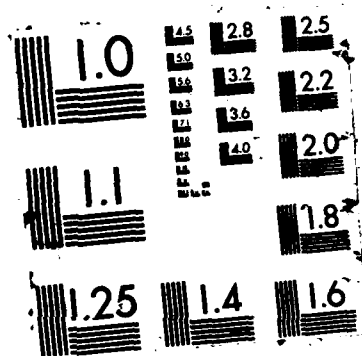
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EXERCISE IN THE HEAT:
EFFECTS OF DINITROPHENOL ADMINISTRATION

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2a. SECURITY CLASSIFICATION AUTHORITY		3. DISTRIBUTION/AVAILABILITY OF REPORT DISTRIBUTION A: Approved for public release; distribution is unlimited.	
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE			
4. PERFORMING ORGANIZATION REPORT NUMBER(S)		5. MONITORING ORGANIZATION REPORT NUMBER(S)	
6a. NAME OF PERFORMING ORGANIZATION US Army Research Institute of Environmental Medicine	6b. OFFICE SYMBOL (if applicable) SGRD-UE-HR	7a. NAME OF MONITORING ORGANIZATION	
6c. ADDRESS (City, State, and ZIP Code) Natick, MA 01760-5007		7b. ADDRESS (City, State, and ZIP Code)	
8a. NAME OF FUNDING/SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (if applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c. ADDRESS (City, State, and ZIP Code)		10. SOURCE OF FUNDING NUMBERS	
		PROGRAM ELEMENT NO.	PROJECT NO.
		TASK NO.	WORK UNIT ACCESSION NO. 004
11. TITLE (Include Security Classification) Exercise in the heat: effects of dinitrophenol administration			
12. PERSONAL AUTHOR(S) R. Francesconi, R. Hubbard, C. Matthew, M. Durkot, M. Bosselaers, and N. Leva			
13a. TYPE OF REPORT Manuscript	13b. TIME COVERED FROM _____ TO _____	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT 24
16. SUPPLEMENTARY NOTATION			
17. COSATI CODES		18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)	
FIELD	GROUP	SUB-GROUP	
19. ABSTRACT (Continue on reverse if necessary and identify by block number) Although dinitrophenol (DNP) stimulates excessive heat production by uncoupling oxidative phosphorylation, its effects on performance and thermoregulation during exercise in the heat have not been assessed. DNP was administered in two equal dosages (20mg/kg, 30 min interval); the second injection was followed immediately by exercise (9.14m/min) in the heat (30°C) or at room temperature (21°C) until exhaustion or 99 min. At 21°C control (saline-treated) rats manifested a mean endurance of 94 min which was reduced to 32 min among DNP-treated animals. Respective increments in Tre for both groups were 0.02°C/min and 0.08°C/min. At 30°C control rats ran for 65 min (Tre/min=0.05°C) while DNP-treated animals had a mean endurance of only 12 min (Tre/min=0.22°C). DNP-treated rats (30°C) certainly manifested no decrement in tail-skin heat loss (Tsk/min=0.17°C vs 0.10°C) or saliva secretion (0.78g/min, DNP vs 0.19g/min, control) for their brief treadmill duration. Heat stress and DNP prevented the normal reduction in hematocrit and plasma protein levels during exercise while DNP increased osmolality and potassium levels post-exercise. Thus, the increased metabolic heat production or metabolic inefficiency of DNP administration severely reduced			
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performance and thermoregulation in the heat or a moderate environment, and may have affected muscle membrane integrity resulting in increasing potassium efflux.

Abstract

Although dinitrophenol (DNP) stimulates excessive heat production by uncoupling oxidative phosphorylation, its effects on performance and thermoregulation during exercise in the heat have not been assessed. DNP was administered in two equal dosages (20mg/kg, 30 min interval); the second injection was followed immediately by exercise (9.14m/min) in the heat (30°C) or at room temperature (21°C) until exhaustion or 99 min. At 21°C control (saline-treated) rats manifested a mean endurance of 94 min which was reduced to 32 min among DNP-treated animals. Respective increments in T_{re} for both groups were 0.02°C/min and 0.08°C/min. At 30°C control rats ran for 65 min ($\Delta T_{re}/min=0.05^{\circ}C$) while DNP-treated animals had a mean endurance of only 12 min ($\Delta T_{re}/min=0.22^{\circ}C$). DNP-treated rats (30°C) certainly manifested no decrements in tail-skin heat loss ($\Delta T_{sk}/min=0.17^{\circ}C$ vs $0.10^{\circ}C$) or saliva secretion (0.78g/min, DNP vs 0.19g/min, control) for their brief treadmill duration. Heat stress and DNP prevented the normal reduction in hematocrit and plasma protein levels during exercise while DNP increased osmolality and potassium levels post-exercise. Thus, the increased metabolic heat production or metabolic inefficiency of DNP administration severely reduced performance and thermoregulation in the heat or a moderate environment, and may have affected muscle membrane integrity resulting in increasing potassium efflux.

INTRODUCTION

For several years we have been quantitating the effects of pharmacological and physiological interventions on the physical, thermoregulatory, and clinical chemical responses to exercise in the heat in a validated rat model of human heat/exercise injury (7,17,19). For example, we have reported that when rats were exercised in a hot (35°C) environment, treatment regimens which reduced core temperature prior to the experimental contingency significantly increased endurance capacity before the onset of hyperthermic exhaustion (8,9). Alternatively, we have demonstrated that factors which predispose to heat injury or tend to reduce performance in the heat, such as alcohol consumption (10), treatment with tricyclic antidepressants (11), or pre-induced hyperthermia (12), similarly reduced the time required to reach hyperthermic exhaustion in our exercising rat model. Generally, these reductions in endurance were ordinarily accompanied by increased heating rates, increased circulating levels of indices of heat injury, and, in several instances, increased loss of body fluids through salivation without accompanying thermoregulatory benefit (6,23).

While a physiological state of increased metabolic heat production induced by endocrinological imbalance may predispose an individual to heat injury, very few studies have quantitatively investigated this condition. Sulman et al. (26) have described a heat stress syndrome in over 100 patients in whom the primary pathological manifestation appeared to be a hypermetabolic state secondary to hyperthyreosis. Similarly, Collins (2) concluded that the endocrinological or chemical suppression of metabolism can be construed as a useful adaptation among individuals living in or acutely exposed to extremely hot conditions. Generally, repressed thyroidal activity during exercise in the heat, in comparison to exercise at moderate temperatures, may be adaptive to repressed heat generation at the warmer temperatures (5,14).

Dinitrophenol (DNP) has been used extensively for its unique ability to stimulate markedly oxygen consumption and increase metabolic heat production without concomitant biosynthesis of high energy phosphate compounds. Issekutz (20) has reported that the infusion of 8.5mg/kg DNP to mongrel dogs elicited a 4°C elevation of rectal temperature (Tre) which was unaffected by propranolol administration. Interestingly, despite the absence of effects on Tre, the hyperlactacidemia effected by DNP administration in the previous experiment was offset by the propranolol. Geiser et al. (13) used DNP to increase the oxygen consumption of ducks by a factor of seven, but Tre was not reported in these experiments. While the effects of DNP on muscle mitochondrial metabolism have been extensively investigated (1,24,25), a very small number of these studies included thermoregulatory or performance measures among the dependent variables of interest. In the current experiments we have used DNP administration and a heat/exercise contingency to assess and quantify the effects of a chemically induced metabolic inefficiency on the ability to work in the heat. Endurance capacity, thermoregulation, and clinical chemical responses were closely evaluated.

METHODS

Adult, male rats (Sprague-Dawley, Charles River Breeding Labs, Wilmington, MA) were used in all experiments. Upon arrival at the laboratory rats (200-250g) were held in individual, wire-bottomed cages in windowless rooms at $21 \pm 1^{\circ}\text{C}$ with food (Agway Inc., Standard Rodent Chow) and water available ad lib except for the time of the actual experimental trial. Fluorescent lighting was automatically controlled (on, 0600-1800h). Prior to use the rats were weighed frequently and Tre measured to acclimate the animals to several of the experimental procedures. Ordinarily, 7-10 days were required for the animals to grow to the desired experimental weight (approximately 300g).

On the day prior to an experimental trial, each rat was fitted with a permanently indwelling catheter in the external jugular vein for rapid and convenient blood sampling. Aseptic techniques were used; the animals were anesthetized with sodium pentobarbital (40mg/kg), and manifested no untoward effects of the brief surgical intervention. They were returned to their home cages where they remained until initiation of the experiment between 0730 and 0800h of the following morning.

Rats were randomly assigned to one of 4 treatment groups (n=6-8 animals/group): two of the groups (control, CONT) received by intraperitoneal injection 1 ml of sterile, non-pyrogenic saline at time 0 and time 30 min while the remaining 2 groups (experimental, DNP) were injected intraperitoneally with 1 ml 2,4 dinitrophenol (Sigma Chemical Company, St Louis) dissolved in 0.01M sodium tetraborate, pH=9.18 at time 0 (20mg/kg, approx. 1 ml) and time 30 (20mg/kg, approx. 1 ml). During the 30 min between injections the rats were confined to restraining cages; rectal temperature (T_{re} , probe inserted and securely affixed 6cm beyond the anal sphincter) and skin temperature (T_{sk} , probe firmly affixed mid-length on the tail) were monitored at 5 min intervals using a Cole-Parmer 8502-20 or Digitec 5810 digital thermometer.

Following the second injection (DNP or saline), rats were quickly removed to one of two environmentally controlled stainless steel chambers. For the exercise test at room temperature the environmental temperature was maintained at $21 \pm 1^{\circ}\text{C}$ and the relative humidity was 40-50%. During the heat stress test a large (3x4m) stainless steel chamber was maintained at 30°C , 30-35% relative humidity. In either chamber rats were exercised at a mild intensity (9.14 m/min, 0° angle of incline). Under both environmental conditions DNP-treated rats ordinarily ran to hyperthermic exhaustion ($T_{re}=41.5-42.5^{\circ}\text{C}$, animal unable

to right itself) while at 21°C control or saline-treated rats generally were removed from the treadmill after 99 min although several could have run longer. At 30°C even the saline-treated rats manifested marked hyperpyrexia ($\bar{X}T_{re}=41.1^{\circ}\text{C}$), and were exhausted at the completion of the run. During the treadmill interval T_{re} and T_{sk} were monitored on a minute-by-minute basis using a fully automated data collection system (Hewlett-Packard Inc., Model 85 computer, 3495 A scanner, and 3456A digital voltmeter). Upon termination of the run rats were returned to their home cages (21°C) after weighing.

Immediately prior to the initial saline or DNP injection and immediately subsequent to the termination of the treadmill run, a small (0.7ml) sample of blood was withdrawn from the previously implanted catheter. A small fraction of the sample was used for duplicate determinations of microhematocrit and total protein levels (refractometry). The remainder was centrifuged (2000g, 4°C), and the plasma was assayed on the same day for osmolality (uOsmette, Precision Systems, Inc.) and sodium (Na^{+}) and potassium (K^{+}) levels (FLM 3 Flame Photometer, Radiometer, Copenhagen).

Group mean values for saline- or DNP- treated rats run at each ambient temperature were compared by a non-paired t test for independent data. When intra-group pre-run and post-run data were compared, a paired t test for dependent data was performed (21). The null hypothesis was rejected at $P<0.05$.

RESULTS

The combination of DNP administration and elevated ambient temperature had severely decremental effects on the endurance capacity of untrained rats. Fig. 1 illustrates that at 30°C DNP-treated animals had a mean endurance of only slightly longer than 12 min whereas saline-treated rats ran for nearly 65 min ($P<0.001$) at the same temperature. At the cooler environmental temperature

(21°C) control rats achieved a steady-state T_{re} ($\bar{X}T_{re}$ end of run = 39.3°C, Figure 2) and manifested a group mean endurance of 94 min while the DNP-treated group ran for only 32 min ($P < 0.001$, Fig. 1) before terminating the run with a collective T_{re} of 41.5°C ($P < 0.001$, Fig 2). Fig. 1 also demonstrates at either environmental temperature that weight (water) loss through salivation, the major mechanism for evaporative heat loss in hyperthermic rats (15,16), was not reduced by DNP treatment. In fact, at 30°C the rate of water loss (0.78 g/min) represents one of the highest rates of salivary water loss that we have observed; however, it should be noted that these rats were hyperthermic even at the start of run probably already salivating at this time. At either environmental temperature the rate of water loss among control rats was significantly ($P < 0.01$) less than the DNP-treated at the respective ambient temperature.

Fig. 3 demonstrates graphically the sharply increased rate of heat gain again at either environmental temperature in the DNP-treated groups ($P < 0.01$, minimal significance). However, of perhaps more interest in Fig. 3 is the observation that the rate of increase of T_{sk} among DNP-treated rats at 30°C indicates that the DNP administration does not attenuate the anticipated increase in tail-skin blood flow for peripheral heat dissipation. In fact, the data confirm a significantly ($P < 0.001$) increased rate of skin temperature increase in the DNP-treated rats at 30°C which was not observed at 21°C.

Ordinarily, the mild exercise protocol used in the current study elicits moderate decrements in hematocrit during the treadmill interval. The results in Fig. 4 are in general agreement with this observation with significant ($P < 0.05$, minimal) pre- to post-exercise reductions in hematocrit except for the 30°C, DNP trial which resulted in no significant change in hematocrit. However, it must

be remembered that under these conditions the group mean endurance was just over 12 min, which may be insufficient time for the fluid shifts which preserve plasma volume to occur. The data depicted in Fig. 5 support this hypothesis since by far the greatest elevation in plasma osmolality also occurred in this group. The osmotic effects of the DNP and the brief endurance may have contributed to this excessively elevated osmolality. Additionally, the data observed for total protein (Fig. 6) support this conclusion since in all trials except again for the 30°C, DNP combination, the pre-run to post-run measures manifested small, but significant ($P < 0.01$), decrements in total protein. Neither DNP treatment nor exercise in the heat had any effects on circulating sodium levels (Fig 7, $P < 0.05$). However, the results obtained for plasma potassium (K^+) concentration are much more complex. When rats ran for a relatively prolonged period with moderate increments in Tre as well as the achievement of a steady state rectal temperature (SAL, 21°C), then there occurred a significant ($p < 0.001$) decrease in plasma K^+ . At the same environmental temperature (21°C) following treatment with DNP, run time was reduced, Tre was markedly elevated, and plasma K^+ was significantly ($P < 0.01$) elevated. At 30°C and following SAL treatment mean endurance and Tre were intermediate, and plasma K^+ levels were unaffected ($P > 0.05$). Again, however, with the 30°C, DNP combination, endurance was significantly reduced, Tre was markedly elevated, and plasma K^+ was likewise significantly ($P < 0.01$) increased.

DISCUSSION

We have previously demonstrated in rats that preinduced hyperthermia, elicited by prostaglandin E_1 administration, significantly reduced the time required to reach hyperthermic exhaustion when the animals were exercised in the heat (12). Using human test subjects Mac Dougall et al. (22) reported that the

induction of hyperthermia using a water-perfused suit similarly significantly attenuated work tolerance time. Interestingly enough, despite the obvious disparity in choice of test subjects between MacDougall's (22) and the current experiments, a striking analogy may be observed with respect to water loss rate during the treadmill interval in the hot environment. In the human experiment (22) test subjects manifested a mean sweat rate of 40.2g/min in the hyperthermic condition vs. 26.4g/min in the normothermic condition. In our experiments with the laboratory rat at 30°C, DNP treatment induced a salivary water loss of 0.78g/min while at 21°C the comparable rate was 0.35g/min. Interestingly, in both the human and the rat hypermetabolic experiments, these considerable water loss rates did not translate to thermoregulatory benefit. The humans had lowered evaporative capacity due to the reduced permeability of the lightweight suits, and the rats, due to the treadmill contingency, could not behaviorally spread the saliva for evaporative heat loss.

A secondary mechanism available to the rat for heat dissipation during exercise in a hot environment is vasodilation of the veins and venules of the tail (3,27), a response which is analogous to the increase in peripheral blood flow observed during heat exposure in humans. Our data indicate that DNP administration did not interfere with this mechanism in the rat since the rate of Tsk increase was maximal in the group treated with DNP and exercised at 30°C. It is noteworthy that the apparently depressed rate of elevation of Tsk in the DNP-treated rats run at 21°C is due to their elevated Tsk at the start of the run. These rats had been treated with DNP 30 min earlier, were already hyperthermic, and were actively engaged in heat dissipation through tail-skin vasodilation. Mean Tsk at the start of the treadmill run for SAL-treated rats was approximately 25°C while the same variable for DNP-treated animals was

28.9°C. These observations are important in that it indicates that the hyperthermia of DNP treatment is apparently associated solely with an increment in heat production rather than any decrement in heat dissipation through salivation mechanisms or peripheral vasodilation. Our preliminary data on metabolic rate studies indicate that our regimen of DNP treatment stimulates O_2 consumption by 35-50%.

Considered together, the data observed for hematocrit, plasma protein, and plasma osmolality may all be related to the observation that at 30°C DNP-treated rats had a mean endurance of only slightly longer than 12 min. For example, it is noteworthy that for the other 3 conditions pre to post levels of hematocrit and plasma protein were significantly reduced while for the 30°C, DNP trial both these variables were not significantly affected by the 12 min exercise trial. We interpret this as indicating that in the other 3 trials (minimum mean endurance=35 min), exercise in the heat was accompanied by an influx of hypotonic interstitial fluid designed to maintain plasma volume (4); during these three trials, run time was sufficient to permit these homeostatic fluid fluxes to occur. In the 12-min trial (DNP, 30°C) it could be hypothesized that the brief period of the exercise contingency precluded the appropriate fluid shifts. Analogously, plasma osmolality was much more markedly increased during the 30°C, DNP trial. Ordinarily, during exercise in the heat elevations of circulating lactate, urea nitrogen, sodium, potassium, and creatinine contribute to this effect. It could again be argued that in the DNP, 30°C trial metabolic products had already accumulated, and their effects on osmolality were exacerbated by the absence of fluid influxes to counter the accumulation of these catabolites. The significant elevation of potassium levels following exercise during this trial may also be explained by an interaction of the

exercise hyperthermia and DNP combination affecting muscle cell membrane integrity and increasing potassium efflux. The present results are also consistent with a novel hypothesis relating metabolic efficiency during exercise directly to performance time and inversely to rates of core heating (18). DNP treatment provides, of course, a worst-case scenario of metabolic inefficiency.

We have concluded from these studies that stimulating heat production by a metabolic uncoupler had severe effects on endurance and heating rate during exercise and especially during exercise in a warm environment. The extreme hyperthermia, especially at 30° ambient temperature, was evidently due entirely to stimulated heat production and not to an inability to secrete saliva or dissipate heat through tail-skin vasodilation. Data for several variables indicated that during the DNP, 30°C trial, the extremely truncated endurance contributed to an inability of homeostatic fluid fluxes to preserve plasma volume. Studies on the effects of DNP on metabolic and clinical chemical responses are continuing.

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Figure Legend

Fig. 1. Effects of DNP administration and exercise at 21°C and 30°C on endurance (open-bars) and the rate of weight (water) loss (solid bars). Mean values + SEM are depicted for each variable.

Fig. 2. Effects of DNP and exercise at two environmental temperatures (21°C and 30°C) on mean rectal temperature. While temperatures were monitored at 1 min intervals during exercise, this figure depicts mean temperature at 5 min intervals for the sake of clarity. SEM's are not shown because in many cases they fell within the limits of the symbols.

Fig. 3. Effects of DNP and exercise at two environmental temperatures on rates of rectal and skin temperature increase during the treadmill interval. In this and in all following figures mean values + SEM are noted.

Fig. 4. Effects of DNP administration and exercise at 21°C and 30°C on hematocrit immediately prior and subsequent to the exercise regimen. Blood samples were withdrawn from previously implanted jugular cannulae.

Fig. 5. Effects of DNP administration and exercise at 21°C and 30°C on plasma osmolality. Osmolality was measured in refrigerated, fresh plasma shortly after sample collection.

Fig. 6. Effects of DNP administration and exercise at 21°C and 30°C on plasma protein levels. These levels were assessed in fresh plasma immediately following sample collection and centrifugation.

Fig. 7. Effects of DNP administration and exercise at 21°C and 30°C on circulating sodium concentrations. These levels were quantitated in freshly frozen plasma samples.

Fig. 8. Effects of DNP administration and exercise at 21°C and 30° on circulating potassium levels measured in frozen plasma samples.

Acknowledgements

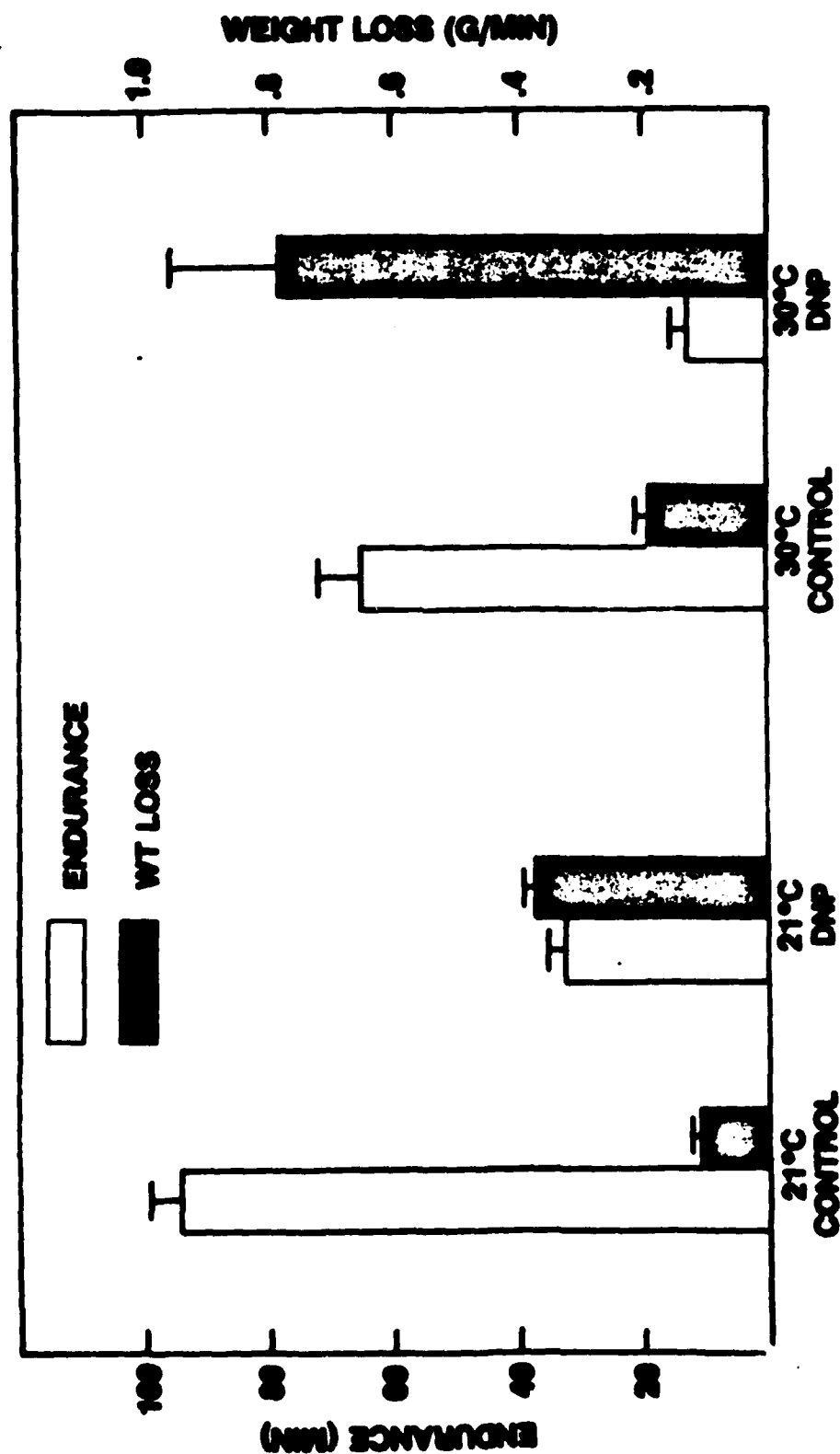
The authors express their sincere appreciation to Ms. Susan E.P. Henry and Ms. Diane Danielski for the outstanding word processing support.

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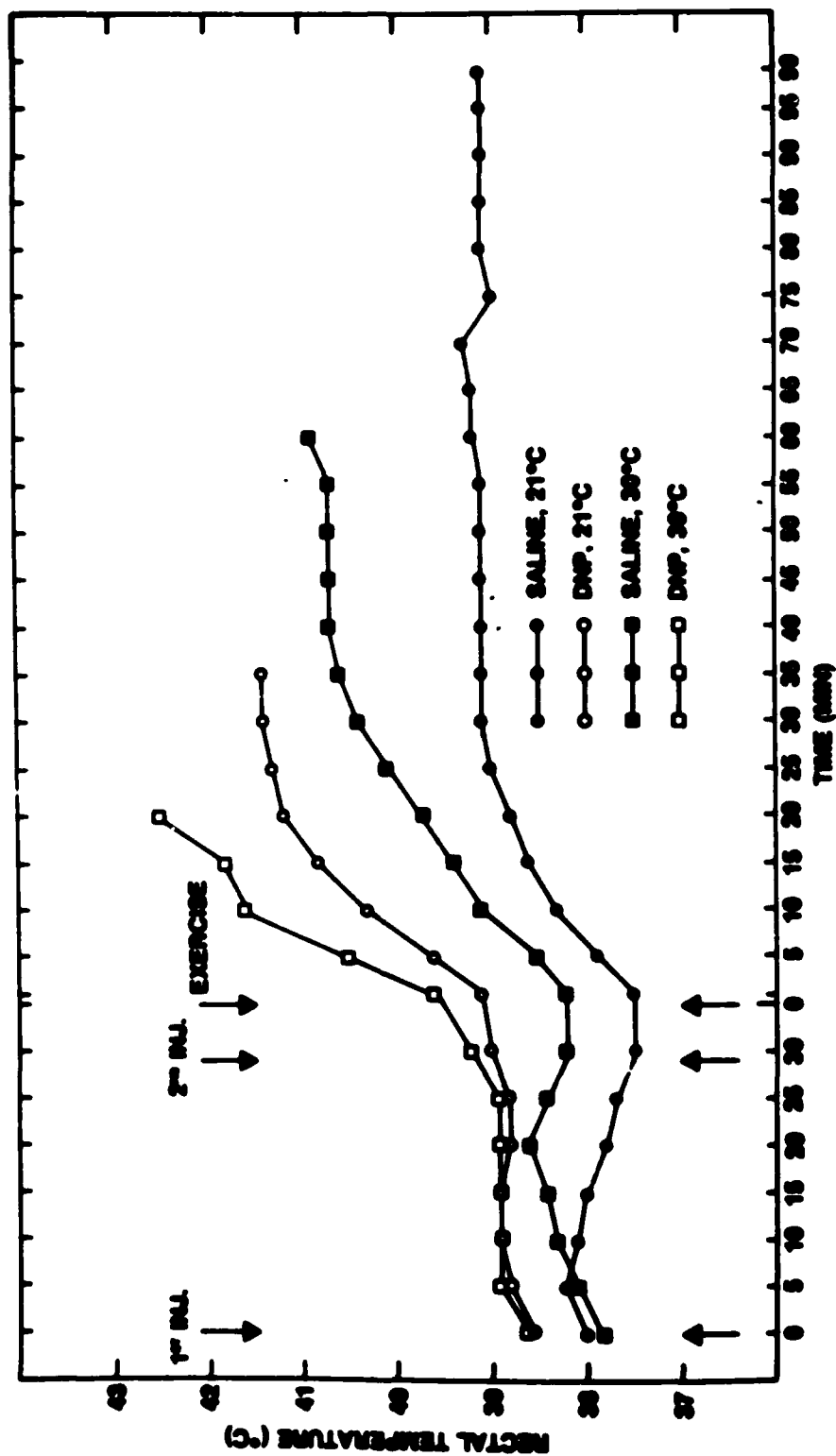
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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

EFFECTS OF DINITROPHENOL AND AMBIENT TEMPERATURE ON ENDURANCE AND WEIGHT LOSS DURING EXERCISE



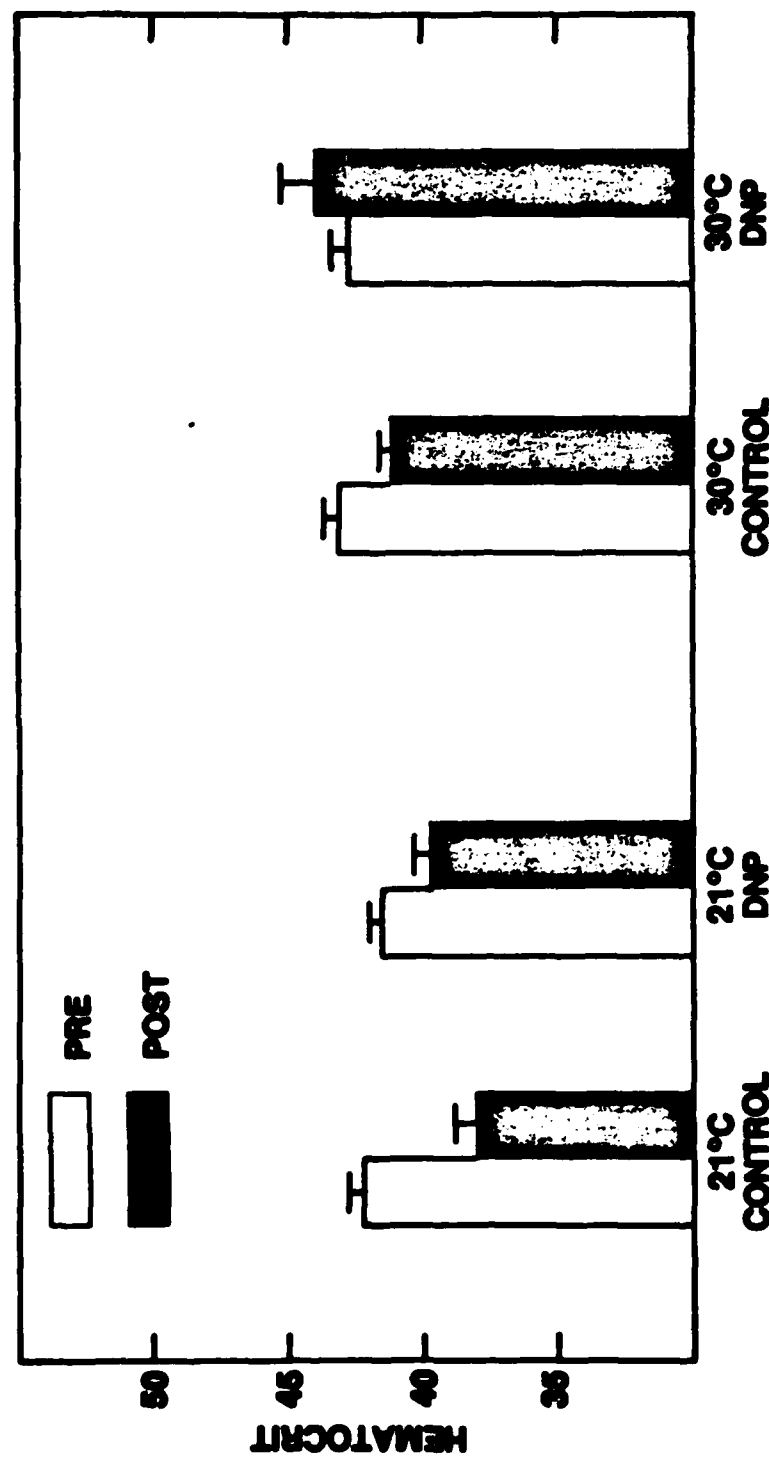
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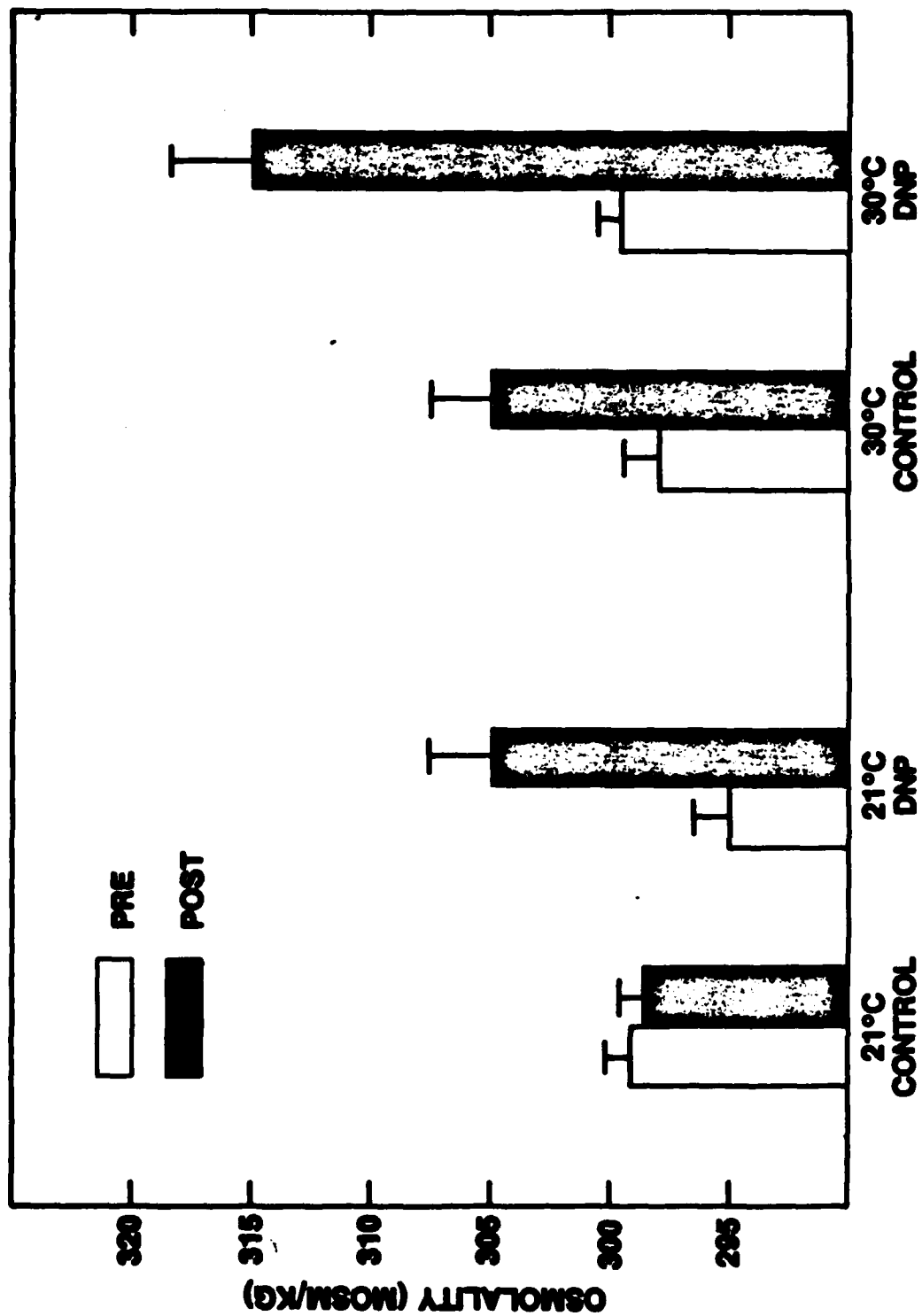
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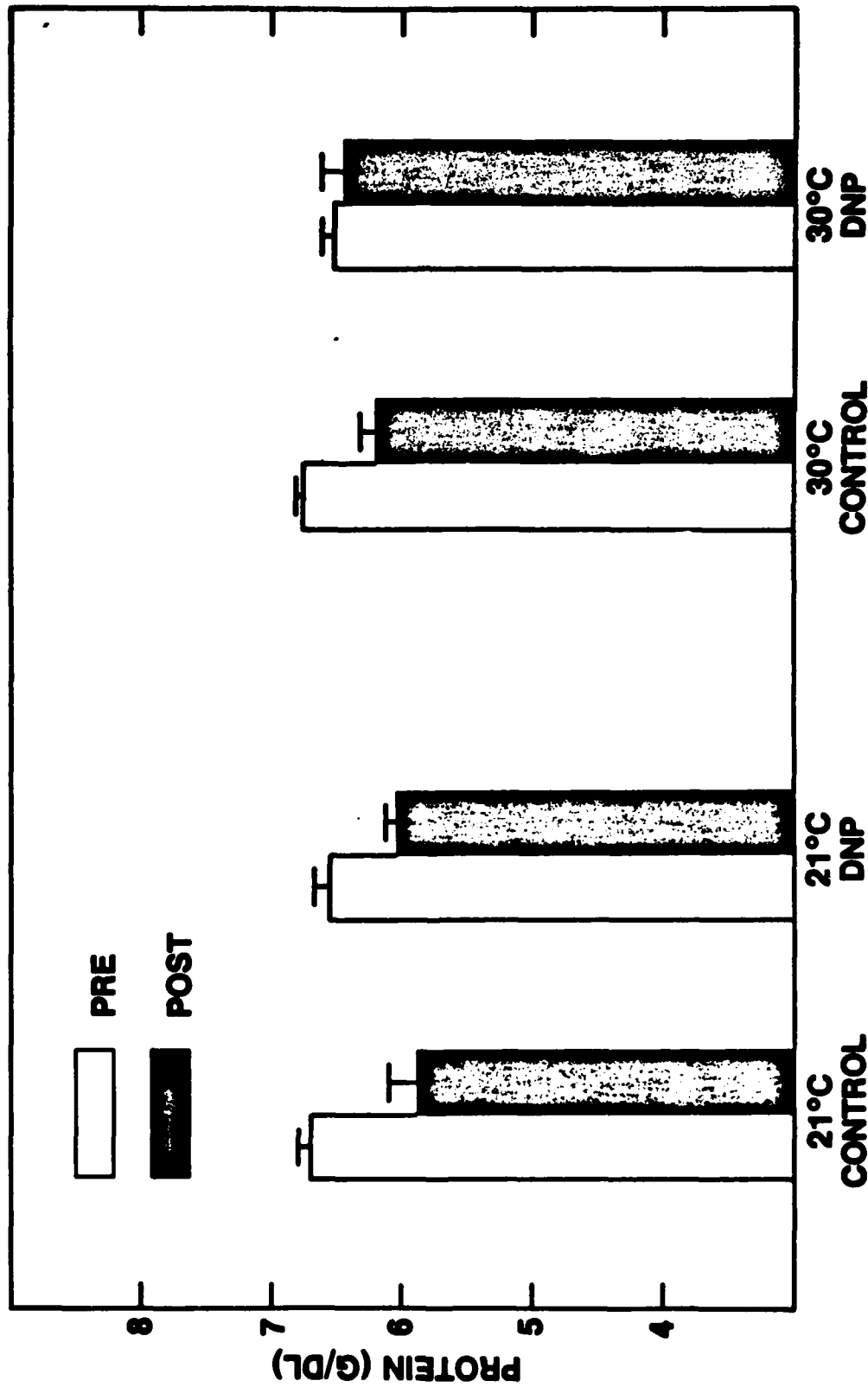
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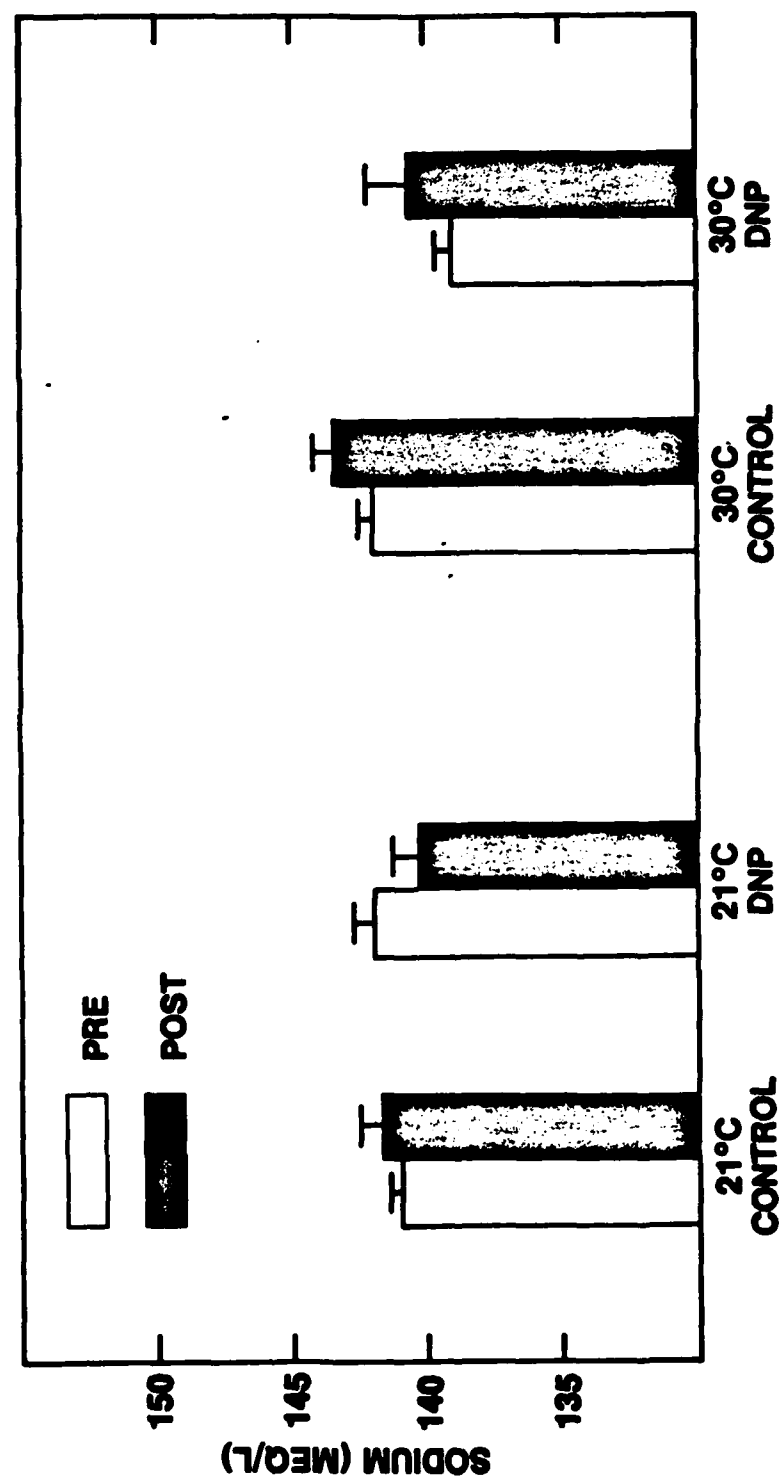
EFFECTS OF DINITROPHENOL, AMBIENT TEMPERATURE, AND EXERCISE ON PLASMA OSMOLALITY



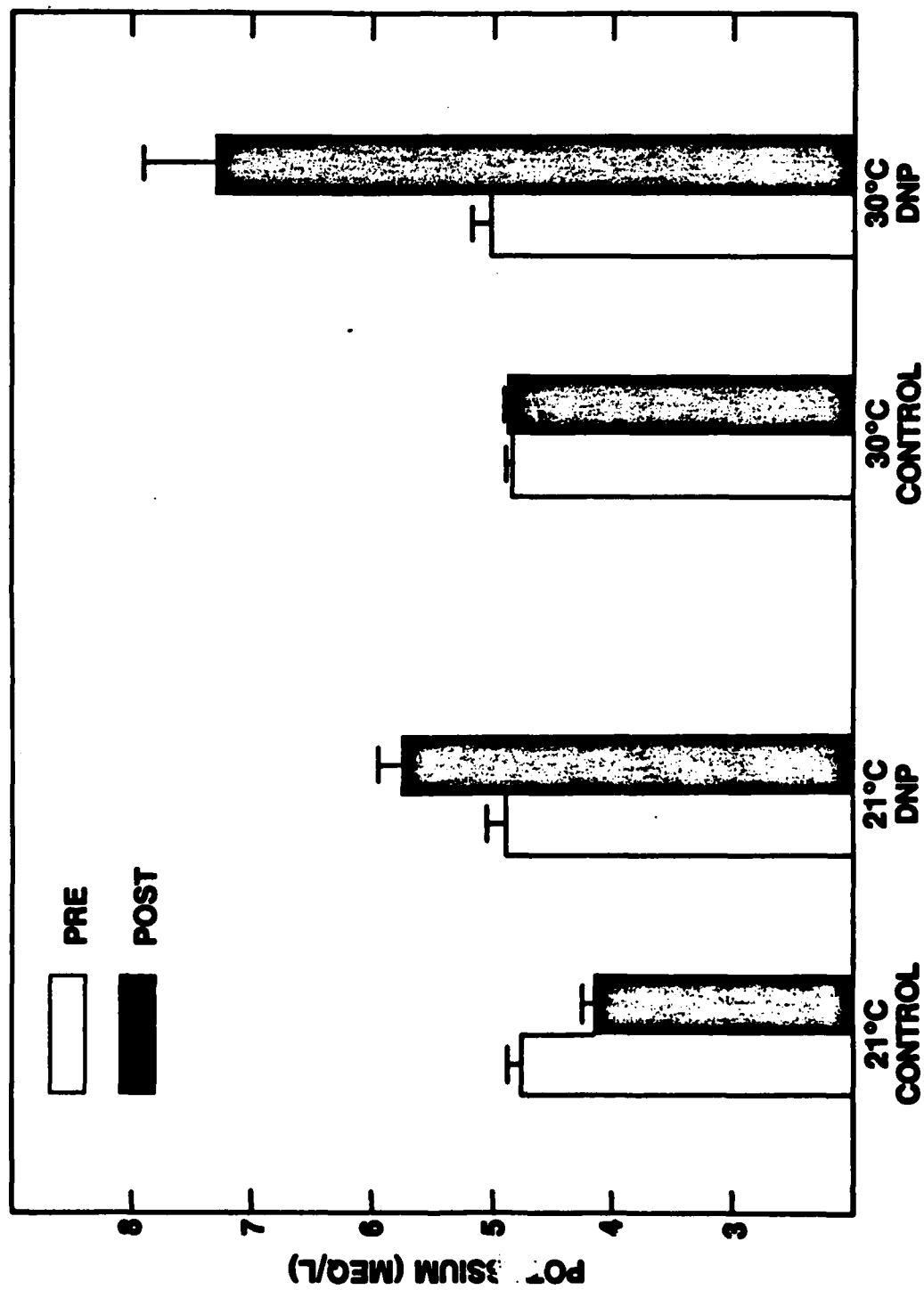
**EFFECTS OF DINITROPHENOL, AMBIENT TEMPERATURE,
AND EXERCISE ON PLASMA PROTEIN**



**EFFECTS OF DINITROPHENOL, AMBIENT TEMPERATURE,
AND EXERCISE ON PLASMA SODIUM**



**EFFECTS OF DINITROPHENOL, AMBIENT TEMPERATURE,
AND EXERCISE ON PLASMA POTASSIUM**



END

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