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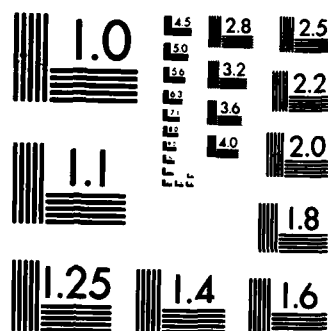
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wettedness was measured by dew point sensors and arm R+C by analysis of radiative and convective heat exchange components. Rectal (T_{re}), mean skin temperatures ($\bar{T}_{sk}$), $\dot{V}O_2$, and heart rate were measured. A significant decrement ($P < 0.05$) in w (50% reduction) occurred after atropine injection. Whereas control experiments always resulted in minimal heat loss or a frank heat gain depending on environmental condition, arm (R+C) after atropine injection was significantly increased with skin wettedness depression. Two patterns of response in arm (R+C) were apparent: one related to rapid increases in arm (R+C) occurring with net changes in $\Delta T_{re} \leq 0.3^\circ\text{C}$ above that due to exercise alone and a more prolonged response exhibited at $\Delta T_{re} > 0.4$ to 1.2°C . The results show that injection of atropine in heat acclimated individuals at three discrete environments apparently causes equal inhibition of local sweating but differential local heat loss responses which are affected by state of vasomotor activity and humidity.

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Effect of Atropine on Local Skin Wettedness
and Sensible Heat Loss

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Abstract

This study examined arm skin wettedness (w) and dry heat loss (arm R+C) responses during atropine injection (2 mg im, vastus lateralis) or saline injection in heat acclimated subjects. Six male subjects dressed in shorts and sneakers, each exercised (1h to 1 1/2h) on a treadmill ($1.34 \text{ m}\cdot\text{s}^{-1}$) in three different environments which facilitated evaporative heat exchange ($T_g=41^\circ\text{C}$; $P_w=12 \text{ Torr}$), impeded dry heat loss ($T_g=35^\circ\text{C}$; $P_w=22 \text{ Torr}$) or allowed both sensible and insensible heat exchange ($T_g=32^\circ\text{C}$; $P_w=22 \text{ Torr}$). Local skin wettedness was measured by dew point sensors and arm R+C by analysis of radiative and convective heat exchange components. Rectal (T_{re}), mean skin temperatures ($\bar{T}_{sk}$), $\dot{V}O_2$, and heart rate were measured. A significant decrement ($P<0.05$) in w (50% reduction) occurred after atropine injection. Whereas control experiments always resulted in minimal heat loss or a frank heat gain depending on environmental condition, arm (R+C) after atropine injection was significantly increased with skin wettedness depression. Two patterns of response in arm (R+C) were apparent: one related to rapid increases in arm (R+C) occurring with net changes in $\Delta T_{re} \leq 0.3^\circ\text{C}$ above that due to exercise alone and a more prolonged response exhibited at $\Delta T_{re} > 0.4$ to 1.2°C . The results show that injection of atropine in heat acclimated individuals at three discrete environments apparently causes equal inhibition of local sweating but differential local heat loss responses which are affected by state of vasomotor activity and humidity.

key words: anticholinergics, exercise, heat acclimation, dew point sensors, dry heat exchange, local heat loss, vasomotion, temperature regulation

Atropine given systematically in small doses causes a rapid inhibition in eccrine sweat gland activity (7,17) primarily by competitive inhibition of receptors sensitive to cholinergic nerve stimulation (20). In the process an ill-defined response of cutaneous circulatory change termed the "atropine flush" is seen to accompany the inhibitory effects on the sweat gland (11). It is not clearly understood whether cutaneous vasodilation is a primary response actively stimulated locally by vasodilatory fibers, vasodilatory agents or atropine itself (6,7,9,10,14) or whether the response is a passive effect from central release of adrenergic vasoconstrictor inhibition (1,4,15,19) due to a significant rise in body temperature.

The activity of the eccrine sweat gland following atropine blockade is modified by heat acclimation (17,21). A specific dose given to heat acclimated subjects was shown to reduce whole body weight changes (sweat loss) to a lesser degree, decrease the effective temperature for heat strain, and extend exercise performance time in the heat (17). We suggested that after heat acclimation an augmented efferent drive to the sweat gland might occur resulting in a greater liberation of acetylcholine or more receptors become available which are not blocked by the same dose given to unacclimated individuals (17,20). Subsequently, a potentiation of sensible heat loss with heat acclimation or higher efficiency of the peripheral circulation could occur which would offset any imbalances in evaporative heat loss. In the present study we were interested in ascertaining whether local thermal responses following heat acclimation are altered by atropine injection at various environmental conditions. Three environmental

conditions were chosen in which insensible heat loss (by evaporation) is favored or in which sensible heat loss (by R+C) is potentiated.

METHODS

Subjects. Six fit males ($\dot{V}O_{2\max}$ $50 \pm 6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) volunteered for the study following consent procedures passed by our local Human Use Committee. The subjects were all healthy, with no history of exercise-induced asthma. They had an average ($\pm$ SD) age of 22 ± 1.9 yrs, height of 176 ± 2.8 cm, weight of 78.8 ± 7.4 kg, DuBois surface area of $1.95 \pm 0.08 \text{ m}^2$, percentage of body fat (hydrostatic weighing) of $16.9 \pm 3.6\%$ and lean body mass of 65.3 ± 5.1 kg.

Protocol. Testing occurred in a large environmental room in June. All subjects were heat-acclimated for a minimum of 6 days. Heat acclimation was confirmed by a levelling off of rectal temperature and/or heart rate. In the acclimation experiments all 6 subjects walked on a treadmill set at $1.34 \text{ m} \cdot \text{s}^{-1}$ (metabolic heat production at 360W) in an ambient temperature of 42°C , 20% rh.

We exposed each heat acclimatized subject two times at each environmental condition. The environmental conditions were: hot/dry, globe temperature (T_g) of 41°C , ambient water vapor pressure (P_w) 12 Torr; moderate, $T_g = 35^\circ\text{C}$, $P_w = 22$ Torr; humid: $T_g = 32^\circ\text{C}$, $P_w = 22$ Torr. The latter two environments were chosen to facilitate insensible heat loss (12) and be in the vasomotor range where skin retains its ability to vasoconstrict (15). These two environments also had the same rational effective temperature (12) (ET^*), 35.5°C and 35.3°C ; the hot/dry condition had an ET^* of 37.7°C .

We injected 2 mg of atropine sulfate (1 ml) into the subject's

vastis lateralis muscle 10 min prior to his beginning the exercise-heat exposure. On another occasion saline (1 ml) was injected prior to heat exposure. The atropine trials were all separated by at least four days with no testing.

Physiological variables. The exercise level was 25% $\dot{V}O_{2\max}$ set by a level motor-driven treadmill ($1.34 \text{ m}\cdot\text{s}^{-1}$). Exposure time was continuous for a period of 100 min or until rectal temperature (T_{re} , °C) exceeded 39.5°C, heart rate (HR, $\text{b}\cdot\text{min}^{-1}$) exceeded 180 b/min for 5 min, or the subject voluntarily decided to terminate the experiment. During all exposures, we recorded continuously T_{re} , average skin temperature ($\bar{T}_{sk}$, °C), and HR. Metabolic heat production (M , $\text{W}\cdot\text{m}^{-2}$) was calculated from $\dot{V}O_2$ at min 30, 60, and 90 min using open circuit techniques (17). Total body sweat rates were determined by pre and post weighings using a Sauter balance ($\pm 5\text{g}$).

Sensible heat loss and skin dew point measurements. In order to determine local effects of atropine injection on the skin during each specific environmental exposure, we measured upper arm dew point using automatic dew point sensors (12). Arm sensible heat loss or gain ($\text{arm } R+C$, $\text{W}\cdot\text{m}^{-2}$) was also determined by using arm heat transfer coefficients (h_c , $\text{W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}$), a linear radiation heat transfer coefficient and the gradient between arm skin temperature ($T_{sk'a}$) and T_g . We used an average local area convective heat transfer coefficient of $7.3 \text{ W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}$ as determined by Nishi and Gagge (18) from direct naphthalene sublimation in similar air motion ($1.16 \text{ m}\cdot\text{s}^{-1}$) and walking speeds done in this chamber. Empirically derived heat transfer relationships based on the physical dimensions and gas flow properties (8) of the upper arm

for a cross sectional diameter of 10.5 cm to 11.8 cm in two subjects gave a range of h_c of 7.9 to 8.9 $W \cdot m^{-2} \cdot K^{-1}$, respectively. The dew point of the upper arm was continuously recorded by automatic dew point sensors (13), directly attached with porous paper tape (Micropore, 3M Corp.). Local skin wettedness (w) was calculated continuously on-line (13) by

$$w = (P_s, dpl - P_w) / P_{s,sk} - P_w \quad N.D.$$

where P_s, dpl is the saturated vapor pressure (torr) of the arm dew point sensor recording and $P_{s,sk}$ is the saturated vapor pressure at arm skin temperature ($T_{sk,a}$).

Statistical treatment. Comparisons were done between groups using time series analysis of variance, multiple variable ANOVAS, with repeated measures and regression analysis. Analysis of variance was followed by Tukey's analysis of critical differences. The null hypothesis was rejected at $P < 0.05$. Data in the figures are presented as means for clarity.

RESULTS

Fig 1 Figure 1 shows the effects of atropine injection on the T_{re} responses during exercise in the heat of 6 men completing 54 min of exercise at all three environments. Final mean T_{re} for the atropine-heated group at environments of ET* 37.7, 35.5 and 35.3°C were 38.6°C, 38.2°C, and 37.8°C, respectively. All were different from each other ($P < 0.05$). The rates of increments in T_{re} were significantly greater ($P < 0.05$) especially between 20-40min of exercise time. Control experiments following saline injection gave a mean T_{re} of $37.5 \pm 0.15^\circ C$,

37.5 $\pm$ 0.13°C and 37.4 $\pm$ 0.16°C, (NS) for each of the environments. The increments in T_{re} between the atropinized subjects and saline-injected subjects were significantly different.

Fig 2 Figure 2 shows a significant decrement in local skin wettedness owing to the inhibition of sweat gland function, amounting to about a 50% reduction at min 50 ($P < 0.05$) in comparison to control runs. The local skin wettedness in the humid experiments ($T_g = 32^\circ\text{C}$, $P_w = 22$ Torr) in the control experiments was also higher ($P < 0.05$) than that present in the other two environments. A plot of local w as a function of ΔT_{re} from initiation of exercise to peak T_{re} (Fig. 3) confirms the fact that the slope was also higher during the control experiments at the $T_g = 32^\circ\text{C}$, $P_w = 22$ torr environment. There was no significant relationship between arm w : ΔT_{re} in the atropine experiments.

Fig 3 Figure 4 demonstrates the effects of atropine and saline injection during exercise in the heat on arm sensible heat loss ($R+C$, $\text{W} \cdot \text{m}^{-2}$). The gradation in heat loss from this site is clearly evident; primarily, heat loss occurred in the moderate and humid environments with atropine injection, a lessened $R+C$ response in the T_g 35°C/ $P_w = 22$ Torr environment following saline injection, and a definite heat gain response in the T_g 41°C/ $P_w = 12$ Torr environment with both saline and atropine injection. At each time period, the arm $R+C$ was significantly different between environments. This figure shows that during the atropinized experiments the response was always toward a heat loss in excess of that apparent in the control experiments. This net ($R+C$) is shown in Fig. 5 plotted as a function of time for each 2-min matched response. There was a significant net heat loss for each

Fig 4

acclimated-exercise exposure ($P < 0.05$). Additionally, the net (R+C) at min 48-50 was higher in the moderate environment compared to the other two exposures.

Figure 6 shows a summary plot of arm (R+C) heat loss or heat gain as rectal temperature rose during exercise in the heat following atropine or saline injections. Whereas saline experiments always resulted in a net heat gain (downward plot) during the experiments, we see that atropine injections showed linear increases in Δ arm R+C up to $\leq 0.5^\circ\text{C} \Delta T_{re}$, distinctly opposite to control experiments. Also apparent is the prolonged elevation in arm R+C up to elevations of $2.0^\circ\text{C} \Delta T_{re}$.

Figure 7 shows the net changes in arm R+C plotted as a function of the net rectal temperature increases above that present in the saline control experiments for all exposures. This figure signifies the net sensible heat loss and net rectal temperature elevation above that owing to exercise in the heat per se. Two patterns of response are apparent: one related to a rapidly increased heat loss occurring with net changes in rectal temperature $\leq 0.3^\circ\text{C}$, related to strong correlation of Δ arm (R+C) to ΔT_{re} seen in Figure 6, and a more prolonged but asymptotic response exhibited at $> 0.4^\circ\text{C}$ to 1.2°C rectal temperature changes. The net change in sensible heat loss during the hot-dry environment was significantly lower than that for the humid exposures during the secondary phase.

DISCUSSION

This study showed that the strong ($> 50\%$) inhibition of sweat gland activity as evident by a suppressed local skin wettedness response, despite a heat acclimated state, was accompanied by a concurrent

compensatory cutaneous heat loss. Although several investigations have been done to uncover the effects of atropine on sweat glands (7,20), very little has been reported on the local vasodilatory response. As shown in this study and earlier (17), the dosage of atropine (2 mg im) was sufficient to block peripheral cholinergic sweat gland activity. It should have blocked, presumably, vasodilation at least at the skeletal muscle as well. But the net arm (R+C) response which parallels active vasodilation (i.e., dilation greater than that accounted for by control (saline) experiments which showed a net heat gain) does not reveal a complete blockade and points to local effects contributed by several mechanisms.

One mode of action may be due to atropine per se (20) or to the greater availability of receptors during the heat acclimatized state as we proposed (17) unblocked by the set dosage allowing ACH to stimulate vasodilatory activity. Sato and Sato (20) have recently alluded to this as "receptor reserve". Such effects of atropine injection would be more prevalent at dry bulb temperatures when ambient water vapor pressure is high (>20 Torr) whereby skin blood flow is potentiated further above a set amount than that due to dry heat stress (12). Gaskell (11), previously showed that 0.8 mg of atropine (intra arterially) blocked the vasodilatory activity of 4 mg acetylcholine given by the same route. At that dosage, ACH infusions have been shown to increase hand blood flow by as much as 35 ml/(100 cc.min). In the same study, Gaskell also studied forearm blood flow response to infusions of 0.2 mg and 0.4 mg atropine, but found no immediate or delayed increases from the control arm.

Another possible mode of action to explain our results might be associated with the thermoregulatory model suggested by the work of Boulant and co-workers (3,16,22). As applied to our study, the heat acclimated state coupled with moderate heat and humidity, activates catecholamines causing potentiation of beta,-adrenergic receptors (in skeletal muscle resistance vessels) or directly activates cholinergic fibers travelling with sympathetic nerves stimulating cutaneous blood vessels. But either response would be inhibited by atropine. In addition, skin warming could well evoke release of hypothalamic endogenous stores of dopamine or norepinephrine (16); dopaminergic synapses have been shown to oppose hyperthermia and facilitate heat loss responses by decreasing cold-sensitive neurons and stimulating warm-sensitive neurons (22). The striking increase in net arm (R+C) associated with a ΔT_{re} in the first minutes of exercise (Fig. 7) compared to the slower, more persistent response later on, suggests such a peripheral action quite attractive to the defense reaction in controlling hyperthermia. We do not know whether the antagonistic response (increased hyperemia, diminished sweating) is merely a passive heat flow response increased by the heat storage following sweat gland inhibition or an active vasomotor loop mediated locally. Fig. 5 suggests, by the biphasic pattern shown in the net (R+C) plot, that an initial depression with a re-increase of net (R+C) might follow a skin blood flow response consonant with vasomotor activity. It should be pointed out that the site (upper arm) which we used to assess (R+C) response and to measure skin dew point exhibits a pattern of vasomotor activity much like that of the forearm; that is, weak vasoconstrictor

activity occurring when a subject is cold and a strong vasodilator innervation often associated with eccrine sweat gland control (2,4,15).

Besides responsiveness to cholinergic stimulation, recently Sato and Sato (20) have reported that the eccrine sweat gland is responsive also to α and B-adrenergic stimulation. Effect of heat acclimation and exercise coupled together might have increased the titer of norepinephrine. Norepinephrine (NE) could well alter α and B receptor activity in the cutaneous blood vessels and sweat gland in two distinct ways. For example, Brick et. al. (5) showed that norepinephrine can stimulate cutaneous vasodilatory properties. Norepinephrine (as well as epinephrine) is known to stimulate B-receptors in the heart and both inotropic and chronotropic responses are inhibited by B-antagonists. Since forearm blood vessels are well supplied with B-receptors, it surprised these workers that NE failed to dilate forearm blood vessels after α -receptor blockade. However, vasodilation by B-stimulation was accomplished by combining both α and B-blockers. When the α receptor was preferentially blocked with phentolamine, vasoconstriction converted to vasodilation (154% increase in blood flow). The increase in blood flow thus was due to B-receptor stimulation since blockade of B-receptors with propanolol prevented NE-vasodilation in the forearm treated with phentolamine. Brick and co-workers' study (5) indicates that NE action in the forearm is the sum of a dominant vasoconstriction due to α -stimulation and a weaker vasodilation due to stimulation of B-receptors.

In receptors localized to coronary arterial vessels, acetylcholine (ACH) has recently been shown to inhibit the exocytotic release of NE

which causes differential vasomotor effects depending on whether the NE activity is on α or B adrenergic receptors (23). A similar case could be drawn for our study localized at the sweat gland site whereby NE stimulates weak vasodilation (5) particularly in the heat following atropine injection. Atropine would compete with ACH for a given number of muscarinic receptors to inhibit sweat gland release. An overabundance of ACH (in response to heat-acclimation) would still be present to inhibit specific NE action on α -adrenergic receptors, allowing B-adrenergic stimulation by NE to occur and allow cutaneous vasodilation thereby facilitating heat loss (3,6). Allen and Roddie (1), for example, showed that sweat loss (by weight changes) increased when adrenaline and norepinephrine was infused (T_a , 29°C). Atropine did not inhibit catecholamine-induced sweat loss albeit B-receptor blockade (with propranolol) reduced the response indicating that cholinergic inhibition did not alter B-adrenergic receptors. However, their study was not done in the heat or employing the approaches Brick et. al. (5) used to ascertain vasodilatory effects.

Since the increased arm (R+C) response (Figs. 6 and 7) was not antagonized by atropine in the heat, unlike the skin wettedness depression (Fig. 3), a stand might be made that the response was not due to acetylcholine-mediated receptors. However, our environments were in the zones where release of vasoconstriction (especially $<35^\circ\text{C}$ T_a) can occur (10,15,19). Rowell, Brengelmann and co-workers (4,19) have shown that forearm blood flow responds to two control activities. A rise in mean skin temperature modulates release of vasoconstriction whereas active vasodilation is governed by increases in core

temperature solely. Fig. 7 lends support to the idea that initial vasodilation is mediated by local skin temperature (peripheral action) with a more prolonged effect of a central response to elevated core temperature. A more amplified vasodilatory response (i.e., greater peripheral thermal sensitivity) may have been apparent using esophageal temperature as a measure of central thermal drive but it was not possible in these experiments.

Our data do not directly reveal whether the increase in cutaneous blood flow following injection of atropine at this dosage was attributable to reflex release of skin arteriolar tone by cholinergic vasodilator influences (6) or related to elevation in skin temperature attributed to changes in R+C which thermally oppose the diminished sweating. Since changes in (R+C) were higher in the environments where skin blood flow is potentiated by release of vasoconstrictor activity (Fig. 5), the initial "atropine flush" we found appears related to a mechanism primarily in response to immediate and diminished sweat gland activity. As shown in the control experiments, release of vasoconstrictor activity to cutaneous vessels was probably constant and related to a steady metabolic level and core temperature drive. The increased cholinergic stimulation was also constant. Indeed, the skin wettedness to ΔT_{re} showed a normal (12) strong correlation ($r^2=0.67$ to 0.92), (Fig. 3) in the control experiments. However, with atropine injection under similar environmental and metabolic conditions, cholinergic stimulation to the sweat gland was impeded, a normal vasoconstrictor reflex to blood vessels quite possibly continued but this effect was counterbalanced by an increased core temperature drive

to cause further facilitation of temperature sensitive neurons in the hypothalamus (3,16) regulating the heat loss response. Although not covered in this study, increases in heart rate (by the vagal inhibition) followed the similar pattern as seen in the $\Delta R+C: \Delta T_{re}$ response (Fig. 7). Immediate increases of skin blood flow alluded to by the heat loss responses seen in Fig. 7 are likely related to a displaced cardiac output to the skin beds (with a release of vasoconstrictor tone) via increased heart rate (owing to decreased vagal activity) since splanchnic blood flow is probably decreased (19).

In summary, this study showed that the injection of atropine in heat acclimated individuals at three discrete environmental conditions caused similar response of inhibition of sweating but differential local heat loss responses (skin blood flow ?) which were affected more markedly by increases in humidity.

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The views, opinions and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the Use of Volunteers in Research.

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Figure Legends

- Figure 1. Rectal temperature responses during treadmill exercise ($1.34 \text{ m} \cdot \text{s}^{-1}$) after saline injection and atropine injection (2 mg, im) in the three environments. ET^* calculated according to ref (12).
- Figure 2. Local skin wettedness (w) of the upper arm varying with time in the three environments. Reduction in w after atropine injection is significantly different ($P < 0.05$) from control experiments after min 30 in all three environments.
- Figure 3. Local skin wettedness as a function of change in rectal temperature (ΔT_{re}) from start of exercise.
- Figure 4. Arm dry heat loss (R+C) as a function of time of exercise.
- Figure 5. Net (R+C) taken as the difference in arm (R+C) with atropine experiments less arm (R+C) with saline experiments.
- Figure 6. Changes in arm (R+C) from start of exercise as a function of ΔT_{re} occurring with saline and atropine injection.
- Figure 7. Net (R+C) from Figure 5 as a function of net rectal temperature changes taken as the difference in T_{re} following atropine injection and that due solely to exercise with saline experiments. Curve fitting taken for changes in (R+C) and $T_{re} > 0$.

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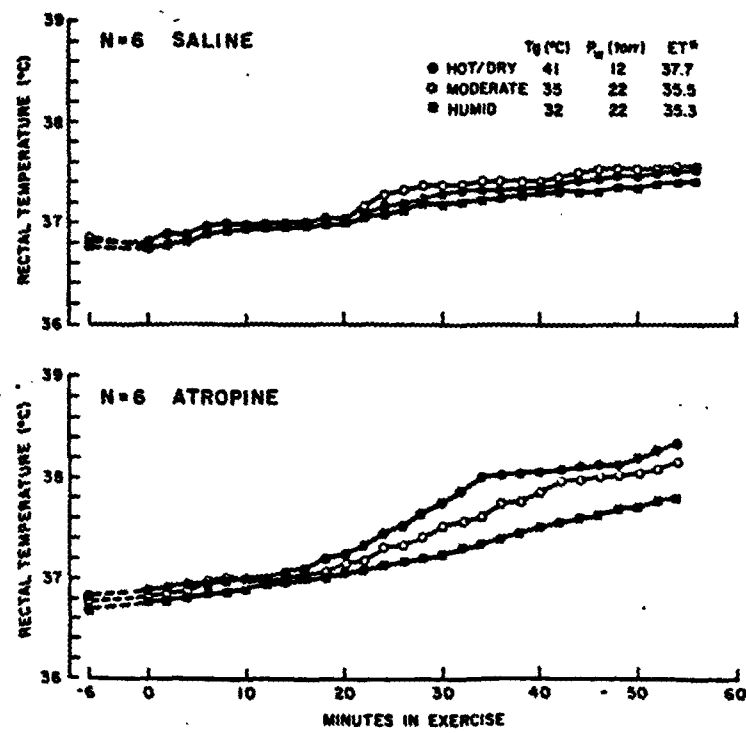


Fig 1.

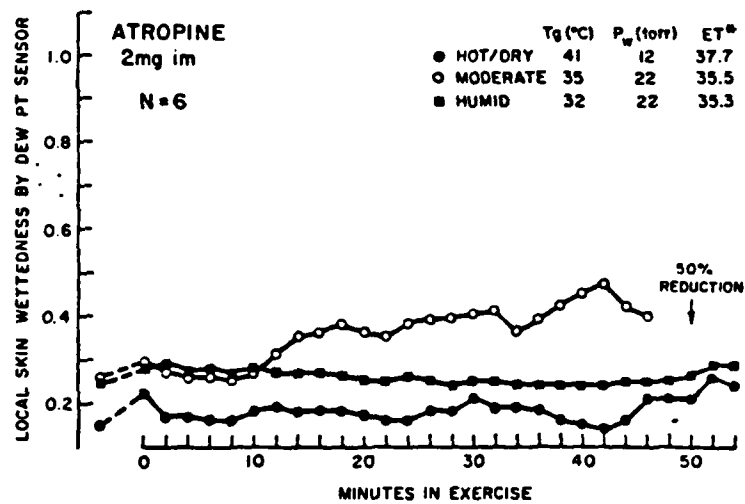
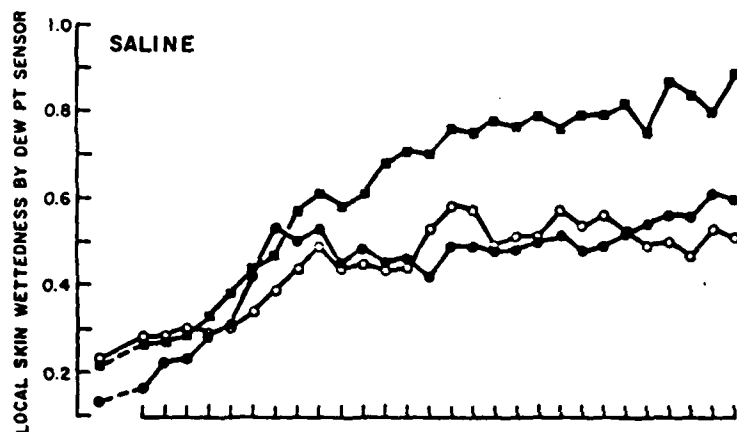


Fig 2

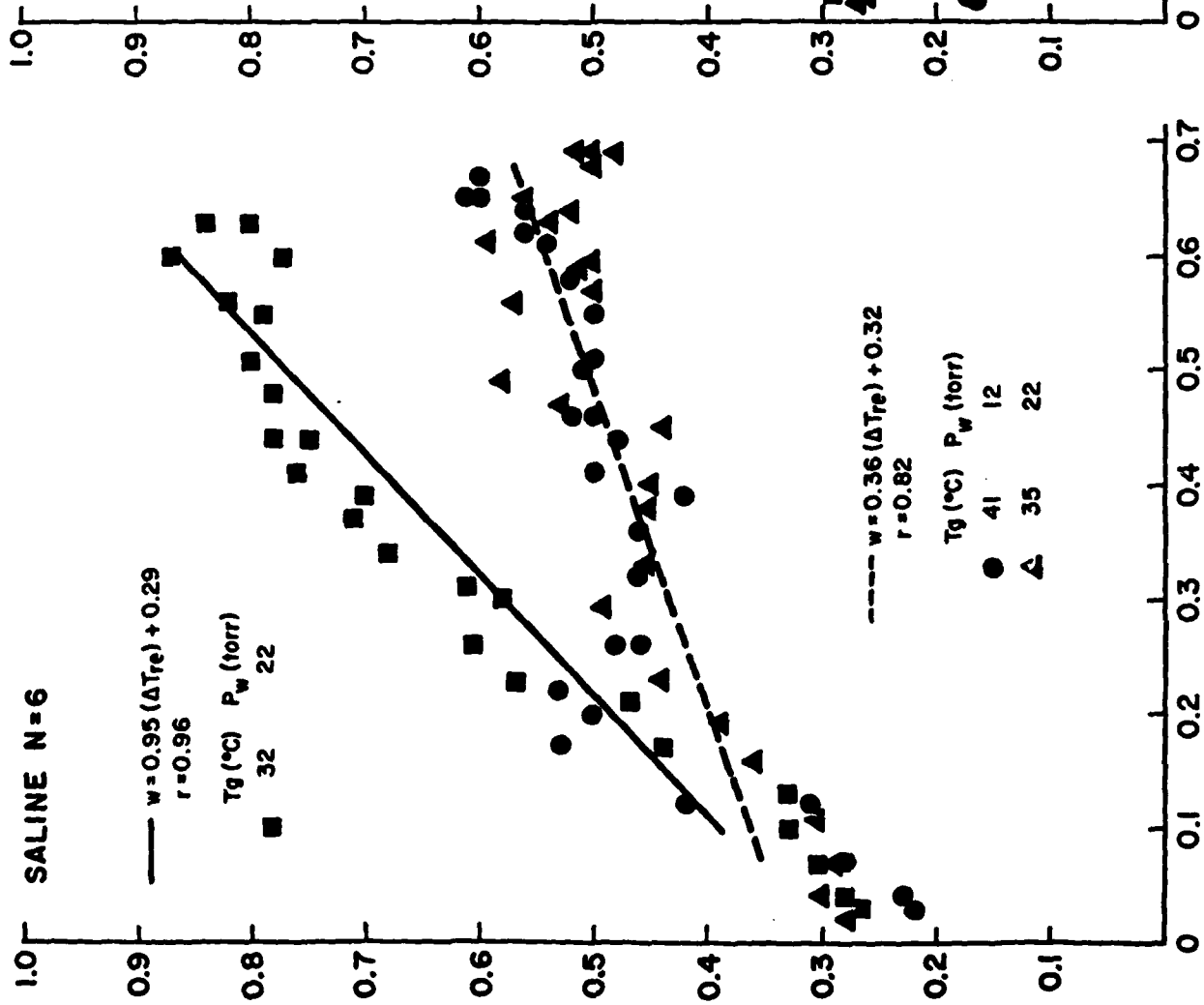
fig #13

SALINE N=6

— $w = 0.95 (\Delta T_{re}) + 0.29$
 $r = 0.96$

Tg (°C) P_w (torr)

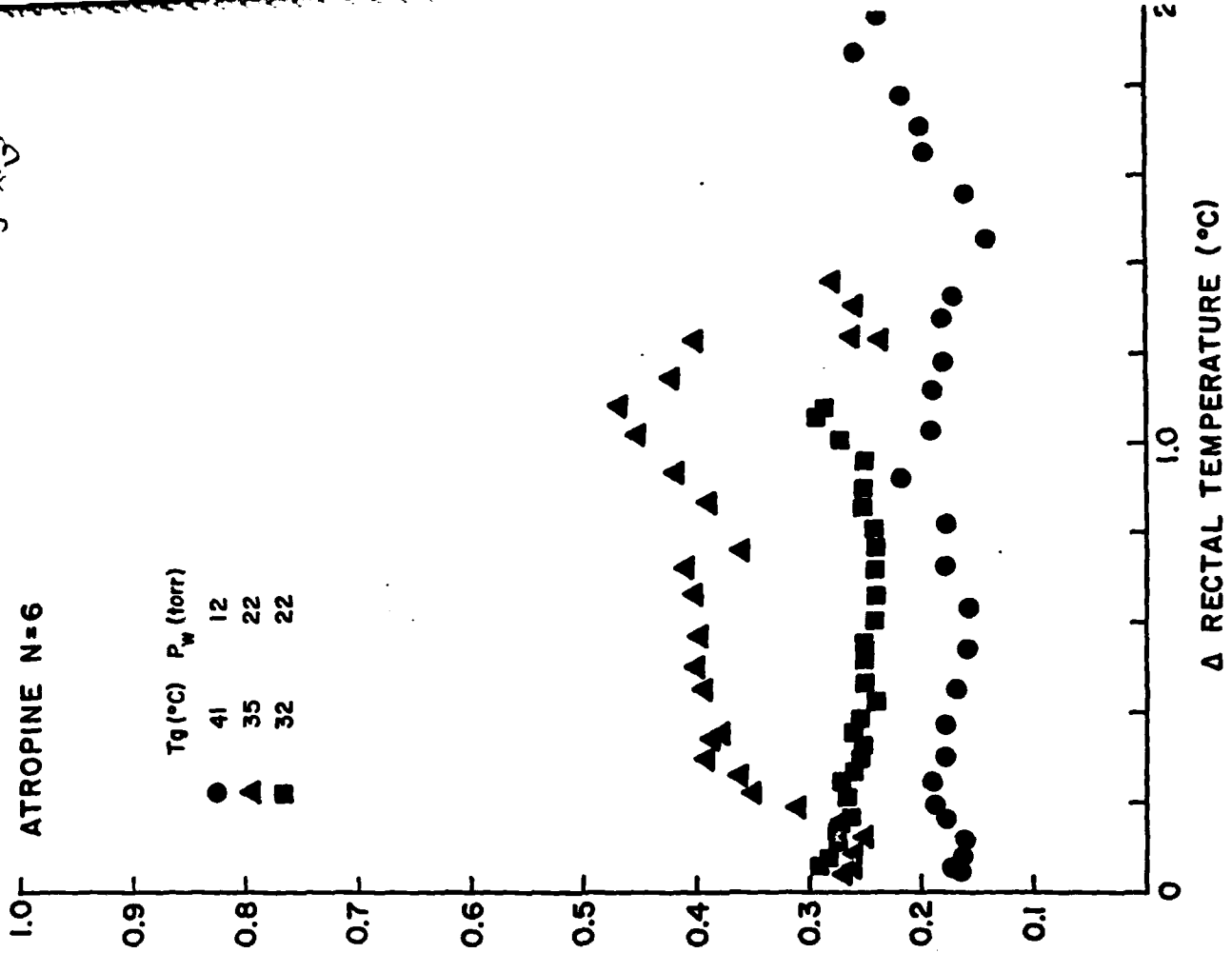
32 22



ATROPINE N=6

Tg (°C) P_w (torr)

41 12
 35 22
 32 22



--- $w = 0.36 (\Delta T_{re}) + 0.32$
 $r = 0.82$

Tg (°C) P_w (torr)

41 12
 35 22

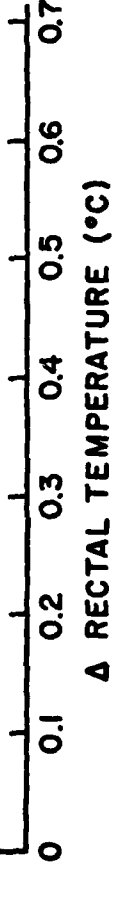
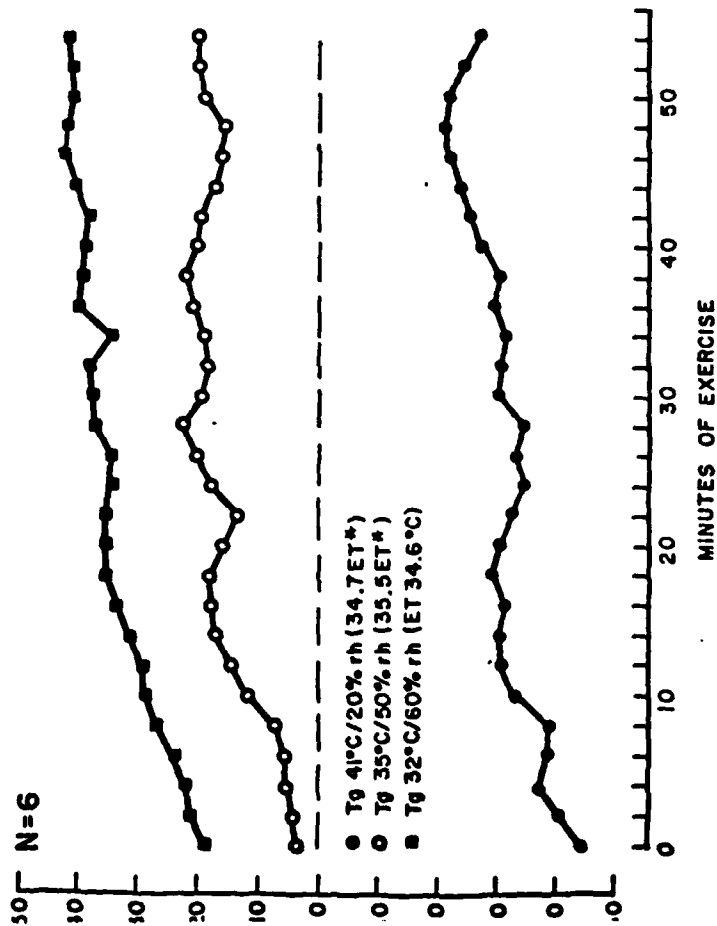


Fig # 4

HEAT ACCLIMATED/ATROPINIZED (2mg 1m)



HEAT ACCLIMATED/SALINE

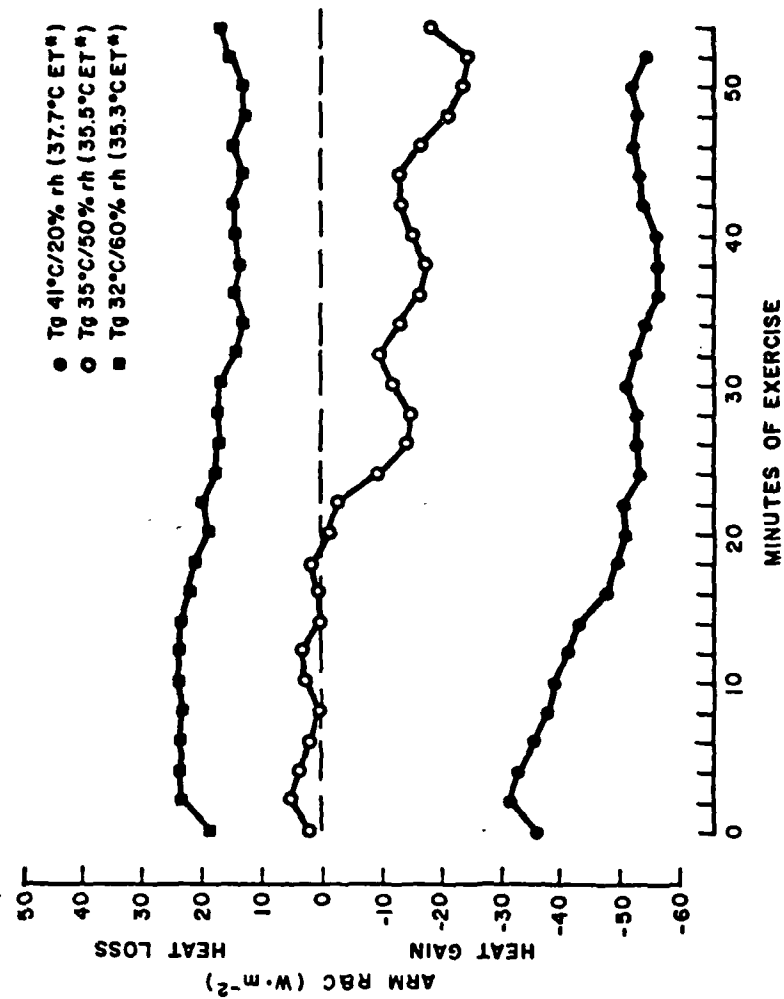


fig #5-

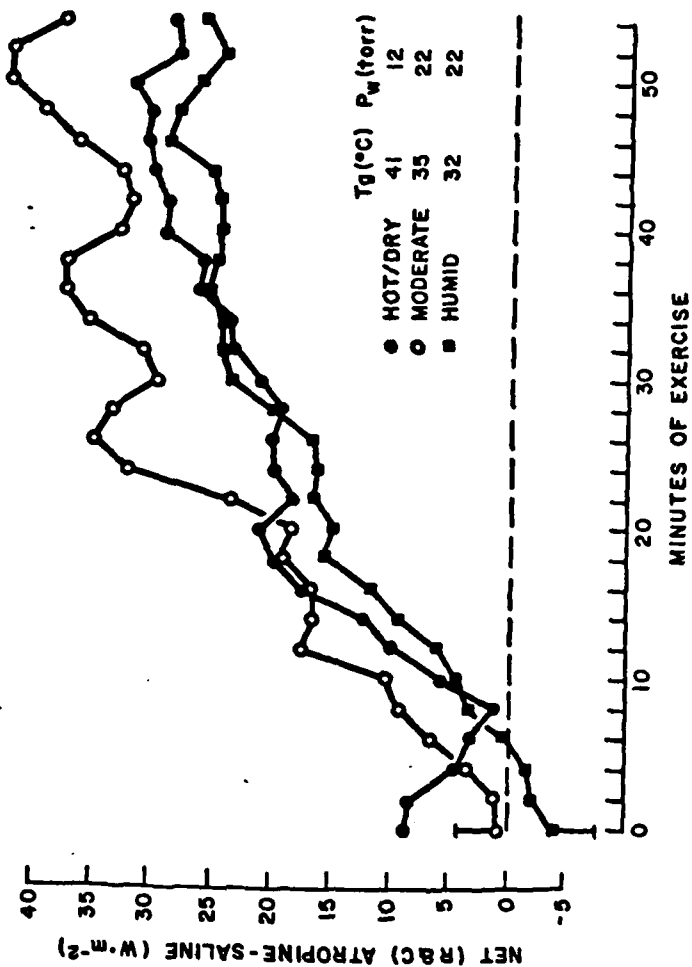


fig #6

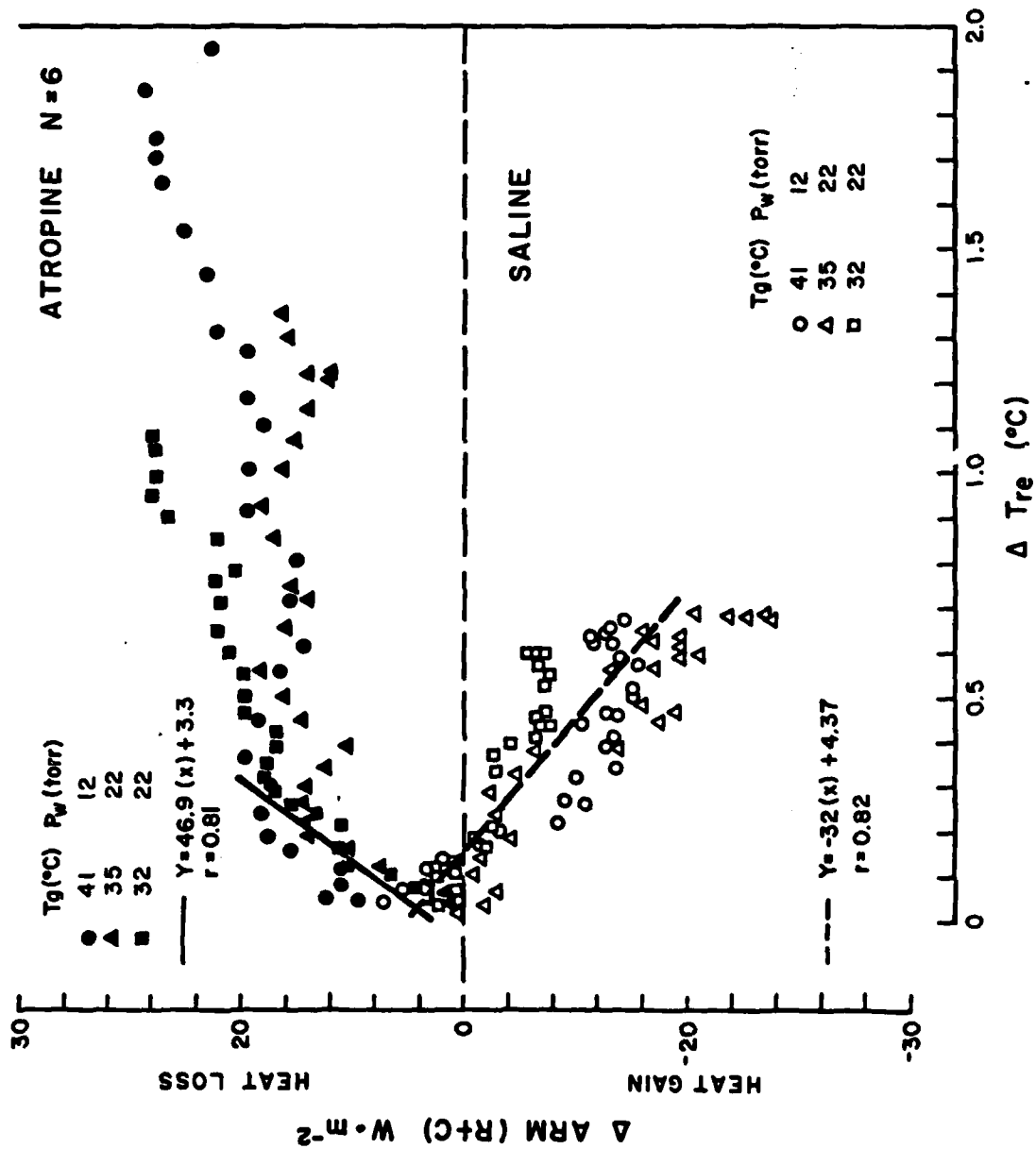
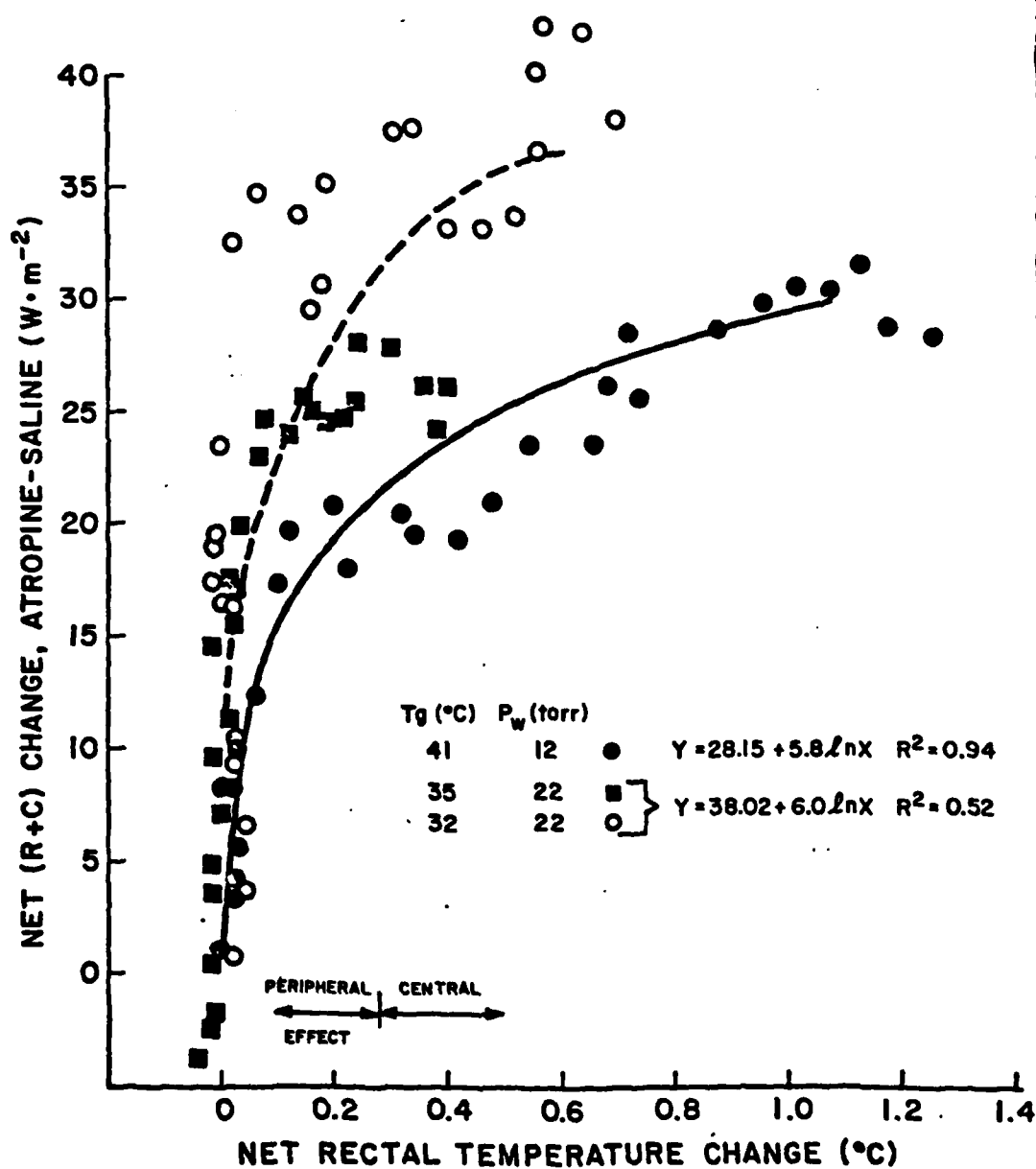


fig #7



END

FILMED

4-85

DTIC