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Influence of a Tranquilizer on Temperature Regulation in Man

**P. F. Iampietro
V. Fiorica
J. R. Dille
E. A. Higgins
G. Funkhouser
R. Moses**

Approved by



**J. ROBERT DILLE, M.D.
CHIEF, CIVIL AEROMEDICAL
INSTITUTE**

Released by



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FOREWORD

The population concerned with the conduct of civil-aviation matters, like the population in general, resorts to the use of many types of drugs to counteract illness, pain, and fatigue and to enhance mental well-being. It is well recognized that many of these commonly available drugs may have untoward side effects. Since a primary demand on those personnel engaged in many civil-aviation duties is aviation safety, it is imperative that the job efficiency of those personnel is in no way compromised. An unrecognized side effect of any of the generally used drugs could well furnish that compromise. It becomes critical, therefore, to recognize the physiological effects that drugs have, especially in the working environment.

The present study was conducted to furnish information on the physiological responses of men under the influence of a commonly used tranquilizer. The results of this investigation indicate that the ability of men to regulate body temperature is impaired by this drug when ambient temperatures increase or decrease from the normal comfortable working environment. How additional physical or mental activity further affects the regulatory impairment described remains unknown and should be the object of further study.

PROBLEMS IN AVIATION PERSONNEL:

Influence of a Tranquilizer on Temperature Regulation in Man

I. Introduction.

Current widespread use of the common tranquilizing agents has prompted considerable research to clarify the dynamics of the psychoactive drugs in modifying animal-behavior patterns, ^{2,6} psychomotor performance, ¹² and the course of certain mental illnesses.⁹ In contrast to this psychopharmacological approach, relatively little attention has been given to the study of such drugs as they affect physiological performance.^{5,10,11} Prior investigations have demonstrated that the temperature regulation of animals under the influence of chlorpromazine is seriously impaired.⁵ Recent studies from this laboratory have further shown that propiopromazine is also effective in altering the thermal-regulatory mechanisms of dogs exposed to either hot or cold environments.³ It is the purpose of the present study to elaborate more fully on the alterations in human thermal balance that follow administration of the propanediol derivative, meprobamate.

II. Experimental Design and Methods.

Thirty-six young men (Table 1) were equally and randomly divided among three environmental exposures [110°F(43.3°C), 50% RH; 80°F (26.7°C), 50% RH; 50°F(10.0°C), 50% RH]. Within each environmental condition, subjects were given either placebo or meprobamate (800 mg) according to a randomized schedule conforming with double-blind procedure.* Table 2 outlines the experimental schedule. TABLE 1. Some characteristics of subjects (six subjects in each group). Mean and range.

Group	Age, yr	Wt, kg	Surface area, sq m
80° F, meprobamate	25	75.0	1.90
	22-26	60.5-83.7	1.74-2.05
80° F, placebo	24	65.6	1.77
	21-26	55.5-80.7	1.60-2.06
50° F, meprobamate	22	73.4	1.88
	20-27	67.2-80.7	1.80-1.98
50° F, placebo	22	72.1	1.89
	20-23	65.0-81.8	1.80-2.00
110° F, meprobamate	22	79.0	2.01
	21-24	63.5-95.0	1.82-2.23
110° F, placebo	22	77.8	1.95
	20-23	64.3-94.5	1.85-2.21

Subjects reported to the laboratory at 8:00 8:00 a.m. without breakfast. During preexperimental preparations and for the course of the exposure, subjects rested in a semireclining position on a plastic-meshed lounge chair. Each run began at approximately 9:00 a.m. and terminated at about 12:30 p.m.

Skin temperatures (17 points; copperconstantan thermocouples) were monitored continuously and recorded on a Leeds-Northrup Speedomax G recorder. Colonic temperatures

TABLE 2. Schedule of events.

Time, min	Event
0	First control measurements; chamber conditions 80°F, 50% RH
10	Second control measurements, first blood sample, treatment (800 mg meprobamate or 800 mg glucose with 200 ml water).
60	First drug control measurements.
70	Second drug control measurements, second blood sample.
75	Rapid change of ambient temperature to either 110°F(43.3°C) or 50°F(10.0°C) or remain at 80°F (26.7°C).
80	Experimental measurements every 10 minutes, blood samples at 130 and 190 minutes.
190	Termination of exposure.

(T_r) were measured with a YSI thermistor probe inserted 10 cm into the rectum and recorded on a Honeywell recorder.

Open-circuit O_2 consumption was determined by means of the arrangement shown in Figure 1. Room air (25 l/m) was passed through a plastic hood encasing the head of the subject. Temperatures inside the hood were maintained at chamber temperatures by appropriate heat-exchange circuits. Outflow air was monitored continuously for O_2 concentration by a Beckman F-3 oxygen analyzer. O_2 consumption was determined as the difference between O_2 contents of inflow and outflow air corrected for total volume flow.

At the times indicated in Table 2, 30 ml of venous blood was withdrawn and analyzed for plasma meprobamate⁴ and total catecholamine levels by a modification of the method of Mer-

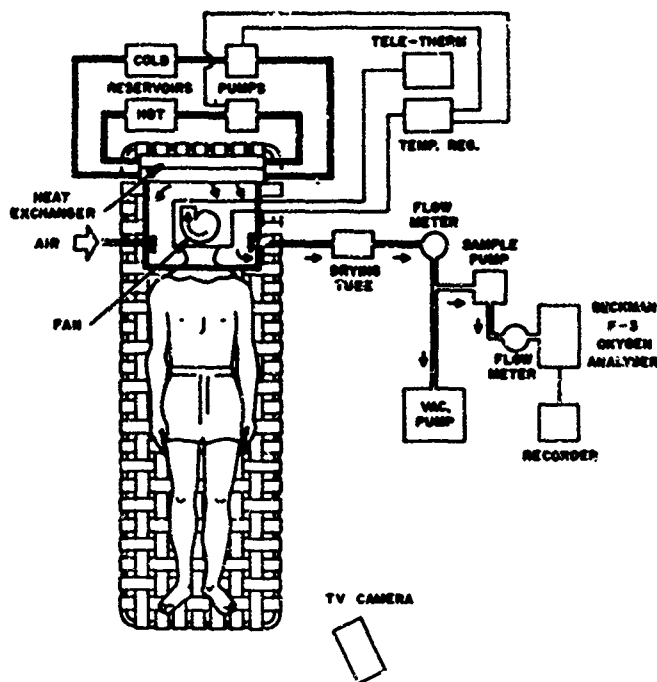


FIGURE 1. Open-circuit system for measurement of oxygen consumption. Inner hood temperatures were maintained to correspond with ambient by the heat-exchange circuits shown.

rills.⁷ Throughout the study, visual observation of the subjects was maintained by closed-circuit television. All instrumentation was located outside the chamber.

Mean weighted skin temperatures (T_s) were computed from weighted values for individual skin points; average body temperatures were determined from skin and rectal temperatures ($0.7 T_s + 0.3 T_r$). Total body-heat content (TBHC) was calculated according to the expression (TBHC = average body temperature, $^{\circ}\text{C} \times 0.83 \times$ body weight, kg). Heat production was computed from oxygen-consumption data.

Differences between placebo and drug groups under each condition were determined by analysis of variance over both preexposure and exposure periods.

III. Results.

A. Meprobamate concentrations in plasma. Concentration of meprobamate in plasma during each of the environmental exposures is shown in Figure 2. Peak levels (10.0 to 10.5 $\mu\text{g}/\text{ml}$) were attained 2 hours after oral administration of the drug (800 mg) and were maintained for the duration of the exposure. No differences between exposure groups were detected in plasma levels of the drug. Within

the 1-hour period prior to exposure, drug levels among the three groups ranged between 7.1 and 8.7 $\mu\text{g}/\text{ml}$; the differences were not significant.

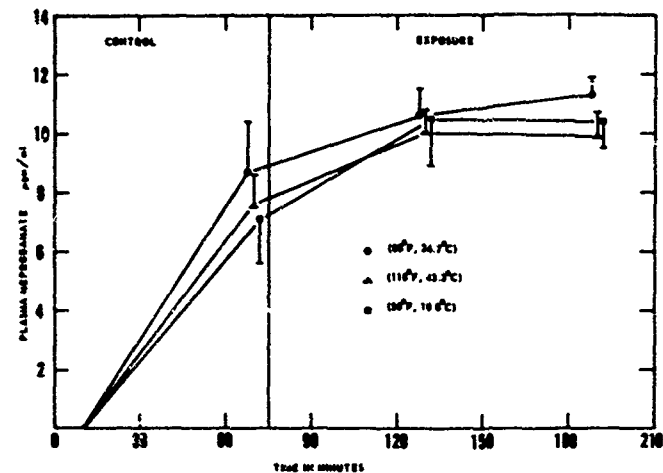


FIGURE 2. Plasma meprobamate levels during the control period and subsequent exposure to three environmental conditions. Each point represents the mean and standard error of six men.

B. Exposure to a neutral environment [80°F (26.7°C), 50% RH]. No alterations in thermal balance were detected in either drug or placebo groups, indicating that meprobamate does not interfere with temperature regulation of resting man in a neutral environment (Figure 3). For purposes of uniformity, all values are reported as changes from the 10-minute control readings.

During the 75-minute preexposure period, T_s fell about 0.5°C (0.9°F) in both groups (Figure 3A). This level was maintained throughout the 80°F exposure, and the differences between groups were not significant ($P = 0.41$). The gradual decline in T_s through the preexposure period was characteristic of all subjects studied. T_r also declined during the preexposure period to a level about 0.25°C (0.4°F) lower than the 10-minute values. This level was also maintained during the period of neutral exposure. No differences were attributed to the drug ($P = 0.41$). Changes in TBHC are shown in Figure 3C. A small reduction in TBHC (0.25 kcal/kg) was observed during the preexposure period in both groups, but no further change was exhibited during neutral exposure. Again, no drug effects were noted ($P = 0.84$). Heat production (Figures 3D) was similar in both drug and placebo groups ($P = 0.21$), with no major changes detectable over the course of the exposure.

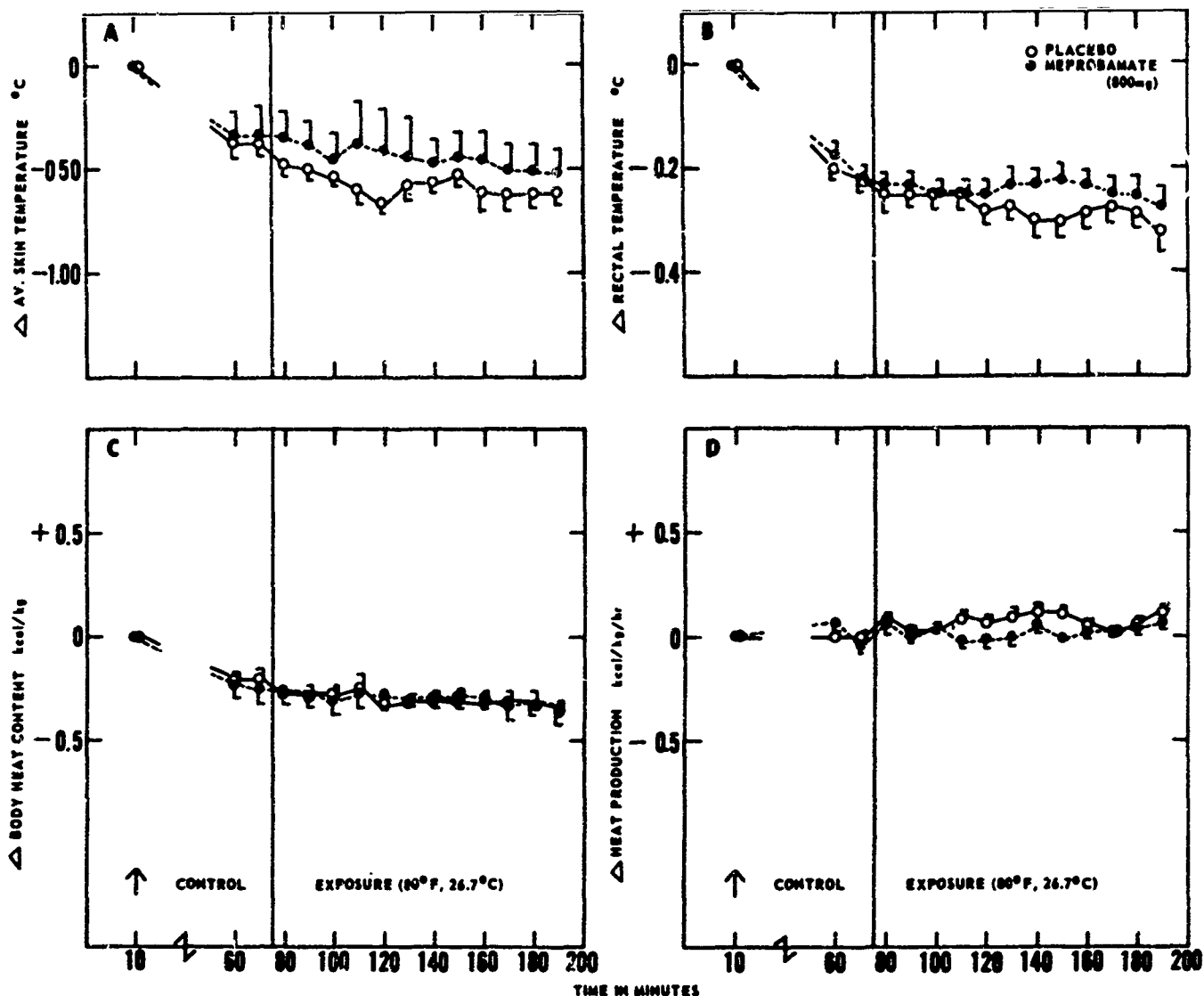


FIGURE 3. Changes in mean skin temperature, rectal temperature, body-heat content, and heat production during exposure to 80°F (26.7°C) are shown as a function of time. Each point represents the mean and standard error of six men. The 10-minute control value is taken as a baseline and all other values are shown as change from this point. Meprobamate (800 mg) or placebo was given immediately following the 10-minute reading.

C. Exposure to a hot environment [110°F (43.3°C), 50% RH]. During the first 25 minutes of exposure to heat, T_r of both groups increased approximately 4°C (7.2°F) and remained at that level for the duration of the exposure (Figure 4A). Drug and placebo groups responded similarly ($P = 0.48$). Following the initial decline during the preexposure period, T_r of both groups increased during heat exposure in a nearly linear fashion (Figures 4B). At end exposure, the drug group T_r increased 0.42°C (0.8°F), while placebo group T_r increased only

0.37°C (0.7°F). During the entire period of exposure, T_r of the drug group was consistently and significantly higher than that of the placebo group ($P = 0.05$). TBHC of both groups increased by approximately 1.25 kcal/kg at the time exposure was terminated (Figure 4C). The difference between groups was not significant ($P = 0.61$). Both groups maintained heat production relatively constant over the course of heat exposure (Figures 4D). No drug involvement in this parameter was evident ($P = 0.16$).

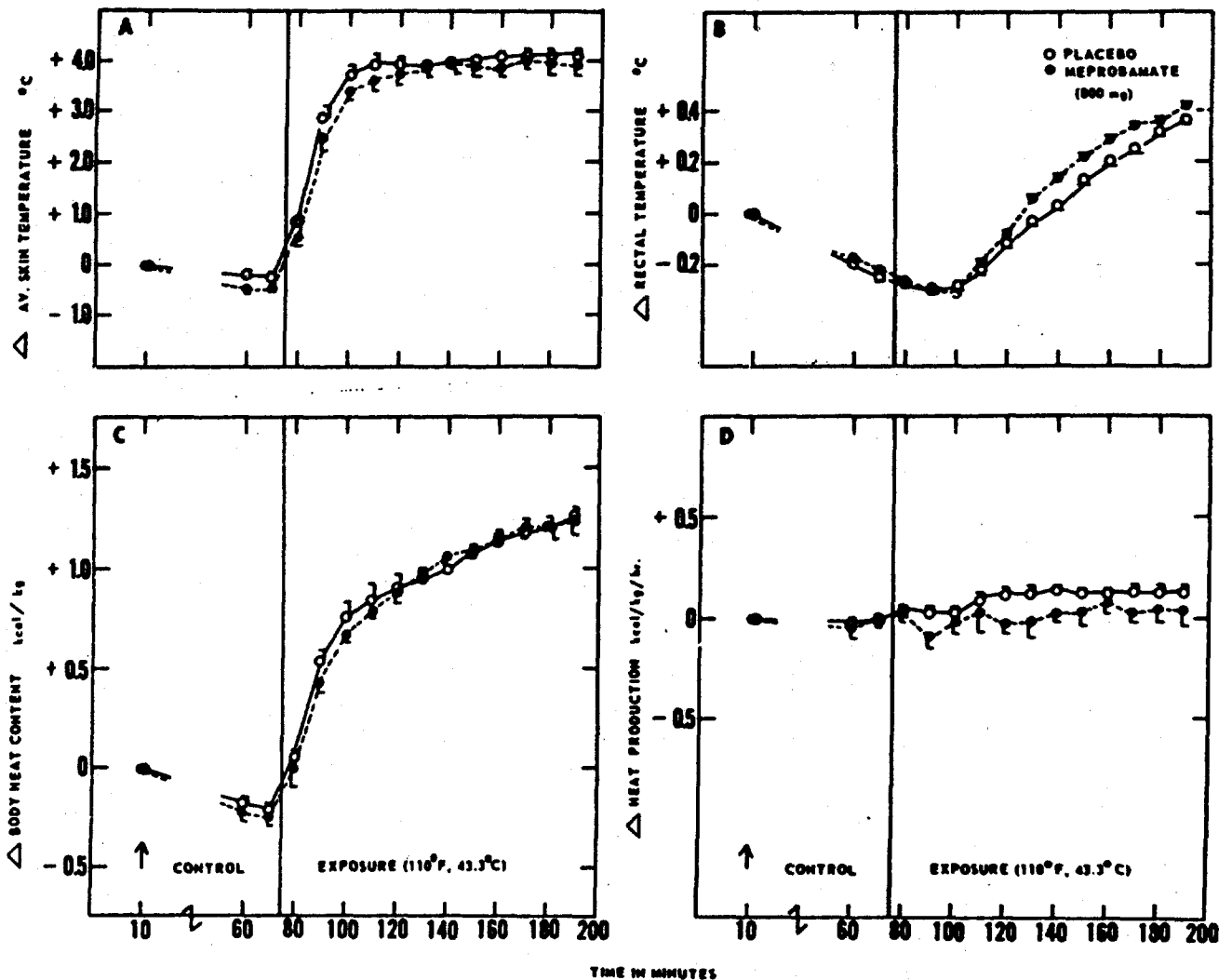


FIGURE 4. Changes in mean skin temperature, rectal temperature, body-heat content, and heat production are shown as a function of time during exposure to 110°F (43.3°C). Each point represents the mean and standard error of six men. The 10-minute control value is taken as a baseline, and all other values are shown as change from this point. Meprobamate (800 mg) or placebo was given immediately following the 10-minute readings. Ambient temperature was changed from 80°F (26.7°C) to 110°F (43.3°C) at 75 minutes.

D. Exposure to a cold environment [50°F (10.0°C), 50% RH]. During exposure to cold, T_{re} for both groups declined progressively (Figure 5A). Although T_{re} of the drug group was lower by 1.25°C (2.25°F) than that of the placebo group at end exposure, no statistical significance was attached to the difference ($P = 0.18$). Overall falls in T_{re} were 8.0°C (14.4°F) and 6.75°C (12.2°F) for the drug and placebo groups, respectively. T_{re} of both groups increased during the first hour of cold exposure, then decreased over the remainder of the exposure (Figures 5B). T_{re} of the drug group was consistently lower during the exposure than that of the placebo group. These differences were significant ($P = 0.001$). At end exposure

T_{re} of the drug group was 0.3°C (0.5°F) lower than that of the placebo group. Throughout the exposure period, the drug group maintained a lower TBHC than did the placebo group ($P = 0.05$). At the termination of exposure, TBHC decreased about 1.6 kcal/kg for the placebo group and 2.1 kcal/kg for the drug group (Figures 5C). Heat production from shivering reached peak levels after 20 minutes of exposure in both groups (Figure 5D). Thereafter, these levels were maintained for the duration of the exposure. Heat production of the placebo group increased approximately 1.0 kcal/kg/hr, while heat production of the drug group increased only 0.6 kcal/kg/hr. The group differences approached significance ($P = 0.06$).

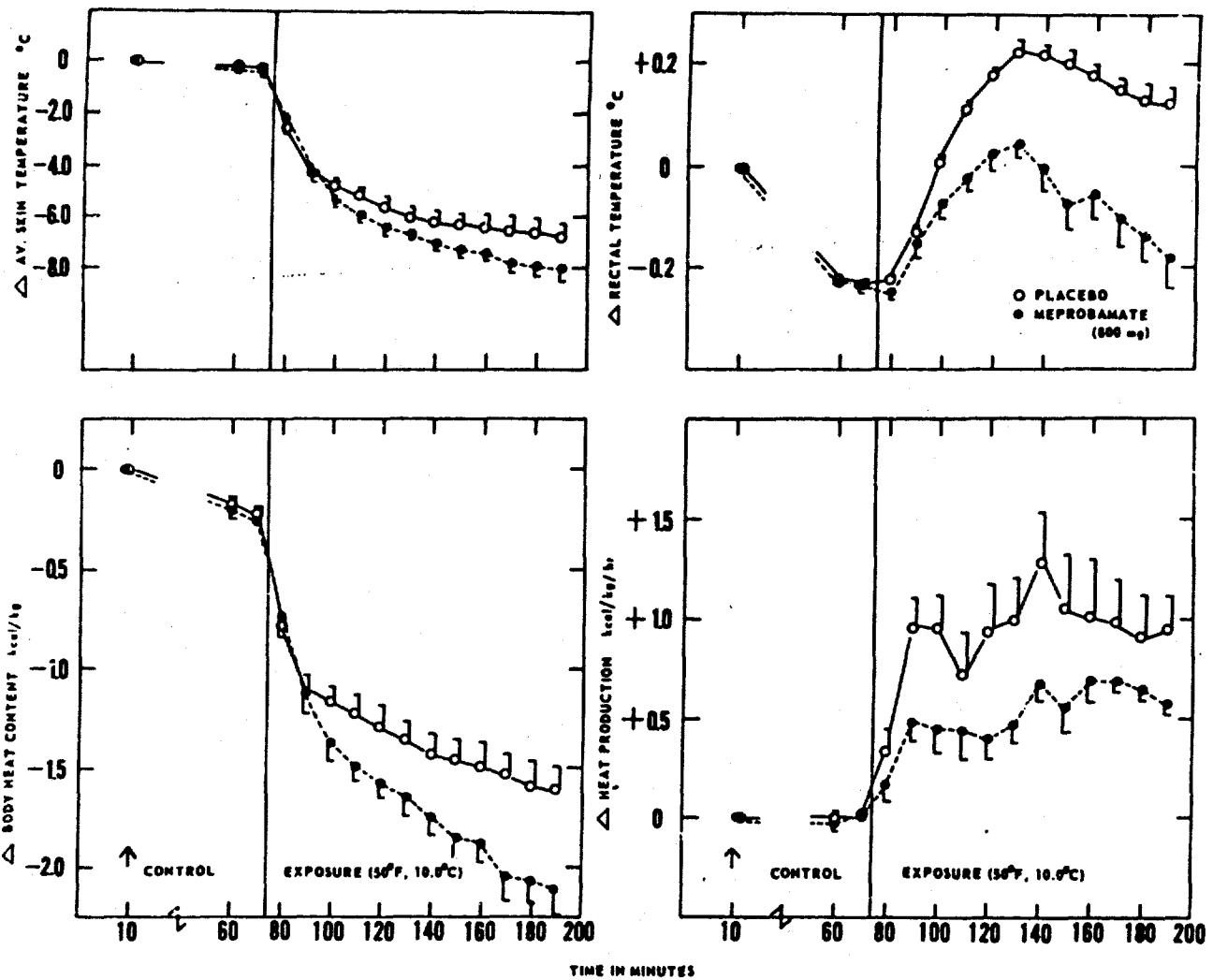


FIGURE 5. Changes in mean temperature, rectal temperature, body-heat content, and heat production are shown as a function of time during exposure to 50°F (10°C). Each point represents the mean and standard error of six men. The 10-minute control value is taken as baseline and all other values are shown as change from this point. Meprobamate (800 mg) or placebo was given immediately following the 10-minute readings. Ambient temperature was changed from 80°F (26.7°C) to 50°F (10°C) at 75 minutes.

E. Catecholamine levels in plasma. No differences in plasma catecholamine levels were detected between drug and placebo groups at any point in the study. To demonstrate the environmental effects on sympathomedullary functions, these data were combined within conditions. Changes in plasma catecholamine levels for the three exposures are shown in Figure 6. During the preexposure periods, no significant changes were observed for any group. Increases in catecholamine concentration during both neutral and heat exposures were slight but not significant. The greatest change in plasma catecholamine levels occurred during cold exposure, where significance ($P < 0.05$) increases of about 50% were detected.

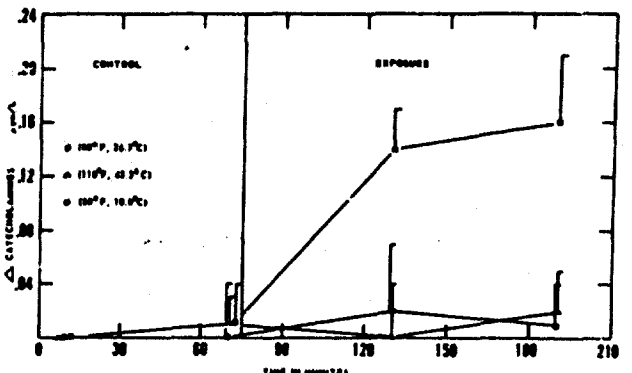


FIGURE 6. Changes in plasma total catecholamines shown as a function of time. Values for placebo and drug groups are combined with environmental conditions. Points represent means and standard error of 12 men.

IV. Discussion.

The results of these experiments demonstrate clearly that a single 800-mg dose of the tranquilizer meprobamate may impair the ability of resting man to maintain thermal balance in hot and, particularly, in cold environments. Whether meprobamate interference with temperature regulation extends to active or working man undergoing environmental stresses remains to be determined by further studies.

At present the mechanisms by which meprobamate alters the ability of man to regulate body temperature are unknown. Considering other studies, meprobamate may, like chlorpromazine and propiopromazine, exert direct effects on the temperature-regulating centers and consequently inhibit those normal responses to thermal stresses; e.g., vasoconstriction, vasodilation, shivering, and sweating.

The most profound disturbances in regulation occurred during exposure to cold where the reduction in heat production of the drug group appears to be primary. This consideration is based on the well-recognized muscle relaxant properties of meprobamate.¹ It must be additionally considered, however, that the controls exerted by the temperature-regulating centers might be sufficiently disordered so that appropriate compensations could not occur (i.e., peripheral vasoconstriction). It appears, therefore, that the disturbance in thermal regulation generated by meprobamate is most pronounced during cold exposure, while during heat exposure the deviations from normal are smaller. At neutral temperatures, meprobamate involvement in thermal regulation is not evident. These results are supported by the fact that plasma catecholamines increase markedly in the cold, while the changes in this stress index are minimal with heat or neutral exposures. That the responses we have measured are the result of variable tranquilization is discounted by the fact that plasma meprobamate levels are comparable from group to group at each of the time intervals examined. This must mean that the disrupting properties of the drug are unmasked only when the demands for thermal regulation are high.

One observation from our studies deserves special mention although no definite explanation for it can be offered at present. During

heat exposure, T_c of the drug group is maintained higher than that of the placebo group, in spite of the fact that in both groups T_{sk} , heat production, and body-heat content were similar. As possible explanations of this point, it is suggested, although no supporting data can be offered, that sweating may not have been uniform between the two groups or that there may be differences in the size of the "core" between groups. Studies are continuing to pursue this point and to investigate more thoroughly the mechanisms of meprobamate action in the regulation of body temperature.

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