THE EFFECT OF AMBIENT TEMPERATURE ON THERMAL RESPONSES TO DRUGS

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ABSTRACT

Thermal responses to a variety of drugs were investigated at various ambient temperatures on lightly restrained or "curarized" rats and dogs. Experiments on lightly restrained rats demonstrated that many drugs produce a hyperthermia above a 'critical' ambient temperature and hypothermia at lower temperatures. The 'critical' ambient temperature was about 30°C for Hydergine, ergotamine, lysergic acid diethylamide and serotonin, approximately 36°C for chlorpromazine and about 20°C for 2,4-dinitrophenol. Reserpine produced a consistent hypothermia at 23°C but somewhat inconsistent effects at ambient temperatures above this (up to 39°C). The hypothermia produced by all these agents except chlorpromazine was abolished by curare.

Pentylenetetrazol produced a hyperthermia in "curarized" dogs at ambient temperatures above a 'critical' range of 23 to 25°C, and consistent hypothermia at lower temperatures. Enhanced heat loss appears to be the major factor in the hypothermic response to this drug, whereas the hyperthermia appears to be largely due to increased heat production. The results of similar experiments on spinal dogs indicate that the responses to pentylenetetrazol are of central origin.

Dinitrophenol-induced hyperthermia is explicable on the basis of the well-known peripheral metabolic stimulation produced by this drug as confirmed in the present studies. Dinitrophenol appears to suppress the thermogenetic response to cold in both rats and dogs but hypothermia occurred only in the former at low ambient temperatures.

The present studies indicate that ambient temperature is a critical factor determining thermal responses to drugs and suggest that many such responses involve some interference with central body temperature regulation.

Dedicated to my wife Mollie, for her help, understanding and patience.

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CHAPTER I

INTRODUCTION

Outline of the Problem

It has been reported occasionally that ambient temperature may modify the thermal responses of animals to certain agents. Gioja and Dmitrijevic (46) found that the thermal responses of rats to β-tetrahydronaphthylamine, 2,4-dinitrophenol and adrenaline are dependent on environmental temperature. These agents all evoked a hyperthermia at an ambient temperature of 30°C, but a hypothermia at 6°. Buchanan, Roberts and Robinson (19) observed that ergotoxine produced a hyperthermia in rats at ambient temperatures above 28°C, variable effects at 22 to 25°C, and hypothermia at 5 to 8°C. Grant (33) reported that fever was elicited in rabbits by typhoid-paratyphoid vaccine at an environmental temperature of 25°C, whereas a hypothermia was produced by the vaccine in shorn rabbits exposed to a cold environment. Killam (66) demonstrated that the thermal responses of rats to naphazoline (Privine) were dependent on ambient temperature. In his experiments, hypothermia was evoked below 26°C, whereas hyperthermia was elicited at ambient temperatures above 28°. Finally, Bein (12) found that reserpine, in doses evoking a typical sedative effect, produced a fall in body temperature in rabbits at ordinary room temperatures, but a hyperthermia at high environmental temperatures.

It should be stated that some of the studies mentioned above were limited to a small number of animals and were not well controlled, which unfortunately has been characteristic of many of the experiments previously reported in this field.

In contrast to the above studies, the majority of reports dealing with the effects of drugs on body temperature fail to include any information about environmental temperature at the time of the experiment or do not attach any significance to it. One of the best examples of the confusion which has arisen because ambient temperature has been ignored is found in the literature on the ergot alkaloids. Although Barger and Dale (4) noted a hyperthermic effect of ergotoxine in rabbits, the earliest extensive investigation of the effect of an ergot alkaloid on body temperature was carried out by Githens (49). He reported that 1 to 4 mgm/kgm of ergotoxine phosphate injected subcutaneously produced a rise in body temperature in rabbits, and a fall in body temperature in rats, mice and pigeons. Miculicich (70) found an increase in body temperature in rabbits after intravenous, but not after subcutaneous injection. Rothlin (86) at first claimed that ergotamine did not cause a rise in body temperature in the rabbit and cock, but in a later paper (87), stated that ergotamine was about half as active as ergotoxine in raising the rabbit's body temperature. Douchmert and Heymans (15) reported that 3 to 4 mgm/kgm of ergotamine salt injected intravenously in rabbits produced no effect on body temperature. A number of other workers have reported that ergotoxine and ergotamine only lowered body temperature in their animals (1,33,83,90). Finally, Buchanan et al. (20) reported that ergotoxine evoked either hypothermia or hyperthermia, depending on the ambient temperature. Hypothermia occurred at low and hyperthermia at high ambient temperatures.

Rothlin (88) reported that the dihydrogenated ergot alkaloid derivatives consistently produced hypothermia in rabbits. This was confirmed on rats by Roberts (85) at ambient temperatures up to 28°C. However, Deutsch (32) observed that the thermal responses to Hydergine — a complex of the dihydrogenated derivatives of ergotoxine — were somewhat variable (hyperthermia in some experiments, hypothermia in others).

The above survey shows that every possible type of change in temperature has been described as occurring after the injection of ergot alkaloids. Two possible explanations for the conflicting results have been suggested by a number of workers; namely, species and dosage differences. (See 102). However, these factors cannot be invoked to explain the variability in results obtained by different investigators, and even by the same investigator, with the same dose and species of animal.

The purpose of the present studies was to investigate the possible importance of ambient temperature as a factor in determining thermal responses to drugs, and to study in more detail the mechanisms involved in the action of two "thermo-active" agents, pentylenetetrazol (Metrazol) and 2,4-dinitrophenol. These drugs were chosen for special study because the former is a compound long known for its effects on the central nervous system, whereas the latter has been presumed to have a predominantly peripheral mode of action. Several other agents, all of which have some action on the central nervous system, also have been investigated. These include chlorpromazine (Largactil), ergotamine, Hydergine, lysergic acid diethylamide

(LSD), serotonin (5-hydroxytryptamine) and reserpine. It will be demonstrated that ambient temperature is a critical factor in determining thermal responses to many drugs and that conflicting results reported in the literature, as in the case of the ergot alkaloids, may well be due to failure to consider the external temperature in evaluating results.

Drugs Investigated (Survey of Pertinent Literature)

Pentylenetetrazol (Metrazol, pentamethylenetetrazol) is a synthetic compound which stimulates all levels of the central nervous system, but which acts predominantly on subcortical centers (63). When given in high dosage, it evokes tonic-clonic convulsions followed by depression. Pentylenetetrazol increases spinal reflex activity, especially after drug-induced depression of the central nervous system. It also stimulates the respiratory, vasomotor, and vagal centers of the medulla oblongata.

This drug also influences the circulation, primarily by stimulation of the vasomotor center. Its peripheral action on the heart and blood vessels is negligible. Convulsant doses raise the blood pressure appreciably due to stimulation of the medullary vasomotor center, and in part to contraction of skeletal muscle and a consequent increase in venous return. In subconvulsant doses, the blood pressure may fall as a result of central vagal stimulation. According to Gollwitzer-Meier (30) and Mueller (72), pentylenetetrazol increases cardiac output in intact anesthetized animals with depressed circulation.

The metabolic effects of pentylenetetrazol in subconvulsant doses appear to be minimal. Schoen and Knubisch (92) and Tsungming (100) reported only slight increases in oxygen consumption in dogs and man after drug injection. Metabolic effects of convulsant doses of pentylenetetrazol have not been clearly elucidated other than the fact that increased skeletal muscle metabolism and a consequent rise in body temperature occur as a result of the greatly enhanced muscle activity.

2,4-Dinitrophenol is an agent whose primary effect is stimulation of oxidative metabolism (69, 96). It is generally accepted that dinitrophenol acts by disrupting the coupling of oxidation and phosphorylation (18). However, unlike other inhibitors of aerobic phosphorylation, such as barbiturates, dinitrophenol exerts no depressant action on tissue respiration except in high doses. As a result, aerobic oxidation results in the generation and dissipation of heat rather than in the formation of high energy phosphates, and hyperthermia results.

Dinitrophenol has long been presumed to act peripherally rather than centrally because hyperthermia evoked by this agent is not influenced by spinal section or extirpation of the thermoregulatory centers of the hypothalamus. Furthermore, the drug-induced increase in oxidative metabolism is not affected by curare and is therefore independent of skeletal muscle work (69, 96). Conclusive evidence has been offered by the above authors to show that dinitrophenol can increase metabolism by a direct effect on tissues. A central component of action, however, has not been completely

ruled out because it is possible that such an effect is masked by a predominantly peripheral action. It is interesting in this connection that Siedek (93) reported that low oral doses of dinitrophenol (3.0 mgm/kgm) consistently elicited increases in oxygen consumption of over 20 per cent in normal human subjects, whereas the same dose caused no significant effect in a series of patients with midbrain lesions. Higher doses, however, significantly increased oxygen consumption in all subjects. Siedek suggested that the peripheral action predominates at higher doses, whereas a central action plays the major role at low doses. Tainter and Cutting (96) and Magne et al. (69) used high doses in their experiments, 10 to 20 mgm/kgm and 100 mgm/kgm respectively.

Although the hyperthermic effect of dinitrophenol is well known, it has also been reported that this drug elicits a fall in body temperature in animals exposed to low ambient temperatures (46, 96). Giaja (46) attributed the dinitrophenol hypothermia to interference with the thermogenetic response to cold. This was confirmed by Hall et al. (57), who reported that dinitrophenol markedly decreased or abolished shivering in anesthetized cats placed in cold baths. On the other hand, Magne et al. (69) did not observe a hypothermia in rabbits placed in cold baths after dinitrophenol injection and did not report an influence of the drug on shivering. The absence of hypothermia in the latter experiment may possibly be explained by the very high dose of drug injected, which may have increased heat production sufficiently to offset the cold-induced enhancement of heat loss.

The possibility that dinitrophenol hypothermia at low ambient temperatures may be facilitated by a drug-induced enhancement of heat loss has to our knowledge not previously been investigated, and has therefore been studied in the present work. It is well known that an increased cutaneous blood flow is associated with dinitrophenol hyperthermia, but this is probably a thermoregulatory response to the elevated body temperature.

A number of investigators have reported that the metabolic effect of dinitrophenol is reduced at low ambient temperatures. Magne et al. (69) noted that the overall metabolism of mice kept at 10°C and given a dose of 20 mgm/kgm of dinitrophenol, did not increase and sometimes even fell. Ginja and Dimotrijevic(46) made similar observations at 6°C on rats given 30 mgm/kgm, adding that the body temperature rise observed at ordinary room temperatures was replaced by a hypothermia in the cold. Painter (97) showed that oxygen consumption, which at normal room temperature increased 130 per cent after 30 mgm/kgm of dinitrophenol, rose only 13 per cent at 3 to 6°C. Riddle and Smith (82) found that the calorigenic action of dinitrophenol in pigeons at an ambient temperature of 15°C is less than at 30°C, and Zumno (105) claimed that the dinitrophenol-induced increase in oxygen consumption of rats and pigeons receiving the drug in the cold is enhanced when they are brought to an environmental temperature of thermal neutrality. Hall et al. (57) also found that dinitrophenol produces only a very small increase in metabolism in anesthetized cats

placed in cold baths. However, he observed that the drug abolished or greatly diminished shivering in these animals. Thus the limited increase in metabolism after dinitrophenol administration to animals at low ambient temperatures could be attributed to a drug-induced diminution of the oxygen cost of shivering rather than to a reduced drug effect on tissue metabolism. The previous finding of a reduced metabolic effect of dinitrophenol at low ambient temperatures may therefore be more apparent than real.

In the present studies, it was of interest to determine the effect of ambient temperature on the metabolic response to dinitrophenol in animals completely paralyzed with a neuromuscular blocking agent, and thereby incapable of shivering in a cold environment.

Chlorpromazine (Largactil, Thorazine), a phenothiazine derivative closely related chemically to promethazine but having little antihistamine activity, is an agent which produces a large number of effects (26). These include hypothermic, tranquilizing, adrenergic blocking, antifibrillatory, antiedema, antishock, anticonvulsant and antiemetic effects. In addition, chlorpromazine has been reported to enhance the potency of a number of analgesic and central depressant drugs and to disrupt conditioned reflexes. The hypothermic action has been described by several groups. Ojeja (47) reported that chlorpromazine produces a marked hypothermia at ambient temperatures ranging from thermal neutrality (28 to 30°C) to much lower temperatures, the effect being more marked at lower temperatures. Decourt (29) concluded that the hypothermic effect of chlorpromazine is

independent of ambient temperature. He presented data purporting to show that chlorpromazine elicited a fall in body temperature when injected into guinea pigs, even after two hours in a room at 43°C. However, the data are not convincing because body temperature in the control guinea pigs also fell, although not as much, and the significance of the difference seems open to question. The author also describes experiments on rabbits exposed to an ambient temperature of 39°C, but no data are given.

On the other hand, Binet and Decourt (14), Laborit (60) and Willems (103) have all reported that at high ambient temperatures the rat responds to chlorpromazine with a hyperthermia. Binet and Decourt found that the drug markedly accelerates the hyperthermic effect of infrared radiation. The other two groups did not present any details of their experiments.

It has been reported that chlorpromazine has little effect on oxidative metabolism. Courvoisier (26) observed that the drug lowers basal metabolism only slightly, and Popovic (78) found that the oxygen consumption of treated and control rats was essentially the same at an ambient temperature of 15°C. He also observed that chlorpromazine did not prevent the increased metabolism induced by dinitrophenol or adrenaline at an ambient temperature of 20°C. Glaja (47) reported that chlorpromazine produced little change in the oxygen consumption of rats at ambient temperatures around 28 to 30°C. He also observed that there was little effect on the ability of the animal to react against cold by increasing itsoxidative metabolism. The latter finding was confirmed by Popovic (78) on rats,

and Chatonnet and Tanche (23) on dogs. However, it has been claimed by Dundee (37, 38) and Rapstein (84) that chlorpromazine facilitates refrigeration hypothermia in both dogs and man by reducing the amount of shivering during the procedure. The possibility that this action on shivering is a specific one is open to question because both groups used anesthetized subjects. The reduced shivering after chlorpromazine could have been due simply to an increased depth of anesthesia, because chlorpromazine's central depressant effect has been shown to be additive with that of barbiturates and other anesthetics (26).

Peruzzo and Forni (73) claimed chlorpromazine had no effect on the respiration of hepatic and renal slices *in vitro*, but did significantly reduce the respiration of cerebral cortical slices, an observation confirmed by Courvoisier (26). However, Finkelstein, Spencer, and Ridgeway (41) had to use high concentrations of chlorpromazine to depress the aerobic metabolism of brain and heart slices and homogenates *in vitro*.

The observations summarized above appear to rule out an effect on oxidative metabolism as a factor of major importance in the hypothermic action of chlorpromazine. It has been assumed by the above authors that increased heat loss is responsible for the hypothermia. Bobkin (34) and Chevillard (24) have presented more direct evidence to substantiate this assumption. Bobkin reported that in man, chlorpromazine elicits marked cutaneous vasodilatation (skin temperatures recorded with an electrical thermometer) associated with hypothermia but little change in oxygen consumption. Chevillard found that chlorpromazine produced vasodilatation

in the guinea pig ear, as indicated by thermocouple recording of skin temperature.

Peripheral vasodilatation may be due in part to the adrenergic blocking action of this drug (26), but it has also been suggested that a direct effect on the thermoregulatory centers may be involved (22, 67). Courvoisier (26) and Laborit (67), in the absence of supporting data, postulated that chlorpromazine had some ganglionic blocking action which contributed to the hypothermic effect. However, Decourt (28) found little or no ganglionic blocking activity. Doses below 20 mgs/kgm intravenously failed to affect submaxillary gland secretion in response to stimulation of the chorda tympani nerve in cats. A dose of 20 mgs/kgm caused some diminution of the responses, but this was not necessarily due to ganglionic blockade because chlorpromazine has some anticholinergic activity (26).

Decourt (30) has attributed the hypothermic action of chlorpromazine to a narcobiotic effect, which he defines as "the inhibition of fundamental metabolic processes of living matter, essential to the normal activity of all cells." The evidence for this theory is quite meager and is based largely on experiments carried out on subjects such as paramecia, sea urchin embryos and anaerobic bacteria.

The ergot alkaloids have been studied extensively since the basic observations of Dale (27). These compounds were the first adrenergic blocking agents discovered, and also have many other actions, the most important of which are direct stimulation of smooth muscle and complex excitation and depression of the central nervous system. Vasomotor reflexes,

the vasomotor center and respiration are depressed, the vagal center is stimulated, and vomiting is produced. Effects on smooth muscle and on the central nervous system occur after doses smaller than those required to produce adrenergic blockade.

The naturally occurring ergot alkaloids such as ergotamine cause a significant rise in blood pressure which is primarily the result of direct peripheral vasoconstriction. The dihydrogenated ergot alkaloids, on the other hand, are much less effective vasoconstrictors (63). Hydergine, a complex of the three dihydrogenated derivatives of ergotoxine, produces very little vasoconstriction, and the over-all vascular effect is usually a fall in arterial pressure, largely the result of selective central nervous system depression. Adrenergic blockade may contribute to the pressure fall when higher doses are employed.

The effects of the ergot alkaloids on body temperature have been mentioned in a preceding section. The work of Buchanan et al. (20) indicates that thermal responses to the natural ergot alkaloids are dependent on ambient temperature. In their experiments, ergotoxine produced hyperthermia when administered to animals in a warm environment, and produced hypothermia in the cold. The hyperthermia was associated with increased oxygen consumption and peripheral vasoconstriction. Increased skeletal muscle activity may have contributed to the increased metabolism because the hyperthermia was diminished but not abolished by curare. The hypothermia at low ambient temperatures was associated with peripheral

vasodilatation. Metabolism was decreased relative to control animals, but this was considered to be secondary to the fall in body temperature. Buchanan et al. (20) assumed that these responses to ergotoxine were the result of a direct action on the thermoregulatory centers of the hypothalamus. Dimitrijevic (33) attributed the hypothermic effect of ergotamine in rats at low ambient temperatures to suppression of thermogenesis in response to cold.

Lysergic acid diethylamide (LSDA), a semisynthetic derivative of ergot, is of interest because it evokes psychic effects in extremely small doses (93), and has been shown to inhibit effects of serotonin (5-hydroxytryptamine) on smooth muscle (45). It has been postulated that serotonin is important in central nervous system function (16, 17).

The pharmacological properties of LSDA have been more adequately studied in schizophrenic patients than in animals. Forrer and Goldner (43) found that in such patients the drug produced a slight increase in blood pressure, pulse rate and deep reflexes, increased salivation and lacrimation, produced mydriasis and some ataxia, but did not significantly affect respiration. LSDA-induced visual hallucinations are commonly observed in both normal and schizophrenic subjects. Euphoria is usually produced in schizophrenics but alternating euphoria and depression is more commonly observed in normal subjects following LSDA (93).

Morita and Dille (64, 65) found that LSDA injected intravenously or subcutaneously in doses ranging from 0.3 to 50 µgm/kgm produced a rise

in body temperature in rabbits, dogs and cats. Rabbits were the most responsive to this action. After injection, ear temperature fell markedly, but peripheral vasoconstriction appeared to be unrelated to the pyretic effect because the fall in ear temperature persisted after the rectal temperature returned to normal. Cervical spinal cord section, tubocurarine or sodium pentobarbital abolished the pyretic effect, whereas antipyrine, Dibenamine, dihydroergotamine or hydergine did not modify the response.

Reserpine, one of the active alkaloids of Rauwolfia serpentina, characteristically produces hypothermia, sedation, miosis, hypotension, hyperperistalsis and relaxation of the nictitating membrane, and inhibits respiratory reflexes (13). The drug acts primarily on the brain and has little peripheral action in usual therapeutic doses. It has no adrenergic blocking (12, 98, 99), anticholinergic (10, 12, 32, 99), antihistaminic (32, 99) or ganglionic blocking activity (12, 104), and does not affect the isolated intestine (12, 77) or heart (71, 98, 99), or relax perfused blood vessels (12, 99). However, many of these actions can be demonstrated when very large doses are employed.

The fall in blood pressure has been attributed to lowering of the peripheral resistance by vasodilatation. Cardiac output does not fall significantly (98). The central site of the hypotensive action of therapeutic doses of reserpine is evidenced by the observation that section of the brain stem of cats between the medulla and midbrain (following which blood pressure remained at a normal level) abolished the depressor action (13).

Reserpine has been reported to produce hypothermia in most experiments (12, 77) but hyperthermia in reserpine-treated rabbits exposed to high environmental temperatures has been observed (12). These effects on body temperature have been attributed to an action on the thermoregulatory centers of the hypothalamus, but no evidence has been offered in support of this assumption.

Serotonin (5-hydroxytryptamine), which is normally present in the brain, gastrointestinal tract, and blood platelets (3, 39), is currently of great interest as a substance of possible physiological significance in central nervous system function.

The vascular effects of serotonin are highly variable and complex. In anesthetized dogs the usual response is triphasic, consisting of (1) an initial quick fall in arterial pressure and bradycardia followed by (2) a more sustained pressor response succeeded in turn by (3) a prolonged vasodepression. As analyzed by Page and McCubbin (74), the initial quick fall is due to a Bezold-Jarisch-like reflex, i.e., hypotension and bradycardia originating from intrathoracic afferents. The pressor phase was shown by perfusion experiments to depend, at least in part, upon a direct vasoconstrictor action. Finally, the prolonged depressor action was said to depend on inhibition of neurogenic vasoconstriction. In contrast to dogs, the normal response of rabbits and cats is depressor, occasionally followed by a transient pressor effect. Page and McCubbin found the predominantly pressor or depressor response in intact animals to be determined largely by the pre-existing neurogenic vasoconstrictor tone. When the latter

was increased by section of the buffer nerves, the systemic response to serotonin was depressor; elimination of vasoconstrictor tone by ganglionic blockade or cord section converted the response to pressor. This change in the response was not determined by the height of the arterial pressure because raising the latter by rapid infusion of saline or injection of renin after ganglionic blockade or cord section did not cause the response to become depressor. Reid (81) found that increased cardiac output is not a factor in the transient pressor response to serotonin occasionally observed in cats, although this agent does increase the amplitude of contraction and rate of the isolated rabbit heart. Schneider and Yonkman (91) confirmed Reid's findings, but suggested that in the intact animal, serotonin caused vagal reflexes which masked its stimulating effects on the heart.

The effect of serotonin on metabolism has been studied in rats by Rapport (80), who reported that serotonin depressed the oxygen consumption of unanesthetized rats, but not that of dogs, guinea pigs or cats. The body temperature of one rat was recorded before injection and again during the peak of the metabolic depression. The body temperature dropped about 4.0°C in that period. However, no controls were presented. Because of the incomplete data, it is not clear whether the depressed oxygen consumption was a cause or an effect of the fall in body temperature.

The subject of a possible role of serotonin in central nervous system function is controversial. The main evidence for such a role, as presented by Brodie et al. (16, 17) is as follows: 1) Serotonin is present in brain

tissue. 2) LSDA, a hallucinogenic agent, is a serotonin antagonist, at least on smooth muscle. 3) Reserpine, a tranquilizing drug, liberates serotonin from brain tissue. Brodie's group have postulated that the actions of reserpine are mediated by release of serotonin from brain tissue, and have implied that the actions of LSDA may result from serotonin antagonism. However, the evidence for these postulations, as well as for a role for serotonin in normal brain function is not fully convincing.

If serotonin is a common denominator in responses to reserpine and LSDA, one would expect the effect of injected serotonin on body temperature to be similar to that of reserpine and opposite to that of LSDA. Although the hypothermic effect of reserpine is one of the actions said to be mediated through serotonin (31), the evidence for this is meager. The effects of serotonin on body temperature have been investigated in the present studies and compared with those of reserpine and LSDA.

CHAPTER II

METHODS

Studies on Lightly Restrained Rats

Discussion of Methods

In the initial investigation of the role of ambient temperature in determining thermal responses to drugs, the adult albino rat was used as the test animal (1) because it allowed the use of a considerable number of animals per experiment, and (2) because the rat is sensitive to the thermal effects of many agents (19,46,66). However, the restrained rat is only a partial homotherm in that the body temperature tends to fall somewhat on exposure to ambient temperatures below the thermoneutral range of 28 to 30°C, and tends to rise at higher temperatures (58,62). Therefore, rigidly controlled experiments are necessary to distinguish the drug-induced component of changes in body temperature. In the present work, each animal was used as its own control in a separate experiment under similar conditions. Even when experimental conditions, including environmental temperature, are apparently identical, body temperature responses may vary among different groups of animals (19). To minimize this source of error, experiments were repeated one or more times on different groups of animals. Additional precautions were to inject each animal only once with a given agent in order to avoid possible development of tolerance, and to record colonic rather than rectal temperatures. Buchanan et al. (19) reported that in the rat, rectal temperature is more subject to modification by the external environment.

Experimental Procedure

Unanesthetized female albino rats (130 to 200 grams body weight) were placed in individual wire-mesh holders in a constant temperature room ($\pm$ 0.5°C), and their colonic temperatures recorded with copper-constantan thermocouples inserted five to six centimeters beyond the anal sphincter. The thermocouples were calibrated before and after each experiment. The calibration curves were always found to be parallel. There was sometimes a slight drift, not more than 0.5 galvanometer unit (0.08°C) in three hours, which was within the margin of error of the method and was consequently disregarded.

After a two-hour equilibration period, the agent under study was injected subcutaneously and colonic temperatures were recorded hourly for an additional three hours. Each rat was used as its own control during a separate equal period at the same ambient temperature. The maximal drug-induced effect was calculated for each animal as the difference between the peak response to the drug and the corresponding temperature change in the control experiment. Body temperature just prior to drug injection was taken as the basal temperature. The significance of the drug-induced changes in body temperature was calculated by the method of individual (paired) comparison (94).

In another series of experiments on unanesthetized rats, the effect of 2,4-dinitrophenol on oxygen consumption was investigated at various ambient temperatures. The apparatus used to determine oxygen consumption is shown diagrammatically in figure 1. The rat was placed in the wire-mesh cylinder and a plastic lid sealed over the end of the holder with lanolin. The

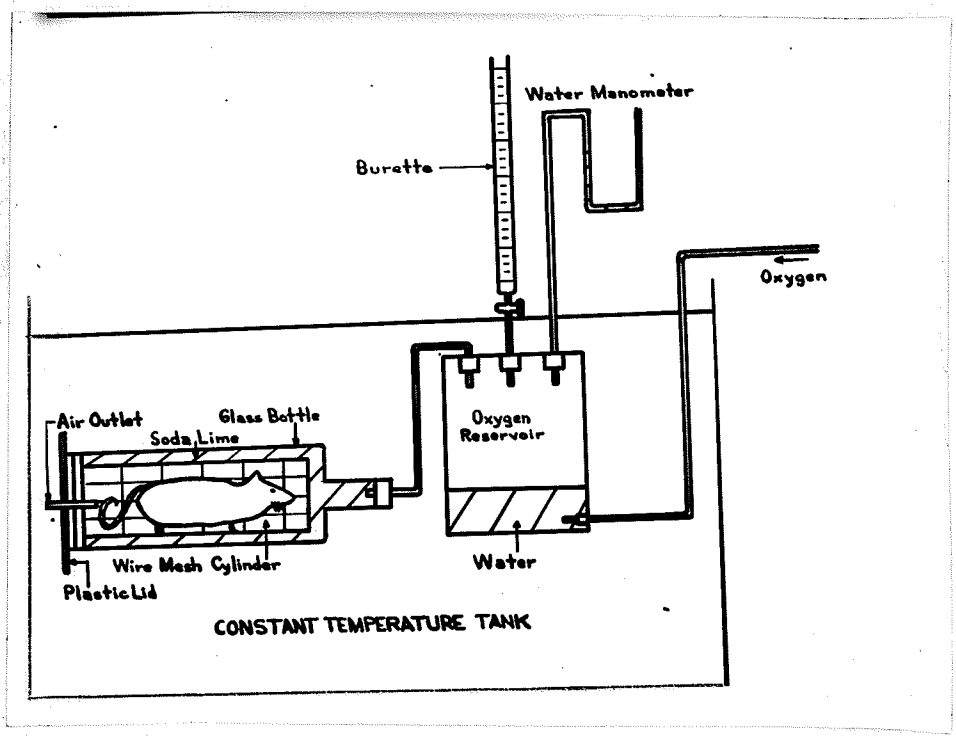

Figure 1. APPARATUS USED TO MEASURE OXYGEN CONSUMPTION OF RATS. See text for description.

apparatus was then flushed with 100 per cent oxygen by way of the oxygen reservoir at a flow of seven l/min. for one minute. During this procedure, the burette stopcock and the connection between the reservoir and manometer were closed, and the oxygen line and air outlet from the rat holder open. After the air in the system had been displaced by oxygen, the last two were closed and the reservoir-manometer connection opened. The rat holder was then lowered into the constant temperature bath. As the rat consumed oxygen, the pressure in the system was maintained constant by introducing water from the burette. The volume of water added to the reservoir was recorded as a measure of the volume of oxygen consumed.

Two control determinations of oxygen consumption were made over ten-minute periods, the first following an equilibration period of fifteen to twenty minutes after lowering the rat holder into the water bath, and the second fifteen minutes later. These determinations usually agreed within five per cent. The average of the two was taken as the basal oxygen consumption. Immediately following the second control measurement, the rat was injected with drug and oxygen consumption redetermined one-half and one hour later. Preliminary experiments indicated that the peak response to dinitrophenol administered subcutaneously usually occurred within one hour after injection. Each rat was used as its own control under similar conditions. The significance of the drug-induced changes in oxygen consumption was calculated by the method of individual (paired) comparison (94).

The resting oxygen consumption values determined by this method

are similar to those quoted by Tainter (97), who used a bellows-type volume recorder to measure oxygen consumption in nonfasted rats at ambient temperatures similar to those in the present study. However, they are somewhat higher than those given by Adolph (2), who used a modification of the open-circuit method of Haldane (36). The lower values obtained by Adolph may have been due in part to the fact that his rats were fasted for sixteen hours prior to the determination of oxygen consumption.

All drugs except reserpine were administered as salts: chlorpromazine hydrochloride, ergotamine tartrate, Hydergine methanesulfonate, serotonin creatinine sulfate, lysergic acid diethylamide tartrate and the sodium salt of 2,4-dinitrophenol. Drugs were dissolved in the following vehicles: chlorpromazine, serotonin and dinitrophenol in isotonic saline; ergotamine and LSDA in 0.5 per cent tartaric acid; and reserpine in a vehicle consisting of benzyl alcohol, citric acid, polyethyleneglycol 300 and water. Control animals were injected with the appropriate drug vehicle in volumes equivalent to those administered to treated animals. Dosages for chlorpromazine, ergotamine and LSDA are stated in terms of the salt, whereas those for reserpine, Hydergine, dinitrophenol and serotonin represent the free base.

Studies on Curarized Rats

Discussion of Methods

The homothermic animal maintains a constant body temperature in a cold environment partly by cutaneous vasoconstriction and insulation by body fur, but primarily by an increase in skeletal muscle tone (thermogenesis) manifested by shivering (59,61). The shivering may not necessarily

be detectable by gross observation. Electromyographic studies have shown that increased skeletal muscle activity, accompanied by a rise in oxygen consumption, can be elicited in response to a moderately cold environment in the absence of clinically detectable shivering (91).

If the thermogenetic response to cold is impaired, a fall in body temperature may result. Ginja (46) suggested that dinitrophenol, adrenaline and β-tetrahydronaphthylamine may promote hypothermia in rats by inhibiting this thermoregulatory mechanism. He found that the oxygen consumption of treated rats at an ambient temperature of 6°C was not significantly higher than the "BMR" (measured at thermoneutrality), whereas the metabolism of control animals increased two- to three-fold.

Effects of drugs on the thermogenetic response to cold may be detected also by the use of a neuromuscular blocking agent such as tubocurarine. When a paralyzed animal is exposed to cold, it can not increase skeletal muscle activity, and heat production remains at a basal level. Therefore, an agent producing hypothermia by impairing cold-induced thermogenesis in a normal unanesthetized animal will have no effect on a curarized animal. On the other hand, hypothermia could be induced in a curarized animal by an agent which enhances heat loss by producing cutaneous vasodilatation or decreases heat production by depressing basal metabolism. This type of study is interpretable only if the rate of fall in body temperature in untreated animals is not near-maximal. For this reason, the present studies on curarized rats were carried out at a moderate ambient temperature. Minimal curarizing doses of tubocurarine

were used to minimize ganglionic blockade and histamine release, which can be complicating factors when higher doses are employed.

Experimental Procedure

Female albino rats (150 to 200 grams body weight) were brought into a room maintained at a constant temperature of 16 ± 1°C., and paralyzed with tubocurarine chloride (0.75 mgm/kgm intramuscularly). Tracheotomy was quickly accomplished under local procaine anesthesia, a tracheal cannula inserted and artificial respiration started. Complete skeletal muscle flaccidity was maintained throughout the experiment with small supplements of tubocurarine. Colonic temperatures were recorded with constantan-copper thermocouples inserted five to six centimeters beyond the anal sphincter. After a half-hour equilibration period, the agent under study was injected subcutaneously and the colonic temperature recorded every half-hour for an additional two hours. Control experiments were carried out on another group of animals under identical conditions. In the calculation of responses, the body temperature just prior to drug injection was taken as the basal temperature, and the maximal change in body temperature in the ensuing two hours noted. The significance of the changes induced by the drugs investigated was calculated using the method of group comparison (94).

Studies on "Curarized" Dogs"

Discussion of Methods

In an attempt to elucidate in more detail the mechanisms of the thermal effects of pentylenetetrazol and dinitrophenol, the dog was used as the experimental animal because (1) it allowed the use of each animal

as its own control in a separate experiment under conditions of neuromuscular blockade, (2) many parameters such as blood pressure, oxygen consumption, skin temperature, rectal temperature and venous hematocrit could be measured easily and reliably, and (3) in contrast to the cat and monkey, vasomotor control of body temperature in the dog, as indicated by skin temperature responses to heat and cold, has been shown by Hardy (60) to be quite similar to that of man.

In determining the mechanism by which a drug alters body temperature, the experiments must be designed to determine the effects of the agent on both heat loss and heat production because it is the balance between these two factors that is responsible for the maintenance of a constant body temperature. In the present studies, skin temperature was recorded from the shaved ear and dorsum of the foot as a measure of cutaneous blood flow and heat loss from the body surface. Some workers (40) have objected to the use of skin temperature as a quantitative, minute-to-minute index of changes in cutaneous blood flow, but it is generally agreed that skin temperature is a reliable and convenient method of determining relatively slow directional changes in cutaneous blood flow. Skin temperature is determined not only by the rate of blood flow, but also by the temperature, humidity and movement of the surrounding air. The room temperature in these studies was constant to $\pm$ 0.5 or 1.0°C, and the air movement was maintained uniform with circulating fans. Humidity was not controlled in most experiments, but this is probably of minor consequence in skin temperature studies on dogs because this animal does not sweat appreciably except on the foot pads.

Heat production was determined indirectly by measuring oxygen consumption. In interpreting the significance of changes in oxygen consumption following drug administration, allowance must be made for changes secondary to alterations in body temperature. Van't Hoff (101) found that the velocity of most chemical reactions increases two to three times for each 10°C rise in temperature (Q_{10} = 2 to 3), and Q_{10} values of 2.0 and 2.3 for the overall metabolism of laboratory animals (73) and man (36) respectively have been demonstrated. An effect on heat production as a mechanism of a drug-induced change in body temperature can be concluded only when the effect on metabolism is greater than can be accounted for by the observed alteration of body temperature. In the experiments reported here, the drug-induced effect on oxygen consumption was calculated as the difference between the maximal change after drug injection and the corresponding change in the control experiment. The difference was then corrected for the effect of body temperature change on oxygen consumption using a Q_{10} of 2.0. An illustration of this calculation is as follows:

After drug administration a dog's oxygen consumption increased forty per cent, whereas in the control experiment in the same animal the corresponding change was a decrease of six per cent. A rise in rectal temperature of 2.0°C was associated with the increased oxygen consumption in the treated animal, whereas the corresponding change in the control experiment was -0.1°C.

Drug-induced effect on oxygen consumption	= + 46 per cent
Drug-induced effect on body temperature	= + 2.1°C
Estimated increase in oxygen consumption due to hyperthermia	= + 21 per cent
Drug-induced effect on oxygen consumption corrected for van't Hoff factor	= + 23 per cent

Blood pressure was recorded to provide a possible basis for interpreting changes in skin temperature. By itself, blood pressure does not supply enough information to establish the mechanism of flow changes in any given vascular bed. However, it may suggest a mechanism. For example, a rise of blood pressure accompanied by a rise in skin temperature may imply that the increased cutaneous blood flow results from a baroreceptor-mediated reflex vasodilatation. On the other hand, a rise in blood pressure associated with a fall in skin temperature would suggest a drug-induced vasoconstriction of central or peripheral origin.

Barbour has called attention to the possible role of changes in blood "concentration" (concentration of total solids in his studies) in body temperature regulation. These changes paralleled alterations in blood volume and may have been correlated with changes in blood flow. He observed hemoconcentration when the body temperature was elevated by infection, cocaine, β-tetrahydronaphthylamine, hay infusion or Shiga vaccine (8). The blood concentration was restored to normal, i.e., lowered, by antipyretics such as salicylates, which in the absence of fever have little effect on either body temperature or blood concentration (6). Hemodilution induced by the injection of 30% glucose solution also lowered febrile temperatures, but did not affect normal temperatures (7). Experiments by a number of investigators have demonstrated that exposure to cold is associated with hemoconcentration and exposure to heat with hemodilution (5,11,25,35).

These findings suggest that changes in blood volume may contribute to body temperature regulation. In the present studies, venous hematocrits were determined to allow a possible correlation of hemoconcentration with changes in body temperature, and to provide a basis for deciding whether changes in blood concentration are causally related to alterations in cutaneous blood flow.

The significance of drug-induced changes of various parameters was calculated by the method of individual (paired) comparison in all experiments on dogs except those on spinal cord-sectioned animals, in which case the method of group comparison was used (94).

Experimental Procedure

Pentylenetetrasol Experiments

Dogs were paralyzed with a neuromuscular blocking agent, tubocurarine hydrochloride or decamethonium iodide, and then artificially respired uniformly (18 cc/kgm/inspiration) at the rate of 16/min. through an endotracheal tube equipped with an inflatable cuff. After an equilibration period of 1 1/2 to 2 hours, the drug was administered intravenously in seven doses of 13 mgm/kgm at twenty-minute intervals. Supplements of the neuromuscular blocking agent were given as needed to maintain complete skeletal muscle flaccidity. Skin temperatures were measured with constantan-copper thermocouples and rectal temperature was recorded with a thermocouple, or in a few early experiments with a mercury thermometer. Oxygen consumption was determined by means of a Benedict-Roth spirometer interconnected with the respirator. The animals were ventilated with 100 per cent oxygen during oxygen consumption determinations and with room air between

determinations. Blood pressure was recorded from either a carotid or femoral artery with a mercury manometer, using peritol (15 mgm/kgm intravenously) as an anticoagulant.

Similar experiments were carried out on dogs following acute spinal cord section at C_4 to C_6. The operative procedure was carried out under ether anesthesia and artificial respiration was then given. Pentylenetetrazol administration was started two hours later, and rectal and skin temperatures, oxygen consumption, blood pressure and venous hematocrit were recorded as previously described. Another group of animals with spinal cord sections at the same level served as controls in similar experiments.

Dinitrophenol Experiments

The procedure was identical to that described for pentylenetetrazol except that the drug was administered only once at the end of the equilibration period in a dose of 3.0 mgm/kgm intravenously, or in a second group of animals by intracarotid infusion over a ten-minute period.

Studies on Lightly Restrained Dogs

Another series of experiments was carried out on lightly restrained dogs exposed to room temperatures of 10 and 4°C (± 1°C). After an equilibration period of two hours, dinitrophenol (3.0 or 20 mgm/kgm) was administered and rectal temperature recorded every half-hour for an additional two hours. The presence or absence of shivering was also recorded.

CHAPTER III

RESULTS

Thermal Responses of Lightly Restrained Rats at Various Ambient Temperatures

The type of data obtained is illustrated in figure 2, which shows the results of representative experiments in which dinitrophenol (30 mgm/kgm subcutaneously) was administered to two different animals exposed to room temperatures of 18 and 23°C. Each animal was used as its own control during a separate equal period at the same ambient temperature. Dinitrophenol evoked a hyperthermia at 23°C and a hypothermia at 18°C. The somewhat low preinjection colonic temperatures, first recorded one hour after the animals were brought into the room are probably due to the fact that the restrained rat is a partial homotherm whose body temperature characteristically falls somewhat on exposure to ambient temperatures below the thermoneutral range of 28 to 30°C.

The maximal drug-induced changes in body temperature for all rats treated with dinitrophenol at various ambient temperatures are presented in figure 3. The maximal response to the drug was calculated for each animal as the difference between the peak response to the drug and the corresponding temperature change in the control experiment. A consistent hyperthermia was produced above a critical ambient temperature range of 20 to 22°C and a consistent hypothermia below this range.

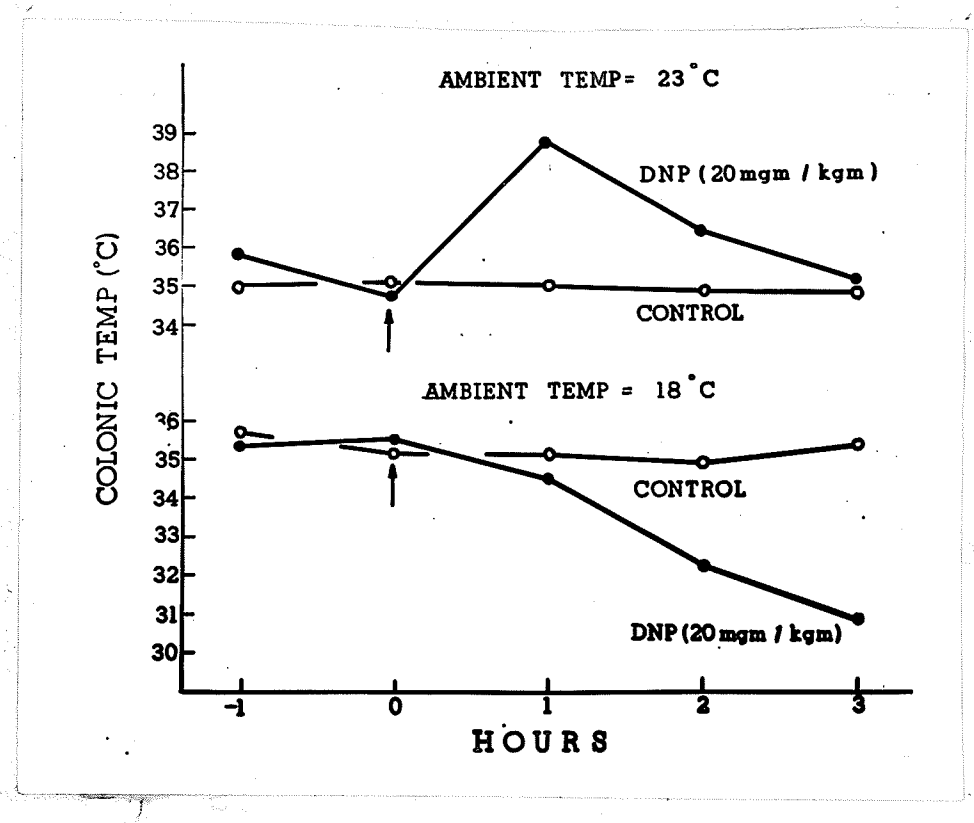

Figure 2. EFFECT OF DINITROPHENOL ON THERMAL RESPONSES OF LIGHTLY RESTRAINED RATS AT AMBIENT TEMPERATURES OF 18 and 23°C. Representative experiments in which dinitrophenol was administered to two different animals, each used as its own control. Drug injected at zero time (arrows). The maximal drug-induced change in body temperature was calculated for each animal as the difference between the peak response to the drug and the corresponding temperature change in the control experiment, one and three hours respectively in the experiments at 23 and 18°C.

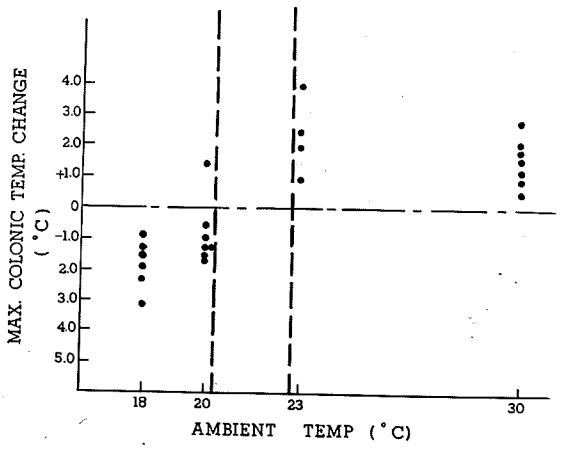

Figure 3. RELATIONSHIP OF AMBIENT TEMPERATURE TO THERMAL RESPONSES OF LIGHTLY RESTRAINED RATS TO DINITROPHENOL. Maximal drug-induced changes in body temperature are shown for all animals treated with dinitrophenol (20 mgm/kgm subcutaneously) at various ambient temperatures. Each point represents observations on a single animal.

The average maximal changes in body temperature produced by each of the agents studied at ambient temperatures ranging from 18 to 39°C are shown in table I. Chlorpromazine evoked a significant hypothermia at ambient temperatures of 30 and 33°C, and a significant rise in body temperature at 39°C. Hydergine, ergotamine, serotonin and LSD all produced a significant hypothermia at 25°C, no consistent effect at 30°C and a significant hyperthermia at 33°C. Reserpine caused a significant hypothermia at 25°C, but produced somewhat inconsistent effects at higher temperatures (up to 39°C).

Thermal Responses of Curarized Rats at an Ambient Temperature of 16°C

The effects of various agents on the body temperature of curarized rats under artificial respiration in a room maintained at 16 ±1°C are shown in table II.

The average fall in body temperature over a two-hour period following drug injection was recorded. Chlorpromazine was the only agent that elicited a significantly greater hypothermia than that observed in the control animals. The body temperature of the chlorpromazine group decreased an average of 8.5°C, whereas that of the control group fell 6.3°C ($P < .01$).

Thermal Responses of "Curarized" Dogs to Pentylenetetrazol

The relationship of room temperature to pentylenetetrazol-induced changes in body temperature of dogs paralyzed with either tubocurarine hydrochloride or decamethonium iodide is shown in figure 4. No differences between the two neuromuscular blocking agents were noted. A consistent hyperthermia was produced above a critical range of ambient temperature, approximately 23 to 25°C, and a consistent hypothermia at lower temperatures.

Table I

Thermal Responses of Lightly Restrained Rats at Various Ambient Temperatures

Agent	Dose mgm/kgm	Drug-induced Changes in Colonic Temperature (°C)						
		15°C	20°C	23°C	25°C	30°C	33°C	39°C
Dinitrophenol	20	-1.6 P < .01 (6)*	-0.8 P > .05 (7)	+2.3 P < .01 (4)		+1.6 P < .01 (7)		
Chlorpromazine	25					-2.2 P < .01 (6)	-1.4 P < .05 (4)	+1.5 P < .01 (7)
Hydergine	1.0	-0.9 P < .02 (5)			-1.1 P < .01 (5)	-0.2 P > 0.3 (10)	+0.6 P < .02 (10)	
Ergotamine	5.0	-1.2 P > .05 (5)			-1.9 P < .01 (8)	+0.8 P > .05 (12)	+2.0 P < .01 (4)	
Serotonin	8.0				-2.2 P < .01 (8)	+0.4 P > .05 (13)	+1.5 P < .01 (7)	
LSDA	1.0				-1.0 P < .01 (8)	+0.2 P > 0.5 (9)	+0.8 P < .05 (9)	
Reserpine	1.0			-3.4 P < .05 (5)	+0.0 P > 0.7 (10)	+0.6 P < .01 (10)	+0.5 P > 0.2 (10)	+0.3 P > 0.2 (9)

* Figures in parentheses indicate the number of animals used

Table II

Thermal Responses of Curarized Rats at an Ambient Temperature of 16°C

	Dose mgm/kgm	No. of Animals	Change in Colonic Temperature* (°C) ± S.E.
Controls	-	6	-0.5 ± 0.5
Dinitrophenol	20	6	-0.7 ± 0.5
Chlorpromazine	25	7	-0.5 ± 0.4
Hydergine	1.0	8	-0.0 ± 0.3
Ergotamine	5.0	6	-0.7 ± 0.2
Serotonin	8.0	6	-0.4 ± 0.3
LSDA	1.0	6	-0.8 ± 0.3
Reserpine	1.0	6	-0.1 ± 0.3

*Maximal change during a two-hour period following drug injection

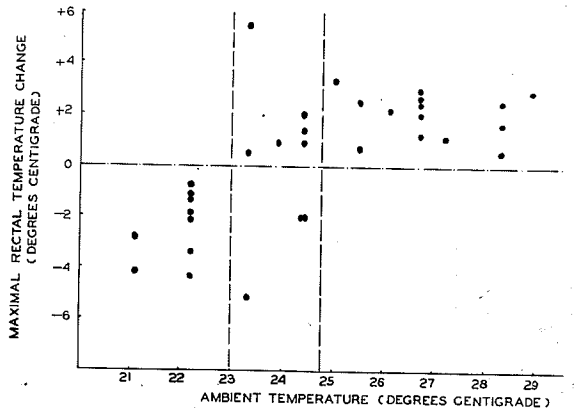

Figure 4. RELATIONSHIP OF AMBIENT TEMPERATURE TO THERMAL RESPONSES OF "CURARIZED" DOGS TO PENTYLENETETRAZOL. Maximal drug-induced changes in body temperature following intravenous administration of pentylenetetrazol (seven doses of 15 mgm/kgm at twenty-minute intervals). Each point represents observations on a single animal.

In experiments designed to ascertain the mechanisms of these responses, changes in skin and rectal temperatures, blood pressure, oxygen consumption and venous hematocrit were determined at room temperatures of 22 and 27°C. The averaged results from experiments on six dogs exposed to a room temperature of 22 ±0.5°C are presented in figure 3. Each animal was used as its own control in a separate experiment at the same ambient temperature. Rectal temperature fell an average of about 1°C in animals treated with pentylenetetrazol, while the forefoot skin temperature increased an average of about 5°C to a mean peak of 32°C. This increase usually began after administration of the second dose of the drug, reached a peak one-half to one hour after the start of drug treatment, and slowly decreased towards the pretreatment level. Skin temperature changes of the hind foot and ear were similar to those of the forefoot. The major fall in rectal temperature, which was significantly greater in the treated animals than in the controls ($P < .01$), did not begin until the skin temperature started to rise. When the skin temperature fell again, the rectal temperature tended to level off. In the control experiments, rectal temperature remained essentially constant while the forefoot skin temperature fell an average of about 5°C. The decrease in skin temperature in these animals was probably the result of a thermoregulatory response to the decreased skeletal muscle heat production and the relatively cool environment.

Oxygen consumption decreased an average of seventeen per cent in the treated animals, but this could be almost entirely attributed to a decrease in the velocity of chemical reactions with the observed fall in body temperature. Mean arterial pressure increased after each dose of drug, to as high as 200 mm Hg

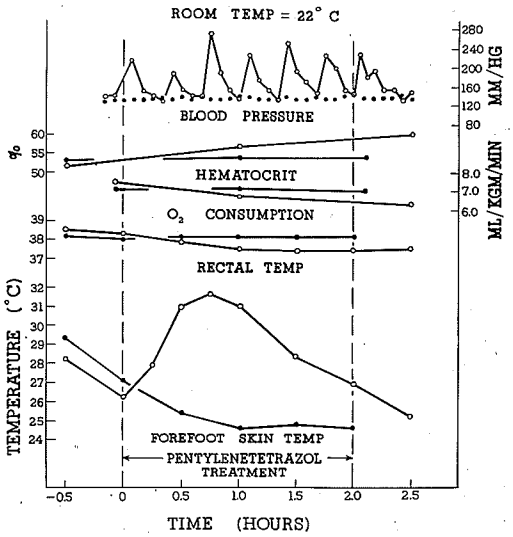

Figure 5. EFFECTS OF PENTYLENETETRAZOL ON "CURARIZED" DOGS AT AN AMBIENT TEMPERATURE OF 22°C. Solid-circled lines show the averaged results of control experiments on six animals; open-circled lines the averaged results of experiments on the same animals treated with pentylenetetrazol (seven doses of 15 mgm/kgm intravenously at twenty-minute intervals).

in some experiments, and usually returned to the preinjection level within ten minutes. The venous hematocrit increased markedly during drug administration. Blood pressure, oxygen consumption and hematocrit were essentially unchanged during the control experiments.

The averaged results from similar experiments on six dogs exposed to a room temperature of 27 $\pm$0.5°C are shown in figure 6. There was an average initial rise in skin temperature of about 3°C, which usually began after the second dose of pentylenetetrazol and reached a mean peak of 34°C about one hour after beginning treatment. This was followed by a slow fall to the predrug level. Rectal temperature rose an average of 1°C ($P < .01$) in two hours and 1.6°C in 2 1/2 hours. Unfortunately, no oxygen consumption measurements were obtained at 2 1/2 hours, but the average increase at two hours was thirty per cent. Only one-third of this increase could be attributed to an increased velocity of chemical reactions with the observed rise of body temperature. The venous hematocrit increased markedly during drug treatment. Blood pressure increased after each dose of drug, but the pressor responses were less marked during the second hour of drug administration. In the control experiments, hematocrit, oxygen consumption, blood pressure and rectal temperature remained essentially constant, while skin temperature fell slightly, but not significantly.

In similar experiments following acute spinal cord section at C_4 to C_6 (figures 7 and 8), the effects of pentylenetetrazol on rectal and skin temperatures, oxygen consumption, and venous hematocrit were absent. The drug-treated and control animals did not differ significantly with respect to any of these indices in the experiments at either 22 or 27°C. Blood pressure was either unchanged or decreased slightly after each injection of pentylenetetrazol.

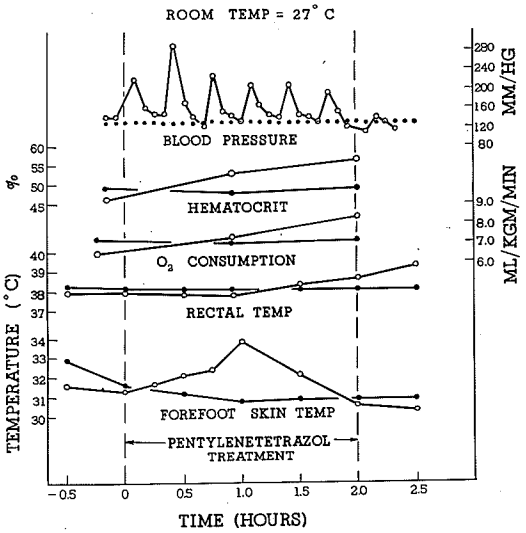

Figure 6. EFFECTS OF PENTYLENETETRAZOL ON "CURARIZED" DOGS AT AN AMBIENT TEMPERATURE OF 27°C. Solid-circled lines show the averaged results of control experiments on six animals; open-circled lines the averaged results of experiments on the same animals treated with pentylenetetrazol (seven doses of 15 mgm/kgm intravenously at twenty-minute intervals).

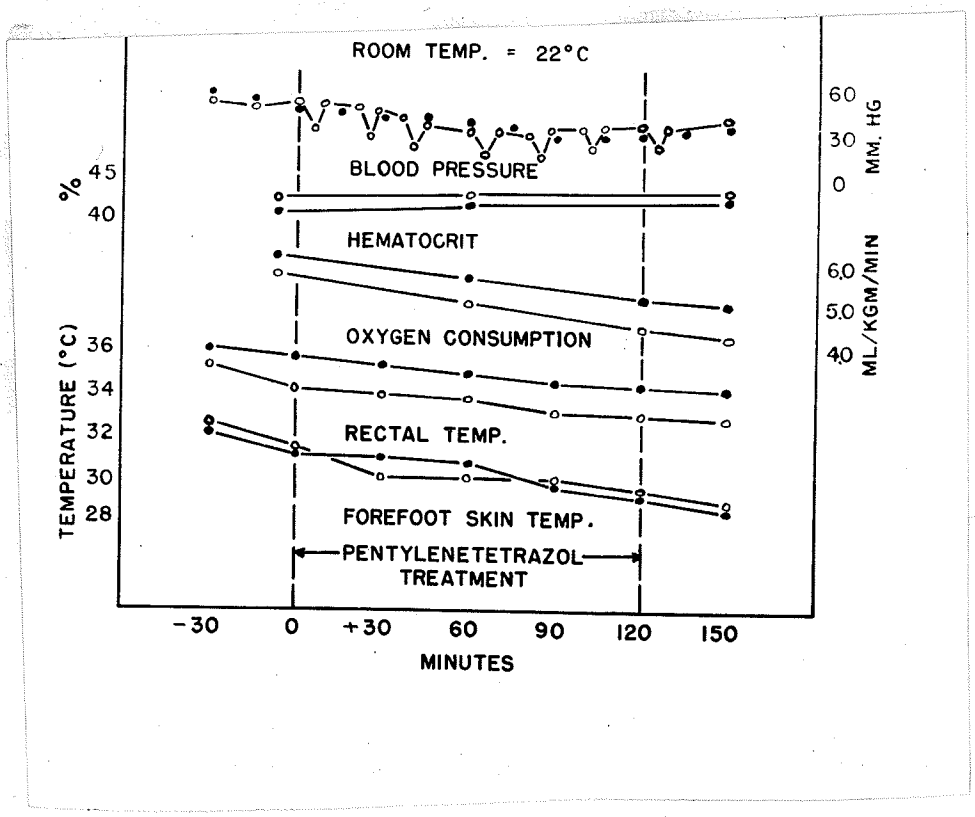

Figure 7. EFFECTS OF PENTYLENETETRAZOL ON DOGS AFTER ACUTE SPINAL CORD SECTION (C_1 to C_2) AT AN AMBIENT TEMPERATURE OF 22°C. Solid-circled lines show the averaged results of four control experiments; open-circled lines the averaged results of four experiments on animals treated with pentylenetetrazol (seven doses of 15 mgm/kgm intravenously at two thirty-minute intervals).

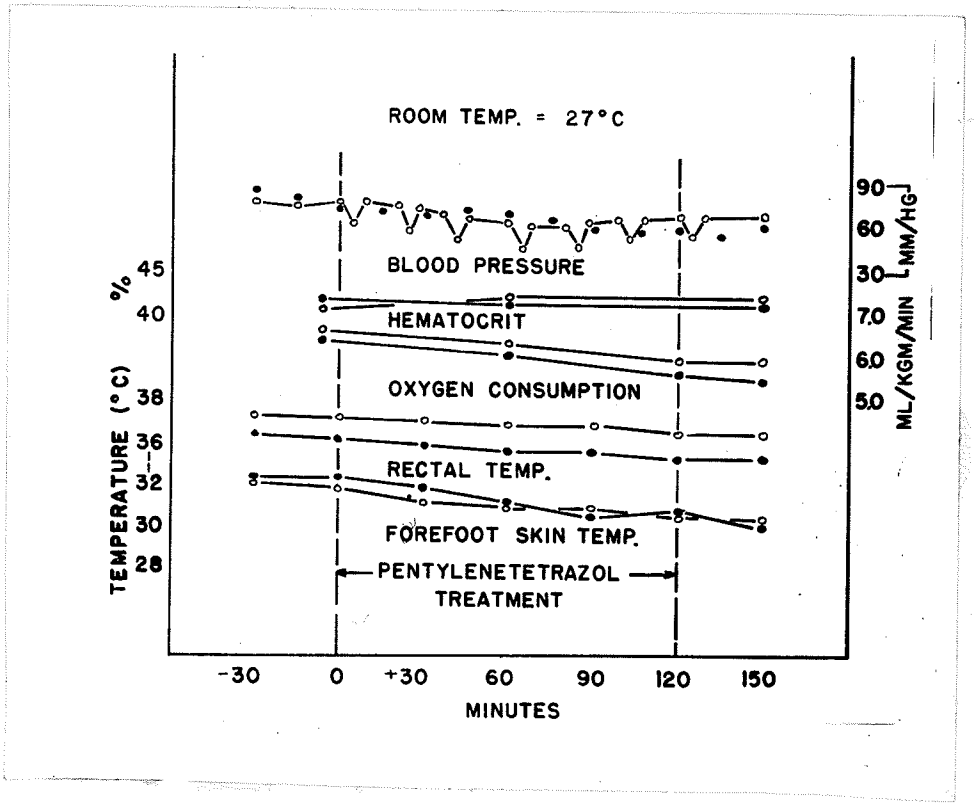

Figure 8. EFFECTS OF PENTYLENETETRAZOL ON DOGS AFTER ACUTE SPINAL CORD SECTION (C_4 to C_6) AT AN AMBIENT TEMPERATURE OF 27°C. Solid-circled lines show the averaged results of four control experiments; open-circled lines the averaged results of four experiments on animals treated with pentylenetetrazol (seven doses of 15 mgm/kgm intravenously at two-minute intervals).

Thermal Responses of "Curarized" Dogs to 2,4-Dinitrophenol

The averaged results of experiments on six dogs paralysed with a neuromuscular blocking agent and exposed to room temperatures of 18 to 20°C (± 0.5°C in each experiment) are presented in figure 9. Following dinitrophenol injection (3.0 mgm/kgm intravenously) the rectal temperature increased an average of 2.2°C, associated with a peak rise in oxygen consumption averaging 48 per cent. The increase in oxygen consumption attributable to the observed rise in body temperature was less than half of the total. The hyperthermia was associated with an average rise in skin temperature of approximately 4°C, probably a thermoregulatory response to the increased body temperature. The drug-induced rise in skin temperature occurred only when the rectal temperature rose to a peak of 40°C or above. In three treated animals in which skin temperatures did not rise and actually fell slightly, as in the control experiments, the peak rectal temperatures were below 40°C. Rectal temperature, forefoot skin temperature and oxygen consumption decreased slightly in the control experiments. Blood pressure fell slightly in both the dinitrophenol and control experiments.

In experiments on six dogs under the same conditions as above, but at room temperatures of 10 to 12°C (± 0.5°C in each experiment) dinitrophenol still elicited a relative hyperthermia (figure 10). Rectal temperatures decreased an average of 2.2°C in the control experiments, whereas no significant change occurred in the treated animals. This relative hyperthermia was associated with a peak increase in oxygen consumption averaging 36 per cent, a figure not significantly different from the peak increase at the higher room

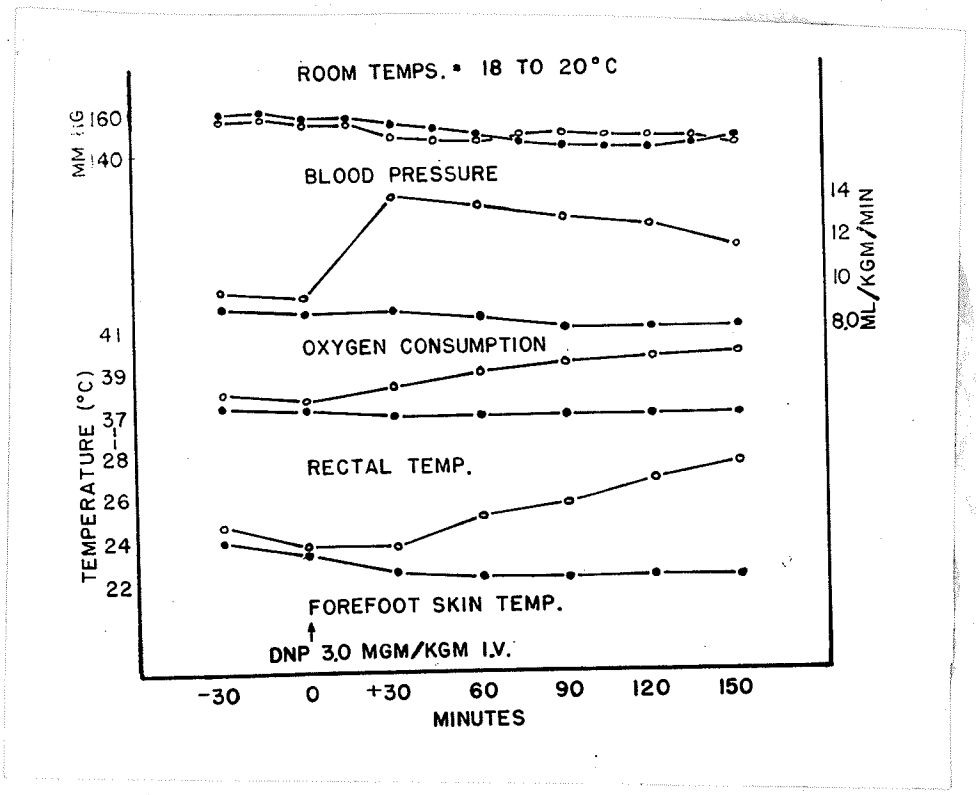

Figure 9. EFFECTS OF DINITROPHENOL ON "CURARIZED" DOGS AT AMBIENT TEMPERATURES OF 18 to 20°C. Close-circled lines show the averaged results of control experiments on six animals; open-circled lines the averaged results of experiments on the same animals treated with dinitrophenol (3.0 mgm/kgm intravenously).

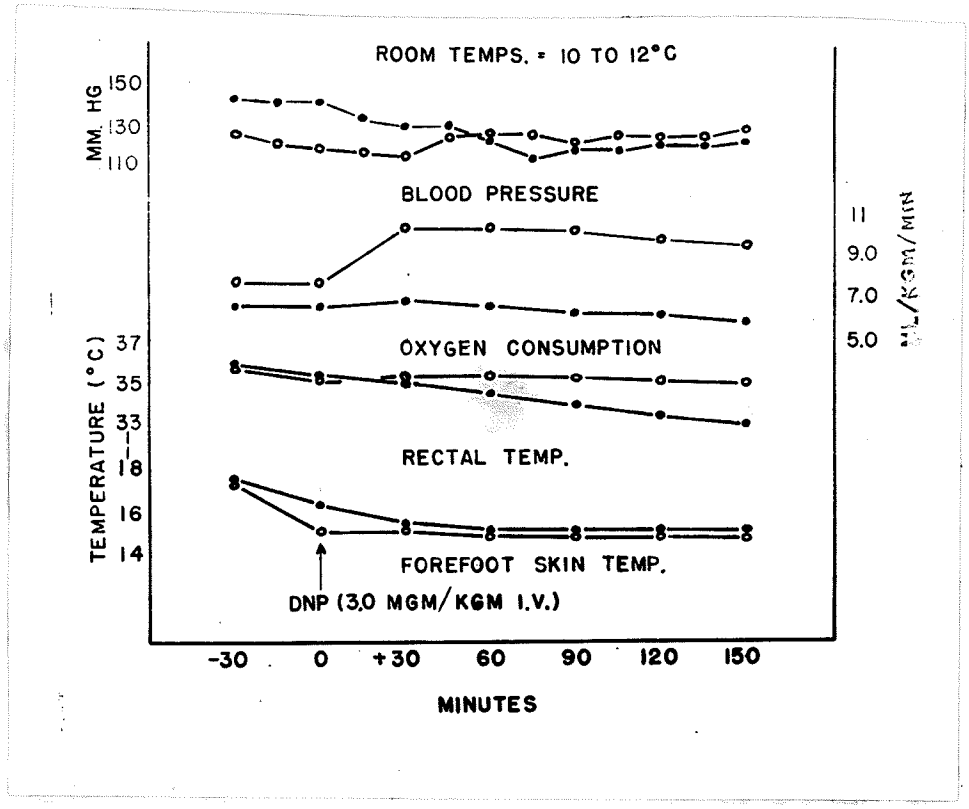

Figure 10. EFFECTS OF DINITROPHENOL ON "CURARIZED" DOGS AT AMBIENT TEMPERATURES OF 10 TO 12°C. Close-circled lines show the averaged results of control experiments on six animals; open-circled lines the averaged results of experiments on the same animals treated with dinitrophenol (3.0 mgm/kgm intravenously).

temperatures ($P > 0.5$). Skin temperature fell an average of about $2^{\circ}C$ in both the treated and control groups.

In a series of six experiments at a temperature of $18 \pm 1.0^{\circ}C$, dinitrophenol (3.0 mgm/kgm) was infused into the right common carotid artery over a period of ten minutes. These experiments were identical with those described above except for the route and rate of administration of dinitrophenol. No significant changes in rectal or skin temperature were produced by dinitrophenol administered by this route (figure 11). Oxygen consumption increased an average of eleven per cent after drug administration, significantly less ($P < .05$) than the increase in oxygen consumption caused by rapid intravenous injection of the same dose at the same ambient temperature (see figure 9).

To check whether altered potency of the drug solution and/or the different rate of administration were responsible for the significantly smaller response to dinitrophenol after intracarotid administration, two dogs were injected intravenously over a ten-minute period with 3.0 mgm/kgm of the same solution used above. The drug elicited increases in oxygen consumption of 36 and 42 per cent, essentially the same as in the experiments with rapid intravenous injection.

Thermal Responses of Lightly Restrained Dogs to 2,4-Dinitrophenol

Experiments were carried out on five lightly restrained dogs given 3.0 mgm/kgm dinitrophenol intravenously and maintained at an ambient temperature of $10^{\circ}C$. Each dog was used as its own control. Rectal temperature remained essentially constant in both control and drug-treated animals during

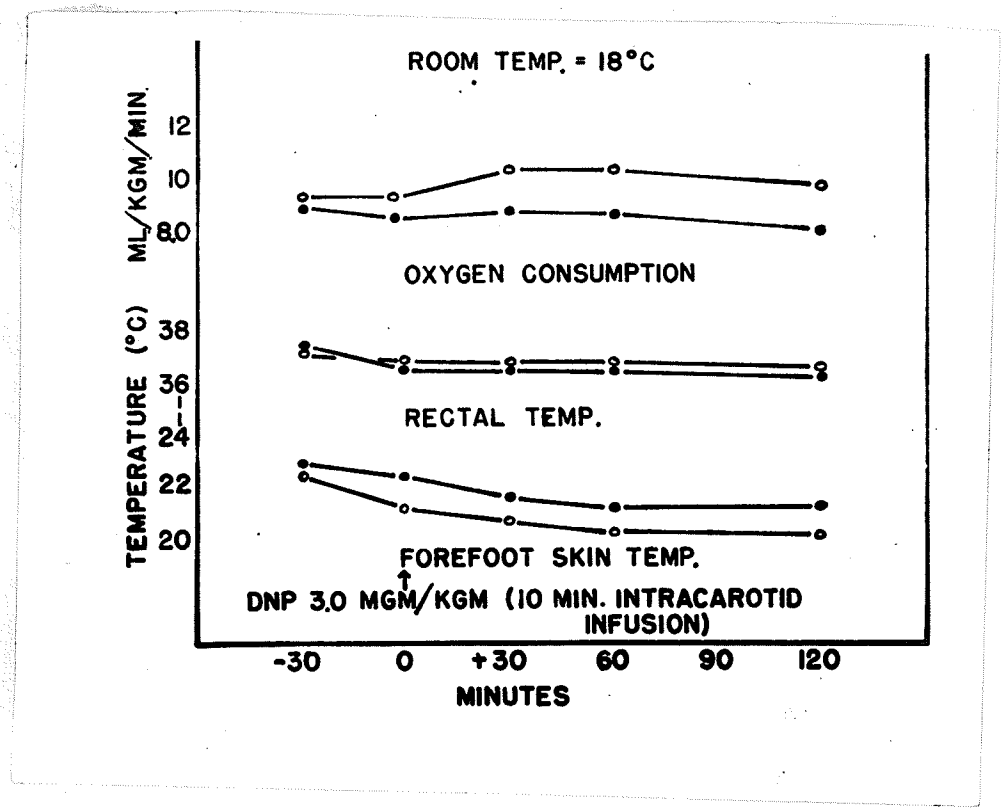

Figure 11. EFFECTS OF INTRACAROTID INFUSION OF DINITROPHENOL ON "CURARIZED" DOGS AT AN AMBIENT TEMPERATURE OF 18°C. Close-circled lines show the averaged results of control experiments on six animals; open-circled lines the averaged results of experiments on the same animals treated with dinitrophenol (3.0 mgm/kgm).

a two-hour period after injection. Visible shivering, which occurred in all animals, was not noticeably influenced by the drug.

In similar experiments on three lightly restrained dogs administered 20 mgm/kgm dinitrophenol subcutaneously (the same dose and route of administration used with rats) and exposed to an ambient temperature of $4 \pm 1.0^{\circ}C$, rectal temperature remained essentially constant in both control and drug-treated animals during a two-hour period after injection. However, it was noted that visible shivering was almost entirely abolished by this dose of drug.

Metabolic Responses of Lightly Restrained Rats to 2,4-Dinitrophenol

The results of experiments in which the effect of dinitrophenol on the oxygen consumption of lightly restrained rats was determined at water bath temperatures of 27, 23, and $17^{\circ}C$ are presented in table III. The preinjection oxygen consumption, the average of two ten-minute readings, increased as the bath temperature was lowered. This probably reflected an increasing thermogenetic response to progressively lower ambient temperatures. Dinitrophenol (20 mgm/kgm subcutaneously) caused an increase in oxygen consumption which averaged 112 per cent at $27^{\circ}C$, 53 per cent at $23^{\circ}C$ and 6 per cent at $17^{\circ}C$. These values all differ significantly from one another ($P < .05$). The drug-induced change in oxygen consumption at $17^{\circ}C$ is not significantly different from that in the control experiments ($P > 0.3$).

Colonic temperature was recorded before and one hour after dinitrophenol administration in two animals exposed to a bath temperature of $17^{\circ}C$. Each animal was used as its own control. Colonic temperature changes in

the treated animals (-2.5, -2.2°C) were similar to those in the control experiments (-2.4, -2.0°C). Hypothermia, which consistently occurs in lightly restrained, dinitrophenol-treated rats exposed to air temperatures below 20°C, was not evoked in rats exposed to a water bath temperature of 17°C, probably because the temperature within the small rat holder may have been a few degrees higher than that of the water bath due to heat given off by the rat.

Table III

Dinitrophenol-induced Changes in Oxygen Consumption of Lightly Restrained Rats at Various Ambient Temperatures

Bath Temp. (°C)	No. of Rats	Oxygen Consumption (cc/kgm/min)* Preinjection	Postinjection (maximum)	Per cent Change ± S.E
27	5	Control 26 Treated 29 Difference	27 34	+ 4 +116 +112 ± 20
23	5	Control 32 Treated 36 Difference	32 55	0 + 53 + 53 ± 4
17	5	Control 50 Treated 51 Difference	49 53	- 2 + 4 + 6 ± 4

* Determined over a ten-minute period

CHAPTER IV

DISCUSSION

Discussion of Results with Pentylenetetrazol

Pentylenetetrazol administered in repeated convulsant doses to dogs completely paralyzed with a neuromuscular blocking agent produces a consistent hyperthermia at ambient temperatures above a critical range of 23 to 25°C, and a consistent hypothermia at ambient temperatures below this range.

Increased cutaneous blood flow, measured as a rise in skin temperature, with a resulting loss of body heat, appears to play a major role in the hypothermic response to pentylenetetrazol at an ambient temperature of 22°C, whereas increased heat production appears to be the major factor in the hyperthermic response to the drug at 27°C.

In all experiments the cutaneous blood flow began to rise shortly after the beginning of pentylenetetrazol administration, reached a maximum in about one hour and then fell slowly. The mechanism of the initial increase in cutaneous blood flow has not been definitely determined, but it appears to be unrelated to changes in blood pressure for two reasons: (1) The skin temperature did not follow the blood pressure changes (a sharp rise in blood pressure followed each injection). (2) The blood pressure pattern was the same during the initial rise in skin temperature as during the subsequent fall. Therefore, the observed changes in cutaneous blood flow cannot be due to reflex changes in the caliber of the cutaneous blood vessels induced by blood pressure fluctuations. It is also apparent that cutaneous vasoconstriction is not a major component of the pressor response to pentylenetetrazol. The increased cutaneous blood flow may have been due to inhibition

of cutaneous vasoconstrictor tone, but a direct vasodilator effect (vide infra) cannot be ruled out as a possible factor. Involvement of cutaneous vasodilator nerves is unlikely because there is no convincing evidence for their existence in the dog. Bulbring and Burn (21) claimed that the dog ear is supplied with such nerves, but this conclusion is seriously questioned by the extensive work of Folkow et al. (42).

At an ambient temperature of 27°C, the hyperthermic response to pentylenetetrazol was associated with an increased heat production, measured as a rise in oxygen consumption, only one-third of which could be accounted for by the observed rise in body temperature. The possibility that the increased heat production was due to inadequate neuromuscular blockade and a consequent increase in skeletal muscle activity during the period of pentylenetetrazol administration is unlikely for two reasons: (1) Supplements of the neuromuscular blocking agent were given as needed to maintain visibly complete skeletal muscle flaccidity throughout each experiment. (2) The animals at 22°C received essentially the same amount of neuromuscular blocking agent as the animals at 27°C; yet the oxygen consumption of the former did not increase significantly after drug administration, whereas that of the latter increased consistently. For example, oxygen consumption decreased twelve and fifteen per cent respectively in two pentylenetetrazol-treated dogs at an ambient temperature of 22°C, whereas drug-induced increases in oxygen consumption of thirty-three and fourty-four per cent occurred in two comparable dogs at 27°C. The same

total dose of decamethonium iodide (1.0 mgm/kgm) was administered to each of these animals and it maintained complete skeletal muscle flaccidity in all, at least within the limits of gross observation.

The fact that spinal cord section at C_4 to C_6 abolished the calorigenic response to pentylenetetrazol at 27°C indicates that the response resulted from effects of the drug on the central nervous system above the level of section. The observation of a drug-induced, centrally-mediated increase in heat production independent of skeletal muscle activity has to our knowledge not been reported previously. The most probable explanation of the observed increase in heat production appears to be that it is due to a centrally-mediated release of adrenaline and noradrenaline from the adrenal medulla and postganglionic sympathetic nerve endings. The calorigenic action of adrenaline is well known, but the mechanisms involved have not been fully elucidated. However, its action can be attributed, at least in part, to mechanisms independent of changes in skeletal muscle tone (54). The occurrence of an increased sympathetic discharge after convulsant doses of pentylenetetrazol is evidenced in the present experiments by the sharp rise in blood pressure which followed each injection of pentylenetetrazol, probably the result of direct stimulation of the vasomotor center (63). Hahn et al. (55) also observed increased sympathetic activity following convulsant doses of pentylenetetrazol.

Increased thyroid hormone release is probably not a factor in the observed calorigenic effect of pentylenetetrazol because the latter was abolished by spinal cord section, and also because of the discrepancy

between the relatively rapid response observed and the long latent period for thyroid hormone action (48). Participation of adrenal corticoids cannot similarly be ruled out because adrenaline significantly increases the secretion of these substances in the dog and other animals (76).

Decreased cutaneous blood flow, with resulting conservation of body heat, probably does not contribute to the hyperthermia at 27°C because the skin temperatures of treated animals did not consistently decrease to levels lower than those of the controls. Hyperthermia occurred in experiments in which the skin temperature was higher than that of the control during the entire period following drug administration. The initial cutaneous vasodilatation actually may have limited the rise in body temperature, which was delayed until this had largely subsided.

The hematocrit increased markedly after drug treatment at both 27 and 22°C. These findings are not in accord with Barbour's claim of a parallelism between changes in blood "concentration" and body temperature. However, the increase in hematocrit may have been due predominantly to an increase in circulating erythrocytes rather than to a reduction in plasma volume. The increased sympathetic activity induced by the administration of convulsant doses of pentylenetetrazol probably evoked a discharge of erythrocytes from the spleen, an important reservoir in the dog (9), and might also have reduced the circulating blood volume. It is not possible to assess the relative importance of these two factors on the basis of the experiments reported above.

The present results indicate that the hyperthermic, calorigenic, pressor, and hematocrit responses to pentylenetetrazol are centrally-mediated because they are abolished by spinal cord section. However, the initial drug-induced increase in cutaneous blood flow and concomitant hypothermia cannot be definitively attributed to an action on the central nervous system, although they were abolished by high spinal cord section. This procedure is known to result in near-maximal cutaneous vasodilatation (89) and thus it might have masked a peripheral vasodilator action of pentylenetetrazol. Skin temperature averaged 32°C two hours after spinal cord section, but this does not necessarily indicate submaximal cutaneous vasodilatation for two reasons: (1) Body temperature was subnormal at this time, thus accounting in part for the relatively low skin temperature. (2) The low systemic blood pressure may have resulted in a submaximal blood flow even in a maximally dilated bed.

Finally, it is apparent that the thermal responses to pentylenetetrazol are not simply due to the production of poikilothermia because the responses of the intact animal differed markedly from those of the truly poikilothermic spinal animal.

Discussion of Results with 2,4-Dinitrophenol

Dinitrophenol produced a hyperthermia when administered to lightly restrained rats at ambient temperatures above a critical range of 20 to 22°C and a hypothermia at lower ambient temperatures. The hyperthermia is explicable on the basis of the well-known metabolic stimulation produced by this agent, confirmed in the present studies on both rats and dogs.

However, the basis for the hypothermia at lower ambient temperatures is less well established. The fact that dinitrophenol did not produce a relative hypothermia in curarized rats at an ambient temperature of 16°C suggests that the hypothermia induced in noncurarized animals is primarily due to suppression of the thermogenetic effect of increased skeletal muscle activity which normally occurs in animals exposed to low ambient temperatures. Additional evidence to support this conclusion has been presented by Ojeja (46). The present results indicate that dinitrophenol can suppress the thermogenetic response to cold in both rats and dogs but hypothermia was induced only in the former. Whether a relative hypothermia is produced at low ambient temperatures appears to depend on the balance between suppression of thermogenesis and stimulation of tissue metabolism. In lightly restrained dogs, the two factors appear to be approximately balanced, and no significant effect on body temperature occurs. Hypothermia is produced in lightly restrained rats, probably because the metabolic effect of dinitrophenol in this species is reduced at lower ambient temperatures, and because cold-induced thermogenesis is greater per unit weight in the rat than in the dog.

Dinitrophenol (20 mgm/kgm subcutaneously) produced an increase in oxygen consumption of only six per cent in lightly restrained rats at a water-bath temperature of 17°C, compared to a 53 per cent increase at 23°C and a 112 per cent increase at 27°C. It could be argued that these differences are more apparent than real because the postinjection values are about the same in all three groups, suggesting that these values represent

some metabolic ceiling. However, Tainter (97), using higher doses of dinitrophenol, observed oxygen consumption values twice the maximum reported here. The observed reduction of the metabolic effect of dinitrophenol at lower ambient temperatures can be attributed, at least in part, to inhibition of the thermogenetic response to cold. However, it appears probable that the peripheral metabolic stimulation produced by dinitrophenol is reduced in rats at lower ambient temperatures. This is indicated by the fact that the fall in body temperature of dinitrophenol-treated curarized rats is the same as that of the control animals. If the effect of dinitrophenol on tissue metabolism were not reduced at low ambient temperatures, a relative hyperthermia should have occurred. A relative hyperthermia did occur in "curarized" dogs exposed to low ambient temperatures, and in which dinitrophenol was observed to have a metabolic action comparable to that produced at higher ambient temperatures.

Several authors have reported an apparent reduction in the metabolic effect of dinitrophenol at low ambient temperatures (46,69,82,97,104). However, Hall found that dinitrophenol (10 mgm/kgm) markedly diminished shivering in cats placed in cold baths (97). He suggested that the limited increase in metabolism after dinitrophenol administration may have been due to diminution of the oxygen cost of shivering, and not necessarily to a reduced drug effect on tissue metabolism. The present results indicate that both factors are involved in the dinitrophenol-induced hypothermia in rats.

A drug-induced enhancement of heat loss cannot be ruled out as a

factor contributing to the dinitrophenol hypothermia. Such an effect could have been masked by a calorigenic action of dinitrophenol in the experiments on curarized rats. However, such an action could not be demonstrated in dogs and probably is not of importance in the rat. A rise in skin temperature accompanied the dinitrophenol-induced hyperthermia at higher ambient temperatures, but this was probably a thermoregulatory response to the increased body temperature.

In contrast to the present observation that curare abolishes the hypothermic effect of dinitrophenol in rats at moderately cold ambient temperatures, Tainter and Cutting (96) and Hegnauer et al. (69) found that dinitrophenol fever in rats and other animals is uninfluenced by curare. Thus effects on skeletal muscle activity are not a common denominator in the hypo- and hyperthermic responses to dinitrophenol.

As mentioned above, a possible central component of the metabolic action of dinitrophenol has not been ruled out by previous workers who used high doses. Sladek (93) postulated, as a result of experiments on human subjects with midbrain lesions, that a central effect is predominant at low doses (3.0 mgm/kgm), but is masked at high doses by a peripheral effect. However, the very slight response to this dose of dinitrophenol administered by intracarotid infusion indicates that any centrally-mediated metabolic effect of this agent is very weak. Indeed, the slight increase in metabolism after intracarotid dinitrophenol is probably entirely due to recirculated drug.

General Discussion

The results of the foregoing studies show that ambient temperature is a critical factor in determining thermal responses to many drugs. Investigation of a variety of agents has demonstrated the existence for each drug of a critical ambient temperature, above which hyperthermia occurred and below which hypothermia was evoked. One possible exception was reserpine, which produced a consistent hypothermia at an ambient temperature of 23°C, but somewhat inconsistent effects at higher temperatures. Bein (12) reported reserpine-induced hyperthermia in rabbits at high room temperatures, but his limited data did not reveal the consistency of this effect.

The fact that thermal responses to many drugs are dependent on ambient temperature offers a reasonable basis for explaining the conflicting results of many previous experiments. Species and dosage differences have been suggested as possible explanations by a number of workers. (See 102). These cannot be ruled out in some experiments, but cannot be invoked to explain the variability of results obtained by different investigators and even the same investigator, using the same dose and species of animal. However, species differences do occur and two were noted in the present studies: (1) Dinitrophenol produced a relative hyperthermia at all ambient temperatures from 20 to as low as 5°C in dogs paralyzed by a neuromuscular blocking agent, whereas it exerted no effect on the body temperature of curarized rats at an ambient temperature of 16°C. (2) Dinitrophenol evoked a consistent hypothermia in lightly restrained rats at ambient temperatures below 20°C, but it had no net effect on the body temperature of lightly restrained dogs at ambient temperatures

of 10 and 4°C. The basis for these species differences has been discussed in detail above.

Because changes in body temperature depend on an imbalance of heat production and heat loss, there are several mechanisms through which ambient temperature may play an important role in determining the net thermal response to a drug. Both heat loss and heat production depend to a large degree on environmental temperature. For example, drug-induced enhancement of heat loss is minimized when the ambient temperature is high, because of the reduced gradient between skin and external environment. This effect would be a continuous function of ambient temperature. On the other hand, a drug which suppresses the thermogenetic response to cold would affect body temperature only in the range of ambient temperatures at which this response is elicited. It is obvious that ambient temperature will also alter responses to any agent inducing poikilothermia.

The effect of ambient temperature on thermal responses to drugs noted in the present investigation suggests that effects of these agents involve some interference with central body temperature regulation. Even dinitrophenol, which has been assumed to have a predominantly peripheral effect of increasing heat production, depends on ambient temperature for its thermal effects. This agent has been shown to interfere with the thermogenetic defence against cold, presumably through an action on the central nervous system, and this appears to be a major factor in the hypothermia it produces in rats at ambient temperatures below 20°C. Dinitrophenol hyperthermia, on the other hand, is due almost entirely to peripheral metabolic stimulation.

as evidenced by the present intracarotid infusion experiments on dogs and the investigations of Taintor and Cutting (96) and Magno et al. (69).

It is interesting that the critical ambient temperatures for four of the seven drugs studied in the present investigation lie in the range of thermal neutrality. It is in this range of environmental temperatures that the homothermic animal normally maintains a constant body temperature with minimal physiological control. Above this range, regulation against heat is most active, and below this range, regulation against cold is of major importance. The fact that the critical ambient temperature for lysergine, ergotamine, serotonin, and LSD is 30°C suggests that these drugs may induce poikilothermia, probably by an action on the hypothalamus. The fact that these agents all appear to produce hypothermia by an effect on skeletal muscle activity, as evidenced by their failure to act in curarized rats, is consistent with this interpretation. The thermogenetic effect of increased skeletal muscle activity is the most important mechanism of defence against cold in homothermic animals, and is under central nervous system control (79).

Chlorpromazine and pentylenetetrazol are the only agents included in the present study which appear to enhance heat loss as a major component of their hypothermia action. Both produced hypothermia in curarized animals, and the fact that chlorpromazine produced hypothermia at ambient temperatures above thermoneutrality also suggests that factors other than suppression of skeletal muscle thermogenesis are involved in its action. Chlorpromazine does not appear to depress basal metabolism (26,47,78), but the possibility

that suppression of cold-induced thermogenesis may contribute to its hypothermic action is not ruled out by the present experiments. Chlorpromazine has been reported to diminish shivering in anesthetized dogs and man (37,38,84). However, the significance of this finding is questioned by observations on unanesthetized dogs and rats (23,47), and it may be attributable to the fact that chlorpromazine potentiates anesthesia induced by barbiturates and other agents (26).

The mechanism of the chlorpromazine hyperthermia at high ambient temperatures has not been elucidated, but the present investigation suggests that chlorpromazine, in common with other agents studied, interferes with central control of body temperature. The high critical ambient temperature for this drug (about 36°C) may be the resultant of enhanced heat loss superimposed on central suppression of temperature regulation.

An interesting finding was that the calorigenic effect of pentylenetetrazol noted in dogs at an ambient temperature of 27°C was absent in experiments carried out at 22°C. The metabolic stimulation produced by dinitrophenol in rats also appeared to be sharply reduced at lower ambient temperatures, although no significant reduction occurred in dogs. The mechanisms responsible for such altered responses is not clear. One possibility is that the primary effectiveness of the drugs is less at lower tissue temperatures. However, the body temperatures of the animals treated with pentylenetetrazol at 22 and 27°C were essentially the same at the beginning of drug administration, and Fuhrman and Field (44) have shown that at least some tissues (brain and kidney) are more sensitive to dinitro-

phenol at lower temperatures *in vitro*. A second possibility, for which there is at present no direct evidence, is that the drug effects are conditioned and modified by the flow of afferent impulses from cutaneous temperature receptors.

One of the points of interest in the present work is a comparison of the thermal responses to reserpine, serotonin and LSDA. Deming *et al.* (31) claimed that the hypothermic action of reserpine is mediated through serotonin and it has been implied by Brodie *et al.* (16,17) that the central effects of LSDA are a result of serotonin antagonism. Nothing conclusive can be stated concerning the relationship between reserpine and serotonin on the basis of the present studies, although the responses to the two agents were not identical. However, the finding that LSDA and injected serotonin produce qualitatively identical effects on body temperature at various ambient temperatures indicates that serotonin antagonism cannot be invoked as the mechanism of the thermal responses of rats to LSDA.

CHAPTER V

SUMMARY

1. Thermal responses to a variety of drugs at various ambient temperatures have been investigated on unanesthetised rats and dogs, either lightly restrained or paralysed with a neuromuscular blocking agent.

2. The results indicate that ambient temperature is a critical factor in determining thermal responses to many drugs. Experiments on lightly restrained rats demonstrated that the critical ambient temperature, the temperature above which hyperthermia is evoked and below which hypothermia is produced, is about 30°C (in the thermoneutral range) for Hydergine, ergotamine, LSD and serotonin. The critical ambient temperature for chlorpromazine is approximately 36°C, and that for dinitrophenol 20°C. Reserpine produced a consistent hypothermia at 23°C, but somewhat inconsistent effects at ambient temperatures above this up to 39°C. The finding of both hyper- and hypothermic effects of most of the drugs studied suggests that they influence temperature regulating centers of the central nervous system.

3. Complete curarization abolished the hypothermic effect of all the above agents except chlorpromazine.

4. Pentylenetetrazol, given in repeated convulsant doses to dogs completely paralysed with a neuromuscular blocking agent, produced a consistent hyperthermia at ambient temperatures above a critical range of 23 to 25°C, and a consistent hypothermia at lower temperatures. Increased

cutaneous blood flow, with resulting loss of body heat, appears to be the major factor in the hypothermic response to pentylenetetrazol, whereas increased heat production, independent of skeletal muscle activity, appears to be the major factor in the hyperthermic response to the drug. Experiments on dogs with the spinal cord acutely sectioned at C_4 to C_6 indicate that the thermal responses to pentylenetetrazol are of central origin, but are not simply the result of an induced poikilothermia.

5. Dinitrophenol produced a consistent hyperthermia in lightly restrained rats at ambient temperatures above 20 to 22°C, and a hypothermia at lower temperatures. Curare abolished the hypothermia, suggesting that it is largely due to suppression of the thermogenetic effect of increased skeletal muscle activity. The effect of the reduced thermogenetic response is readily observed in lightly restrained rats because the metabolic stimulation produced by dinitrophenol in rats appears to be reduced at low ambient temperatures. This is suggested by the observed smaller net increase in oxygen consumption at lower temperatures and by the finding that dinitrophenol does not produce a relative hyperthermia in curarized rats at an ambient temperature of 16°C.

In contrast to its effects in rats, dinitrophenol in doses of 3.0 and 20 mgm/kgm did not affect the body temperature of lightly restrained dogs at low ambient temperatures (10 and 4°C). Visible shivering was not noticeably influenced by the dose of 3.0 mgm/kgm but was greatly diminished by 20 mgm/kgm. A relative hyperthermia was produced in dogs completely paralyzed with a neuromuscular blocking agent at all ambient temperatures studied (5 to 20°C). The hyperthermia was due to increased heat production

which was not significantly different at different ambient temperatures.

6. Intracarotid infusion of a small dose of dinitrophenol over a ten-minute period produced a much smaller increase in oxygen consumption than did intravenous administration of the same dose, indicating that an action on the central nervous system is not an important component of dinitrophenol-induced metabolic stimulation.

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Effects of Pentylenetetrazol on "Curarized" Dogs at an Ambient Temperature of 22°C

			Time (Hours)													
	Dog No.	Body Wt.	-0.5		0 Begin Drug**		+0.5		1.0		1.5		2.0 End Drug		2.5	
			C*	T	C	T	C	T	C	T	C	T	C	T	C	T
Rectal Temperature (°C)	1	9.3	38.1	38.2	38.0	38.1	38.3	38.0	38.3	37.6	38.3	37.6	38.2	37.5		37.2
	2	10.0	39.0	39.2	39.0	39.0	39.1	38.6	39.0	37.9	39.0	38.0	39.0	38.0		38.1
	3	10.3	38.1	39.2	38.2	39.0	38.4	38.6	38.5	38.0	38.6	37.9	38.7	38.0		38.3
	4	11.2	37.4	38.5	36.9	37.3	37.2	37.2	37.2	36.2	37.3	36.2	37.4	36.2		36.3
	5	10.0	38.3	38.8	38.2	38.8	38.4	38.5	38.4	37.7	38.3	37.9	38.2	38.0		38.2
	6	9.4	37.4	37.3	37.0	36.9	37.1	36.8	37.0	36.4	36.9	35.5	37.0	35.3		34.9
	Average		38.1	38.5	38.0	38.2	38.1	38.0	38.1	37.3	38.1	37.2	38.1	37.2		37.2
Forefoot Skin Temperature (°C)	1		26.3	26.0	25.0	25.6	24.5	29.6	24.2	27.7	24.5	24.6	24.2	24.2		23.7
	2		30.5	26.5	30.1	24.3	26.1	33.0	24.0	34.5	23.3	27.4	23.4	26.1		23.0
	3		33.9	32.5	28.3	28.2	25.3	34.2	23.5	35.5	23.1	32.0	22.5	31.0		27.7
	4		28.2	28.2	27.6	25.4	26.5	31.4	25.3	28.5	25.7	26.0	25.6	24.7		24.1
	5		28.5	28.0	26.2	27.6	26.0	28.7	25.9	31.1	26.7	28.1	26.7	26.7		25.4
	6		28.5	28.0	26.0	26.0	24.5	29.3	23.4	29.0	23.7	31.5	24.0	29.3		27.5
	Average		29.3	28.2	27.2	26.2	25.5	31.0	24.4	31.1	24.5	28.3	24.4	27.0		25.2
Oxygen Consumption ml/kgm/min	1				6.4	6.8			6.5	6.2			6.6			5.8
	2				7.6	8.0			7.6	6.9			7.4			6.8
	3				7.8	8.2			8.1	8.3			8.0			7.2
	4				7.6	7.9			7.2	7.4			7.1			6.8
	5				7.4	7.7			8.0	7.0			7.6			6.5
	6				6.3	6.7			6.3	6.0			6.4			5.5
	Average				7.2	7.6			7.3	6.9			7.2			6.4
Venous Hematocrit (%)	1				53	51			50	37			51			60
	2				47	44			45	50			46			54
	3				48	44			47	52			48			55
	4				52	48			50	55			50			60
	5				50	47			48	53			49			58
	6				46	42			45	50			45			52
	Average				49	46			47	53			48			57

* C = Control; T = Treated

** Seven doses of 15 mgm/kgm intravenously at twenty-minute intervals

Effects of Pentylenetetrazol on "Curarized" Dogs at an Ambient Temperature of 27°C

	Dog No.	Body Wt.	Time (Hours) -0.5		0 Begin Drug**		+0.5		1.0		1.5		2.0 End Drug		2.5	
			C*	T	C	T	C	T	C	T	C	T	C	T	C	T
Rectal Temperature (°C)	1	6.0	37.6	37.3	37.5	37.2	37.6	37.0	37.5	37.2	37.5	37.7	37.5	38.2	37.5	38.5
	2	11.5	37.8	38.0	37.7	37.8	37.7	37.8	37.8	37.5	37.8	37.9	37.7	38.3	37.7	39.0
	3	10.0	40.4	39.0	40.3	39.0	40.4	38.4	40.4	38.5	40.4	39.9	40.3	40.8	40.3	41.9
	4	7.2	38.2	38.0	38.0	37.5	37.8	37.5	37.8	37.2	37.7	37.3	37.5	37.4	37.6	38.1
	5	11.0	37.3	38.5	37.1	38.5	37.1	38.2	37.1	38.5	37.1	39.0	37.1	39.4	37.1	40.3
	6	8.3	38.0	37.5	38.0	37.9	38.0	37.9	38.0	37.9	38.0	38.3	38.0	39.0	38.0	39.7
	Average		38.2	38.0	38.1	38.0	38.1	37.8	38.1	37.8	38.1	38.4	38.0	38.9	38.0	39.6
Forefoot Skin Temperature (°C)	1		32.0	32.3	30.3	31.6	29.9	33.7	29.5	32.7	29.5	31.6	29.8	30.8	29.5	30.0
	2		33.8	31.1	32.4	30.4	31.8	30.8	31.2	33.8	31.5	32.3	31.9	30.3	31.8	29.2
	3		35.8	34.9	35.3	34.8	35.2	35.2	35.5	37.3	35.7	33.2	35.9	30.9	35.8	32.4
	4		32.8	31.6	33.1	29.6	32.6	29.7	32.0	32.9	31.9	31.5	32.0	30.7	31.8	29.5
	5		29.0	29.8	28.0	30.2	27.0	31.2	26.7	32.5	26.5	33.8	26.6	31.9	26.4	30.6
	6		34.0	30.6	31.9	31.2	31.4	32.3	31.0	33.9	30.9	32.7	31.2	30.8	31.0	30.5
	Average		32.9	31.7	31.8	31.3	31.3	32.1	31.0	33.9	31.0	32.5	31.2	30.9	31.1	30.3
Oxygen Consumption ml/kgm/min	1				6.6	5.9			6.2	6.5			6.6	7.6		
	2				7.2	7.3			7.2	7.9			7.2	8.6		
	3				8.0	7.0			7.1	7.5			7.4	9.6		
	4				6.5	6.1			6.7	6.9			6.9	8.3		
	5				7.6	7.1			7.6	8.0			7.2	9.1		
	6				7.1	6.8			7.2	7.3			7.1	8.8		
	Average				7.2	6.7			7.0	7.4			7.1	8.7		
Venous Hematocrit (%)	1				54	49			51	56			53	60		
	2				45	41			44	47			43	50		
	3				52	49			50	54			54	57		
	4				47	44			48	54			48	56		
	5				51	47			50	54			52	56		
	6				51	46			48	52			50	57		
	Average				50	46			49	53			50	56		

* C = Control; T = Treated

** Seven doses of 15 mgm/kgm intravenously at twenty-minute intervals

Effects of Pentylenotetrazol on Dogs after Acute Spinal Cord Section (C_4 to C_6) at an Ambient Temperature of 22°C

	Dog No.		Body Wt.		Time (Hours)													
					-0.5		0 Begin Drug**		+0.5		1.0		1.5		2.0 End Drug		2.5	
	C*	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
Rectal Temperature (°C)	1	5	7.6	10.0	36.0	33.3	35.7	32.3	35.3	32.0	35.0	31.8	34.5	31.2	34.3	31.0	33.8	30.8
	2	6	6.0	7.1	36.2	36.4	35.9	35.7	35.7	35.3	35.0	35.0	34.7	34.6	34.3	34.5	34.0	34.3
	3	7	6.0	6.8	37.0	36.1	36.9	35.3	36.8	35.0	36.5	34.7	36.2	34.1	36.0	34.0	35.9	33.9
	4	8	8.3	7.2	35.0	35.1	34.3	34.2	34.0	33.8	33.7	33.7	33.2	33.1	32.9	32.9	32.3	32.6
	Average				36.0	35.2	35.7	34.4	35.4	34.0	35.0	33.8	34.6	33.2	34.4	33.1	34.0	32.9
Forefoot Skin Temperature (°C)	1	5			32.7	30.9	31.2	29.8	30.2	28.5	30.6	28.2	29.3	26.0	28.7	27.4	27.9	26.8
	2	6			31.0	33.9	30.5	33.2	30.5	32.1	30.2	32.1	29.2	32.0	28.5	31.5	27.5	30.8
	3	7			33.7	32.8	32.3	32.3	32.5	31.0	31.9	31.0	30.7	30.6	30.2	30.2	30.0	29.4
	4	8			31.7	32.6	31.2	31.4	30.7	30.1	30.2	29.9	29.7	29.5	29.0	29.0	28.5	28.4
	Average				32.3	32.5	31.3	31.7	31.0	30.4	30.7	30.3	29.7	30.0	29.1	29.5	28.5	28.8
Oxygen Consumption (ml/kgm/min)	1	5					5.6	5.0			5.4	4.2			5.1	3.8	5.1	3.8
	2	6					7.2	6.2			6.8	5.5			6.2	4.9	5.7	4.6
	3	7					6.5	6.6			6.4	5.9			5.8	5.3	6.0	5.1
	4	8					5.5	5.6			4.2	4.9			3.6	4.1	3.6	3.8
	Average						6.2	5.8			5.7	5.1			5.2	4.5	5.1	4.3
Venous Hematocrit (%)	1	5					43	45			44	47					44	46
	2	6					42	42			40	42					42	43
	3	7					46	43			45	41					48	43
	4	8					34	44			38	43					38	45
	Average						41	43			42	43					43	44

*C = Control; T = Treated

**Seven doses of 15 mgm/kgm intravenously at twenty-minute intervals

Effects of Pentylenetetrazol on Dogs after Acute Spinal Cord Section (C_4 to C_6) at an Ambient Temperature of 27°C

					Time (Hours)													
	Dog No.		Body Wt.		-05		0 Begin Drug**		-0.5		1.0		1.5		2.0 End Drug		2.5	
	C*	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
Rectal Temperature (°C)	1	5	7.6	8.0	38.9	37.0	38.8	36.9	38.2	36.8	38.1	36.8	38.2	36.7	38.0	36.5	38.0	36.4
	2	6	10.8	6.9	35.7	35.9	35.5	35.9	35.4	35.5	35.3	35.1	35.2	34.9	34.9	34.8	34.5	34.8
	3	7	9.2	7.8	35.2	38.3	35.0	38.2	35.0	38.1	34.4	38.1	34.4	38.1	34.0	38.0	34.1	38.0
	4	8	8.6	10.2	36.0	38.0	35.7	37.8	35.2	37.2	34.6	37.0	34.5	36.7	34.1	36.2	34.2	36.2
	Average				36.4	37.3	36.2	37.2	35.9	36.9	35.6	36.7	35.6	36.6	35.2	36.4	35.2	36.4
Forefoot Skin Temperature (°C)	1	5			32.6	32.4	32.4	32.2	32.4	31.9	31.6	30.6	31.0	29.8	31.2	29.5	30.6	29.5
	2	6			30.9	31.8	30.2	31.8	29.7	31.3	29.5	31.3	29.0	31.2	29.3	31.0	29.0	30.9
	3	7			33.2	31.8	33.1	30.9	32.6	29.8	31.8	29.7	31.0	29.5	31.2	29.3	30.3	29.0
	4	8			33.5	32.8	33.5	32.6	32.9	32.2	32.3	32.4	31.4	32.2	31.7	32.0	31.1	31.8
	Average				32.6	32.2	32.3	31.9	31.9	31.3	31.3	31.0	30.6	30.7	30.8	30.4	30.2	30.3
Oxygen Consumption (ml/kgm/min)	1	5					5.4	6.8			5.0	6.4			4.8	6.4	4.8	6.4
	2	6					7.0	5.6			6.4	5.6			5.9	5.1	5.4	5.0
	3	7					6.6	6.2			6.3	6.2			5.7	6.0	5.7	6.0
	4	8					6.4	7.4			6.1	7.0			5.8	6.0	5.6	6.1
	Average						6.4	6.5			6.0	6.3			5.6	5.9	5.4	5.9
Venous Hematocrit (%)	1	5					42	40			42	41					44	40
	2	6					40	41			40	38					38	39
	3	7					44	39			42	40					42	39
	4	8					39	41			41	47					40	46
	Average						41	40			41	42					41	41

* C = Control; T = Treated

** Seven doses of 15 mgm/kgm intravenously at twenty-minute intervals

Effects of Dinitrophenol in "Curarized" Dogs at Ambient Temperatures of 18 to 20°C

			Time (Minutes)													
	Dog No.	Body Wt. (kgm)	-30		0**		+30		60		90		120		150	
			C*	T	C	T	C	T	C	T	C	T	C	T	C	T
Rectal Temperature (°C)	1	9.8	39.0	39.0	38.8	38.8	39.0	39.2	38.8	39.6	39.2	39.8	39.0	39.8	38.9	39.9
	2	8.6	37.8	38.0	38.2	37.7	37.3	38.2	37.2	38.9	37.1	38.7	37.0	40.0	37.0	40.0
	3	9.8	36.6	38.0	36.4	37.8	36.3	38.0	36.5	39.8	36.7	40.1	36.8	40.3	36.8	40.7
	4	5.6	36.2	37.5	35.9	37.3	35.7	37.7	35.8	38.8	35.9	39.9	36.1	40.7	36.3	41.4
	5	4.8	37.0	38.6	36.7	38.3	36.3	39.3	36.1	39.7	35.8	39.8	35.7	39.8	35.4	39.8
	6	6.0	37.4	37.0	37.1	36.5	37.0	38.8	36.9	38.2	36.9	37.1	36.8	37.0	36.7	37.0
	Average		37.2	38.0	37.2	37.7	36.9	38.4	36.9	39.0	36.9	39.4	36.9	39.6	36.9	39.8
Forefoot Skin Temperature (°C)	1		24.4	24.0	23.7	23.0	22.7	22.7	22.6	22.3	22.5	22.0	22.5	22.3	22.5	24.4
	2		28.4	26.1	28.2	25.2	27.6	24.7	27.0	28.9	26.8	29.8	26.7	32.7	26.5	33.0
	3		25.0	25.4	25.3	25.4	23.3	26.4	23.2	28.0	22.9	29.2	22.7	32.2	22.4	33.5
	4		25.2	23.8	23.8	23.1	22.9	24.6	22.5	28.5	22.5	30.0	22.5	31.4	22.3	31.7
	5		22.0	25.9	21.3	23.9	21.0	22.3	21.0	21.3	21.0	20.7	21.3	20.6	21.6	20.6
	6		20.2	23.8	19.2	23.0	18.8	22.7	18.8	22.8	18.9	23.0	19.2	22.8	19.4	22.7
	Average		24.2	24.8	23.6	23.9	22.7	23.9	22.3	25.3	22.4	25.8	22.5	27.0	22.4	27.7
Oxygen Consumption (ml/kgm/min)	1		10.4	10.6	10.4	10.4	10.1	14.0	9.7	13.2	9.0	12.9	8.9	11.7	8.9	10.4
	2		7.3	8.6	6.5	8.6	6.7	12.4	6.4	12.4	6.5	13.2	6.2	12.2	6.2	10.8
	3		6.2	7.5	6.2	7.5	7.5	12.2	7.5	12.2	6.3	11.8	6.3	11.8	6.5	10.6
	4		10.2	10.0	9.6	10.0	9.0	19.0	9.0	18.0	9.0	17.4	9.0	16.8	9.0	16.2
	5		11.0	12.8	11.0	12.1	10.6	17.1	10.0	15.5	10.0	14.6	10.3	13.8	10.6	12.1
	6		9.1	9.2	8.8	8.7	9.0	10.1	8.6	10.9	8.2	9.6	8.2	9.6	8.0	9.2
	Average		9.0	9.8	8.7	9.5	8.8	14.1	8.5	13.7	8.8	13.2	8.9	12.7	8.9	11.6

* C = Control; T = Treated

** Dinitrophenol (3.0 mgm/kgm) injected intravenously

Effects of Dinitrophenol on "Curarized" Dogs at Ambient Temperature of 10 to 12°C

	Dog No.	Body Wt. (kgm)	Time (Minutes) -30 C*	-30 T	0** C	0** T	+30 C	+30 T	60 C	60 T	90 C	90 T	120 C	120 T	150 C	150 T
Rectal Temperature (°C)	1	8.1	36.2	36.4	36.0	35.9	35.8	36.1	35.7	36.2	35.2	35.9	34.8	35.8	34.2	35.7
	2	9.4	35.6	34.2	35.4	33.4	35.2	32.7	35.1	32.2	34.8	31.7	34.5	31.4	34.4	31.0
	3	9.1	36.2	35.4	35.3	35.1	34.9	35.6	34.2	36.0	33.8	36.2	32.7	36.2	31.8	36.2
	4	10.2	33.8	36.4	33.1	36.0	32.2	36.2	31.2	36.5	30.4	36.7	29.8	36.5	29.4	36.2
	5	12.6	37.8	36.8	37.8	36.5	37.5	36.3	37.2	36.4	37.0	36.6	36.8	36.7	36.2	36.8
	6	6.0	33.6	35.3	34.8	34.4	34.3	34.5	33.9	34.3	33.5	34.1	33.3	34.0	33.2	33.8
	Average		35.9	35.8	35.4	35.2	35.0	35.2	34.5	35.3	34.1	35.2	33.6	35.1	33.2	35.0
Forefoot Skin Temperature (°C)	1		18.0	15.3	16.8	14.3	16.4	14.0	16.0	14.0	15.8	13.9	15.7	13.9	15.5	14.4
	2		17.9	17.3	15.0	17.3	13.5	16.6	12.5	16.3	12.1	15.9	12.1	15.6	12.1	15.2
	3		13.8	17.2	13.5	15.3	13.2	13.6	13.3	13.0	13.7	12.8	13.8	13.1	13.8	13.2
	4		17.0	17.3	16.2	16.0	15.0	15.3	14.0	15.0	13.8	15.0	14.0	14.8	14.0	14.8
	5		20.0	17.7	19.0	15.2	17.7	14.3	17.7	14.0	17.4	14.0	17.2	14.0	16.9	13.8
	6		19.4	19.0	18.6	18.2	18.1	17.7	17.7	17.3	17.3	17.0	17.3	16.2	17.2	16.2
	Average		17.6	17.4	16.5	16.1	15.6	15.3	15.2	15.0	15.0	14.9	15.0	14.9	14.9	14.9
Oxygen Consumption (ml/kgm/min)	1		7.2	8.6	8.2	8.6	8.6	11.2	8.8	11.2	8.5	10.9	8.0	10.5	6.8	10.3
	2		6.4	6.2	6.1	6.2	6.1	6.8	5.8	6.8	5.5	6.7	5.5	6.7	5.8	6.7
	3		6.8	8.2	6.6	8.2	7.2	10.9	6.9	12.8	6.6	15.6	6.0	14.8	6.0	12.8
	4		6.0	8.2	5.5	8.2	5.1	13.3	4.2	12.1	4.6	10.1	4.2	10.1	4.0	10.1
	5		3.9	4.2	3.9	4.8	3.9	6.6	3.9	5.8	3.9	5.8	3.9	5.5	3.6	5.5
	6		9.4	10.4	9.8	10.4	10.0	12.1	9.2	12.1	9.2	12.1	8.8	11.8	8.8	11.8
	Average		6.6	7.6	6.7	7.7	6.8	10.2	6.5	10.0	6.4	10.2	6.1	9.9	5.8	9.6

* C = Control; T = Treated

** Dinitrophenol (3.0 mgm/kgm) injected intravenously

Effects of Intracarotid Dinitrophenol on "Curarized" Dogs at an Ambient Temperature of 18°C

	Dog No.	Body Wt. (kgm)	Time (Minutes) -30 C*	-30 T	0** C	0** T	+30 C	+30 T	60 C	60 T	120 C	120 T
Rectal Temperature (°C)	1	6.0	37.4	37.2	37.0	37.0	37.0	37.0	36.9	37.0	36.8	36.8
	2	6.8	37.6	37.9	37.2	37.7	37.3	38.0	37.0	37.9	36.7	37.7
	3	9.2	38.2	38.5	37.6	37.8	37.6	37.5	37.4	37.2	37.2	37.0
	4	5.2	36.0	35.1	35.3	34.7	35.5	34.2	35.5	33.9	35.4	33.6
	5	5.8	37.0	37.2	36.4	36.5	36.3	37.0	36.2	37.2	36.0	37.3
	6	8.4	36.1	37.3	35.5	36.7	35.5	36.6	35.4	36.7	35.2	36.6
	Average		37.0	37.2	36.5	36.7	36.5	36.7	36.4	36.6	36.2	36.5
Forefoot Skin Temperature	1		22.9	22.4	22.2	21.5	21.4	21.0	21.0	20.8	20.8	20.0
	2		23.3	21.5	22.8	21.0	22.0	20.4	21.7	20.2	21.4	20.0
	3		25.1	24.0	23.9	21.5	23.2	21.0	22.8	20.5	22.4	19.9
	4		22.8	22.6	22.6	21.0	22.0	20.7	22.0	20.4	22.0	20.1
	5		22.2	23.7	22.0	22.5	21.2	21.7	20.6	21.5	20.2	21.1
	6		22.0	22.5	21.3	20.3	20.6	19.8	20.3	19.5	20.0	19.2
	Average		23.0	22.8	22.5	21.3	21.7	20.8	21.4	20.4	21.1	20.0
Oxygen Consumption (ml/kgm/min)	1		9.0	9.4	9.0	9.6	9.2	9.8	8.8	10.3	8.6	10.3
	2		8.6	9.2	8.0	9.0	8.6	11.2	8.4	11.2	8.0	10.6
	3		7.8	8.1	7.4	8.2	7.6	8.8	7.0	8.2	6.8	7.8
	4		10.3	10.9	10.2	10.8	10.2	10.6	10.0	10.6	9.8	10.2
	5		9.4	9.3	9.2	9.5	9.6	11.8	9.2	11.7	8.8	11.3
	6		8.2	8.3	8.0	8.2	8.4	9.3	8.0	9.0	7.8	8.8
	Average		8.8	9.2	8.6	9.2	8.9	10.2	8.6	10.2	8.3	9.8

* C = Control; T = Treated

** Dinitrophenol (3.0 mgm/kgm) infused through right common carotid artery over a ten-minute period