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Responses of Normoglycemic, Hypoglycemic And Hyperglycemic Rats to Thermal Stress

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CERTIFICATE

The work embodied in this dissertation entitled "Responses of Normoglycemic, Hypoglycemic and Hyperglycemic Rats to Thermal Stress" has been conducted in the School of Environmental Sciences, Jawaharlal Nehru University, New Delhi-110057. This work is original and has not been submitted in part or full to this or any other University for any other Degree or Diploma.

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INTRODUCTION

INTRODUCTION

The effect of reduced oxygen in the blood on body's regulatory responses to thermal stress are well documented. The recent findings of Bhatia et al (1969), that the change in body temperature at ambient temperature below and above the neutral temperature is related to the reciprocal of atmospheric pressure suggests that the degree of the disturbance of thermoregulation is inversly related to the oxygen tension in the blood. Since, the normal functions of the cell depend upon the availability of the oxygen as well as of the substrate, changes in the glucose levels in the cell should be reflected in the regulatory responses to thermal stress. Changes in blood glucose are likely to influence the thermal tolerance and thermoregulation through their effect on the thermoregulatory centre in the hypothalamus or/and on the effector mechanisms involved in the maintenance of normal body temperature. Although, a few workers have reported reduced tolerance to cold in diabetic (Poe et al 1963 , Ahmad et al 1976), and insulin (Cassidy et al, 1925) treated animals, very little information is available on the underlying mechanisms.

The present study was carried out on the responses of normoglycemic rats and those treated with glucose, streptozotocin and insulin on exposure to high and low ambient temperatures. The objective was to determine (a) the changes in thermal tolerance brought about by different treatments, (b) whether the observed changes could be attributed to disturbance

in thermal regulation and (c) whether the alteration in thermoregulatory responses could be related to the magnitude and direction of blood glucose levels on exposure to thermal stress in animals with different treatments. Disturbance in thermoregulation was indicated by the change in rate of fall or rise of rectal temperature on exposure to low or high ambient temperatures respectively. The cold tolerance was determined in terms of the survival of the animals to low ambient temperatures and the susceptibility of the limbs to cold injury on exposure to freezing mixtures. The tolerance to heat was measured in terms of survival time of the animal exposed to high ambient temperatures.

REVIEW OF LITERATURE

(A) THERMOREGULATORY RESPONSES TO ACUTE COLD EXPOSURE

Exposure to cold elicits a variety of responses in the homeotherm, which are in general homeostatic mechanisms. After a few minutes exposure to acute cold stress the following events take place. There is cutaneous vasoconstriction, which permits the temperature of the skin and deeper layers under the skin to fall, thus reducing the heat loss from the surface to the environment. The effective thickness of the body shell is increased and this decreases conductivity from the interior. This is achieved by shift of blood from the shell to the core. This means that there must be an increase of blood in the viscera. However, there is an occasional increase in blood flow which increases the temperature of the skin. Lewis (1930), termed this fluctuation in temperature the 'hunting' phenomenon. The phenomenon is most consipicuous on the palm of the hand and on the fingers and toes and it is also observed in the arterio-venous anastomoses in the ear (Grant and Bland, 1931; Fox,1961).

There is a paradoxical increase in heart rate as shown in experiments with man (Smith et al, 1962) and with cats and rodents (Lipp et al, 1960). According to Glasser and Whittow (1957), the systolic blood pressure rises approximately by 18% and the diastolic blood pressure by about 33%; the heart rate rises by 14%. The pulmonary ventilation increases. Piloer-ection takes place which tends to increase the insulation.

There is an increased electrical activity in skeletal muscles which gradually leads to full development of shivering response. As a result of shivering the metabolic rate increases in both the man and dog 3 or 4 folds.

There is a release of norepinephrine and epinephrine from the adrenal medulla. Neurohumoral activation of the hypothalamus brings about the release of anterior pituitary hormones, especially those stimulating the thyroid and adrenal cortex.

All the above result from stimulation of skin cold receptors which bring about reflex response tending to conserve heat.

(B) ENDOCRINE CHANGES DURING ACUTE COLD EXPOSURE

Cold acts as a stress to homeothermic animals. When intially cooled, the homeothermic animal calls upon all its thermoregulatory mechanism, chemical as well as physical. A slight decrease in the body temperature of homeotherms usually leads to a pronounced "stress response" (Sarajas et al, 1967). Deep hypothermia decreases the release of all hormones (Bigelow and Sidlofsky, 1961).

a) Thyroid gland

Thyroid activity has been examined by many workers and the majority of results obtained indicate that an increased thyroid secretion results from exposure to low environmental temperature. Leblond et al (1944) and Starr and Roskelly (1940),

observed thyroid hyperactivity only at the beginning of cold exposure, but according to Cottle and Carlson (1956); and Woods and Carlson (1956), this hyperactivity persists during exposures of 2-6 months. The thyroid has an increased activity during the initial stages of cooling (Sundsten et al, 1966) and the plasma protein - bound iodine is increased (Gale et al, 1970), but when the body temperature is decreased to 15 C or lower the uptake of labeled iodine is inhibited (Popovic and Vidovic,1951). The moderate hypothermia (31C) which develops during preoptic warming in animals leads to an increase in the protein-bound iodine as soon as hypothalamic warming is interrupted(Andersson et al,1962). The role of thyroid hormone in the resistance to cold is confirmed by Leblong (1943). Thus, adult rats thyroidectomized two weeks pregiously die within a week at 2 C, while normal thyroidectomized and thyroxine treated thyroidectomized rats survive for several weeks at the same temperature.

b) Pancreas

It is well known that hibernating animals are hypoglycemic during their winter sleep. In this state there is a marked accumulation of secretion granules in the islet cells of the pancreas (Gabe et al, 1963). The fact that insulin simultaneously reduces the blood sugar level and the temperature of the body exposed to cold is known for many years. Insulin stops shivering if the blood sugar level is sufficiently reduced (Cassidy et al, 1925; Silvette and Britton, 1932). As early as 1925 Cassidy wrote of a "state simulating hibernation" when describing the effect of insulin.

When the body temperature is reduced, hypoglycemia follows. Popovic (1955), followed the blood sugar of rat cooled by hypercapnic anoxia at an ambient temperature of 17 C. Immediately after cooling, the blood sugar was 300 mg/100 ml. As hypothermia deepended there was an exponential decrease; after 6 hrs the blood sugar fell to 100 mg/100 ml. After 16 hrs it had fallen to 50 mg/100 ml.

Giaza et al (1951) reported that death by hypoglycemia occurs at the same blood sugar level whatever the thermal state of the animal! normothermia with high or hypothermia with low energy expenditure. Hypoglycemia attacks are more likely to be related to some direct effect of hypoglycemia on the nervous cells of the brain.

c) Adrenal Medulla

The importance of catecholamines in the defence against cold and in cold adptation has been known for a long time (Depocas et al 1960; Heroux, 1962; Hsieh et al 1957; Ring, 1942; Sellers et al, 1954). In previous work on dogs it was emphasized that epinephrine and norepinephrine were more important calorigenically during cold exposure than at neutral ambient temperatures (Tanche and Therminarias, 1969). Many authors have shown that catecholamine thermogenesis requires the presence of thyroid secretion in different species (Chatonnet,1967; Griffith, 1951; Harrison, 1964; Ring, 1942; Swanson, 1956, 1957; Vaughan, 1967).

It has been reported that plasma epinephrine is either decreased (Stephanyan, 1963) or increased (Holobut, 1963; Holobut

and Stazka, 1962) during cold exposure. The secretion of epinephrine is completely interrupted when the body temperature is below 17 C (Malmejac et al, 1957). It is possible that depletion of the epinephrine content in the adrenals (Davidovic, 1971; and Petrovic, 1966) prevents rewarming after a long-lasting profound hypothermia. Epinephrine administered to rats cooled to a body temperature of 17 C retains its hyperglycemic action. Glucagon, whose mode of action is similar to epinephrine has no biochemical effect at this low body temperature (Agid and Murat, 1970).

d) Adrenal Cortex

It is well established that adrenals are involved in the metabolic response of homeotherms exposed to cold. An increased secretion of corticosteroids has been demonstrated in acute cold exposure (Leblanc, 1961; Bouloward, 1963; Carveth et al, 1965; Gale, 1970; and Grad et al, 1971). However, there are reports of an unchanged (Barlow, 1959) or decreased level of adrenocortical hormones (Hunter et al, 1964).

e) Gonads

Vidovic (1952), studied the effects of hypothermia on pregnancy in the female rats, if cooling is on the Ist day of pregnancy, hypothermia increases its duration; if applied after 11th day, repetitive hypothermia terminates pregnancy.

Changes in endocrinal secretion under cold exposure alter the carbohydrate protein and fat metabolism.

(C) CARBOHYDRATE METABOLISM IN COLD EXPOSURE

Fuhrman and Crismon (1947), observed that in shivering rats provided with ample carbohydrate before cooling, blood glucose levels rose, whereas in absence of shivering and in starved animals or slowly cooled fed animals, blood glucose level was maintained or decreased.

The increase in blood glucose is atributable to an early discharge of epinephrine caused by cold. Kilburn in 1960 has shown that by counteracting the action of epinephrine with hydrazine (ergotoxine), hepatic glycogenolysis which is cause of increase in glucose is supressed.

Hyperglycemia of varying magnitude has been shown to occur during hypothermia depending upon its degree and duration (Barone, 1967; Bickford, 1960; Fisher, 1958; Fuhrman, 1947, 1963; Hannon, 1961; Jayot, 1962; Popovic, 1955; Giaja, 1951; and Kilburn, 1960). In some animal species, cooling induces hypoglycemia from the beginning (Rodbard, 1947,1950). A profound hypoglycemia has also been observed in hibernators during the hibernation period (Agid et al, 1969). It is also known that hypoglycemia and hypothermia appear together in this case (Sahovic et al, 1951).

William et al (1967), determined insulin levels in blood during intravenous glucose tolerance test in hypothermic and normothermic dogs. They concluded that decreased pancreatic

insulin secretion was the factor responsible for the altered glucose metabolism during hypothermia.

Hennerman et al (1958), noted that during hypothermia in man without shivering and with induced hyperventilation, there is decrease in blood lactic acid, pyruvic acid and inorganic phosphorus with a moderate rise in blood glucose. Beaton (1961), has reported a decrease in blood lactic acid and inorganic phosphorus level of fasting hypothermic rats. Beaton and Orme (1961), showed that progressive increase in blood levels of lactic acid and inorganic phosphorus with progressive cooling of rats are related to severity rather than duration of cooling.

Hyperlacticidemia has been reported in hypothermic patients (Ballinger, 1962). It is caused by decreased liver function. The myocardial lactate concentration in hypothermic guinea pigs is slightly elevated (Hanson et al, 1961), but the concentration of cardiac lactic acid returns to the normal level when the animals are cooled more profoundly or when they are kept in hypothermia for several hours. Hannon (1961) and Jayot (1962), also observed a variable increase in the level of lactic acid in the blood and tissues in animals in which hypothermia is maintained for a long time. Hypothermia and hypercapnia have been found to increase the stores of carbohydrate in the brain. Zakhary et al (1967) and Miller et al (1964) studied cardiac glycogen in cooled guinea pigs and other animals and it was found that survival of hypothermic

rats kept in pure nitrogen depends on the cardiac glycogen reserves.

Shipp et al (1965), found that glucose uptake by the isolated rat heart perfused at 17 C was nil and increased progressively with higher temperatures. Lactate formation was virtually absent at 27Cand below. Crofford et al (1965), have reported that glucose uptake by rat adipose tissue is lower at 17 C.

Fuhrman and Fuhrman (1964), studied in vitro uptake of glucose by rat diaphragm and red blood cells at low temperatures. He found glucose uptake by isolated diaphragm was 1.86 mg/g/hr at 38 C, but only 0.28 mg/g/hr at 18 C. He concluded that abnormal glucose metabolism in hypothermia is not caused by a failure of glucose to peneterate cells and there is no unusual sensitivity of hexokinase to change in temperature.

A number of studies have indicated that glycogen stores are more stable at low temperatures than in the normothermic state. Thus, Bishop et al (1965), using the perfused rat liver, found a 75% decrease in liver glycogen at 37-40C, but very little change when the perfusate temperature was 24-28 C. Fuhrman and Fuhrman (1963), found that a glucose load did not induce glycogen deposition in rats at 18 C and concluded that there was an inability to store glycogen. Shipp et al (1965), observed that heart glycogen was depleted when perfused at 37 C but did not show a decrease at 17 or 27 C. Burlington and Klain (1967), observed liver glycogen levels of 27 mg/g in

hibernating ground squirrels at 6 C and 39 mg/g in normothermic ground squirrels. The slower turnover of glycogen stores is apparently reflected in lower blood sugar levels generally found in hypothermic and hibernating animals. Kaiser et al (1965), using the isolated perfused rat liver, found that blood glucose levels dropped steadily when the perfusate temperature was decreased from 37 to 25 or 17 C. The decrease were from about 120 mg % to about 50 mg % .

(D) PROTEIN METABOLISM IN COLD EXPOSURE

Plasma protein levels decrease in hypothermic chickens (Sturkie, 1947); goats (Timet et al, 1967), and in other animals (Ostashkov, 1961). Beaton (1961), however, has reported an increase in the protein concentration of blood during cold exposure. Thauer, (1965), on other hand, is of opinion that plasma protein concentration remains unchanged during cold exposure.

Except for taurine, which appears to be elevated, free amino acid concentration in the blood remains unaltered during hypothermia (Kristofferson, 1968).

In artificially cooled hibernators, the level of free amino acid in the blood decreases. Holobut et al (1966), and Szilagyi et al (1961) proved that serum histamine increases in profound hypothermia. Welch in 1961, has shown that levels of blood ammonia decrease in hypothermia.

Whitten and Klain in 1968 found that in vitro synthesis of protein from methionine 14 C- methyl by ground squirrel liver microsomes was markedly lower in hibernating animals as compared to normothermic animals when the incubations were carried out at 37 C. However, no differences were observed when the incubations were carried out at 6 C.

(E) FAT METABOLISM IN COLD

The hibernator or nonhibernator which prepares itself for the challenge to cold may deposit large quantities of fat in the core or under the skin. Subcutaneous fat serves the purpose of insulation and utilized as energy source. Brown adipose tissue is called as thermogenic tissue and plays extensive role in nonshivering thermogenesis. Buskirk et al (1963), studied different body fats in the cold in men and women. Subcutaneous fat ranged from 13 to 45 % of the body weight. The metabolic response to cold in both males and females was inversely related to the percent of body fat. The large increase in metabolism during shivering is accomplished by the mobilization of the triglycerides of the adipose tissue (Bernstein, 1971). In cold, incomplete utilization of fat in mammalian body results in the accumulation of ketones. These are primarily acetone, acetic acid and hydroxybutyric acid. With the human subjects in the cold, ketosis may occur because of the relative carbohydrate deficiency or because of high fat diet. Passmore and Johnson (1958), suggest that ketogenetic effect of cold may be part of general response to environment and not specifically

related to fat metabolism. Levine (1937., 1949), observed that Eskimos do not show ketosis inspite of living on a high fat diet.

The triglycerides of depot fat are the major reserves of energy in the body. They are mobilized under the influence of norepinephrine and split into free fatty acids and glycerol. Free fatty acid is further broken down, the end product being the two carbon fragment called acetyl Co A. This material is used to liberate energy in the tricarboxylic acid cycle. The pathway can be reversed to utilize excess acetyl Co A to rebuild fatty acid. Johnson and Passmore (1961) emphasized the importance of pentose phosphate shunt in preventing ketosis. In brown adipose tissue fatty acids are used as a metabolic substrate. In the resting state, Brown adipose tissue is in "coupled" state i.e. substrate oxidation is linked to phosphorlyation of ADP to ATP in an energy conserving reaction. In the active state of the mitochondria, substrate oxidation appears "uncoupled" from phosphorylation and respiration can continue without the limiting phosphorylation reactions. The chemical energy thus lost is given out from the brown adipose tissue.

(F) EFFECT OF COLD STRESS IN DIABETIC ANIMALS

In one of the studies of Poe (1962), it was shown that alloxan diabetic rats survive at 25 C for 2-3 months while normal rats survive at 6 C for 19-23 months. Alloxan diabetic rats showed significantly lower rectal temperature than the controls. In alloxan diabetic rats, survival rate

at 5 ± 1 C was markedly reduced. The metabolism of the diabetic animal is severely impaired as studied by Poe et al (1963), by the inability of the diabetic rats to maintain its body temperature and to conserve heat particularly in cold. He hypothesized that the diabetic rats did not survive in cold because of an inability to utilize body food stores for energy. Another factor may have been the reduction in shivering thermogenesis.

The incidence of cold injury was also markedly increased in the diabetic rats. This was manifested by a severe hemorrhagic gangrene of the tail appearing after 20th day of exposure to 5 C. Rate of gangrene was 88 % in the diabetic and 9 % in the control rats.

(G) EFFECT OF COLD STRESS ON INSULIN TREATED ANIMALS

Since both epinephrine and norepinephrine inhibit the release of insulin, a cold exposed animal exhibits a low blood insulin (Beck, 1967). Cold exposure has been reported to markedly increase both the hypoglycemic and the glucose utilization promoting effects of exogenous insulin. Curry et al (1970), observed in rats that hypothermia directly inhibits insulin release and that there exists a direct relationship between tissue temperature and total quantity of insulin released Cassidy et al (1925), have shown that insulin convulsion which is produced by massive doses of exogenous insulin is inhibited by lowering of the body temperature of cats and dogs to 25 C. Lowering of blood sugar abolishes the shivering reflex; adminis-

tration of glucose causes its reappearance. The combined action of cold and insulin in rats and dogs produces a state simulating hibernation. Subsequent injection of glucose restores the animals to normal.

(H) THERMOREGULATORY RESPONSES TO ACUTE HEAT EXPOSURE

The heat to which the body reacts may have its origin in extrinsic factors, or internally in metabolic processes. Changes in body temperature as a result of environmental variations or metabolic agents, produce more or less profound effect on various biologic processes within the body. A general rise of body temperature increases the heart rate through increased metabolic activity of the pacemaker of the heart. Bazzet (1924), and Adolph et al (1947), found an increase of 44 beats/minute for a rise of 2.4 C rectal temperature. An increase in cardiac output and stroke volume was reported by Heyman (1935).

Barcroft and his colleagues (1946), observed an increase in blood volume. Dilution of plasma is one of the early responses to sudden exposure to a hot environment (Barbour, 1929). This is demonstrated by the decrease of haemoglobin, and plasma protein concentration and by increases in vapour pressure of the serum. When heat stress is severe the haemodilution is reversed and haemoconcentration supervenes due to copious sweating in man. Exposure for several days to hot environment leads to a decrease in concentration of plasma protein and haemoglobin.

In thermal sweating Na, K and Cl are lost and consequently sweating tends to cause electrolyte imbalance. Salt deficiency is the principal stimulus to aldosterone secretion, which helps to preserve plasma sodium.

Egger (1956), found that the first response to heat is dilatation of the vascular bed in the skin, bringing a great fraction of the total volume of blood to the surface for cooling Blood pressure is diminished due to reduction in peripheral resistance. Respiratory rate increases. There is decrease in the salivary secretion. (Dorodinistaina, 1937).

In Hyperthermia there is an increase in oxygen demand and production of more Co_2. Metabolic rate rises. Changes in carbohydrate metabolism have been observed.

(I) CARBOHYDRATE METABOLISM IN HEAT EXPOSURE

Kanter (1957,1959) showed that unanesthetized dogs exposed to high environmental temperatures and low humidity without access to water become dehydrated. He found that in dogs during exposure to heat, the glucose levels fell and the rectal temperature increased, while on termination of exposure it was noted that rectal temperature fell and glucose returned towards normal during recovery. Contrary to this finding, a rise in blood sugar levels (hyperglycemia) has been reported under similar environmental conditions in man (Adolph,1947; and Pitts, 1944), and in chickens (Rodbard, 1947). In animals exposed to high temperatures and in men exposed to conditions favourable to the production of heat cramps, an increased

concentration of blood sugar has been reported by Talbott (1935). It was suggested that injestion of glucose may be beneficial in avoiding or treating the heat cramps as well as exhaustion. A suggestion has been advanced that dehydration seems to be necessary for the hyperglycemic effect to occur in man. Adolph (1947), reported that sugar is actively added to the blood as dehydration exhaustion approaches. Pitts et al (1944), described similar findings in man on exposure to heat.

According to Kanter (1959), the tendency of hyperglycemia is present in dogs but the increased utilization of glucose offsets the hemoconcentration and causes a fall in glucose levels even when exogenous glucose is given. This increased utilization has been demonstrated to be mainly due to involvement of the respiratory muscles which are involved in the panting mechanism. Kanter in 1959 demonstrated some insulin or insulin like effect on dogs, so that glucose is deposited as glycogen and blood glucose levels fall. He has suggested that increased muscular activity involving the respiratory muscles used in panting regulates the body temperature, and since the glucose is utilized faster than it can be supplied by liver, there is hypoglycemia. On the other hand, man when faced with high temperature stress manages to regulate his body temperature within narrow limits by profuse sweating and subsequent evaporation.

Fuhrman and Fuhrman (1963) studied the effect of glucose load (10 mg/100g body weight) on anaesthetized rats

with body temperature of 38 C and 19 C. They found that excess glucose disappeared from the rat's blood at 38 C in 15-20 minutes but none had disappeared at 18 C even 2 hours after the termination of exposure. Bishop et al (1965), used the perfused rat liver and found a 75 % decrease in liver glycogen at 37-40 C.

Changes in carbohydrate metabolism as well as many other metabolic changes onheat exposure are mediated through alteration in endocrine function.

(J) ENDOCRINE CHANGES ON EXPOSURE TO ACUTE HEAT STRESS

Environmental heat presents at all levels of biological organization a stress that brings into play in the homeothemic animal a complex of nervous, endocrine, neurohumoral and major functions combining to restore a constant body temperature and to adjust body fluid balance, energy metabolism and behaviour to the needs concomitant with survival in new environment.

The literature on endocrinological aspects of exposure to high temperature has been comprehensively reviewed by Gale (1973) and by Collins and Weiner (1968), and previously by Berde (1951).

a) Thyroid gland

That thyroid activity can be depressed and the release of the thyroid hormone reduced on exposure to heat are conclusions reached by most investigators using a variety of indices

of thyroid function and experimental animals. In the rat, Dampsey and Astwood (1943) have estimated that the amount of thyroxine secreted is 9.5 ug at 1 C, 5.2 ug at 25 C and only 1.7 ug at 35 C. In the ox, Johnson and Ragsdale (1960) have found that the fall of thyroid activity is very abrupt at high temperatures. The decline in the heat has also been shown in rams (Brooks et al, 1962), Pigeons and rabbits (Chaudhri and Sadhu, 1961), mice (Hellmann and Collins, 1957), Guinea pigs (Schmidt and Schmidt, 1938), Poultry (Hoffman and Shaffner, 1950) and pigs (Ingram and Slebodzinski, 1965). Brown et al (1954) showed that when previously cooled rabbit was returned to the warm environment (29C) there was an immediate fall of ^{131}I output from the gland. Male rats exposed to 32-34 C exhibited reduced iodine uptake and release as compared with responses to lower temperatures (19-25C). Depressed thyroid activity in terms of radioiodine uptake and output is also reported in sheep (Hoersch et al, 1961) at 32 C and in dairy goats during summer months (flamboe and Runeke, 1959). Thyroid activity is reduced still further when animals are exposed to temperature raised above thermoneutral conditions (Johnson and Ragsdale, 1960). Cramer and Ludford (1926, 1928) observed that exposure to heat (37C) leads to a flattening of the thyroid epethelial cells. Similar findings have been reported in sheep kept at 32.5 (Hoersch et al 1961).

b) <u>The Adrenal Gland</u>

i) <u>Medullary Hormones</u>

Cramer (1928), argued that adrenaline in heat exposure

would be expected to raise the body temperature through its calorigenic action aided perhaps by some reduction of peripheral vasodilation (Whelan et al 1963). Cramer speculates that the animals without sweat gland will react to exposure to heat by an inhibition of the adrenal gland. Such an inhibition would be analogous to that which the thyroid undergoes with moderate degrees of heat exposure. In the dog the plasma catecholamine concentration is unchanged during acute heat exposure (Florica et al, 1967). In horse there is a strong evidence that secretion actually increases.

ii) Adrenocortical Hormone Glucocorticoids

Adrenalectomized rats succumb to high environmental temperatures (37-40 C) more easily than do controls and to some extent are protected by extracts of adrenal gland (Hermanson and Hartman, 1945). Ascorbic acid content is decreased in rats 1 hr after exposure to 38 C (Sayers and Sayers, 1947). Hyperthermia (rectal temperature of 39-42 C induced by pyrogen or by immerson in hot water of anaesthetized dogs caused 2 to 7 fold increase in the plasma 17- hydroxycorticosteroids (Richards and Egdahl, 1956). This response was abolished by hypophysectomy (Barlow, 1956, Eik-Nes et al, 1956, 1958). Chowers et al (1966), found that cortisol levels increase.

iii) Mineralocorticoids

The principal mineralocorticoid is aldosterone, which accounts for about two thirds of the total sodium retain-

ing activity of the adrenal hormones, whereas the other one-third is exercised by the glucocorticoids. The action of glucocorticoids on the kidney are complex because they tend to increase glomerular filteration rate and initial sodium loss, on the one hand, and promote the later reabsorption of sodium, on the other (Ingram, 1975).

Collins et al (1955), have shown that aldosterone is increased in man during heat exposure, but it is not so much related to heat exposure itself as to the amount of sweating that takes place. It is well known that aldosterone output increases during salt deficiency and decreases on salt loading. It is probable that the rise in aldosterone excretion in the heat is related to the loss of sodium. If salt and water deficiency is prevented during work and sweating during heat exposure, no increase in aldosterone occurs.

O'connor (1962), has drawn attention to the other mechanism that controls the salt loss. For example, the loss of sodium in sweat leads to decrease in extracellular fluid, which in turn increases the plasma protein concentration. The result of this is a decreased glomerular filtration rate and reduction of sodium loss, all of which occurs without the intervenation of hormonal control. Collins and Weiner (1969), have suggested that the role of aldosterone may be in the long term adjustment of salt and water balance on exposure to heat.

Under the influence of aldosterone, the sodium concentration of sweat is reduced, but this fall in sodium loss takes some 6 hours to develop. Part of this time lag is accounted for in the mechanism of aldosterone action, which involves protein synthesis, which takes 1-3 hours as shown in toad bladder. The additional time taken for an effect on the sweat gland may be related to the rather low oxygen concentration. Sweat glands are known to contain large amounts of lactic acid, which suggests an anaerobic glycolysis, whereas aldosterone requires aerobic conditions (Collins and Weiner, 1968). Aldosterone may also reduce the quantity of sweat produced by the glands. Macfarlane (1963), has observed that in sheep exposed to high temperatures, an increase in sodium loss and dehydration are not associated with a change in the secretion of aldosterone. It is only during rehydration, when the extracellular fluid expands that the secretion of aldosterone is stimulated and sodium is retained. Experimentally induced Na^+ defficiency in cattle, sheep and goat dhows that the excess loss of saliva during heat exposure causes considerable reduction in the Na/K ratio of the secretion (Baily et al 1961; Denton, 1965; and Komi et al 1963) which is associated with increased rate of aldosterone secretion (Blair-West et al 1963 and Denton, 1965).

c) Antidiuretic hormone

Exposure to a hot environment in men and animals leads to an increase in water retention that may in some

instances be even greater than the additional evaporative loss. After an initial water deficit both the extracellular volume and the blood volume increase (Robinson, 1949; Yoshimura, 1960). The reduction in urine flow on exposure to heat may be related to a reduced glomerular filtration rate (GFR) consequent on a lower renal blood flow and dehydration in both man and animals (Macfarlane, 1964; Radigan and Robinson, 1949). However, after a period of time GFR increases again (Pitesky and Last, 1951).

The long term reduction in urine flow during heat exposure is related to an increase in the levels of antidiuretic hormone (ADH) (Collins and Weiner, 1968). In man (Hellmann and Weiner, 1953) working in a hot environment, ADH in the plasma increases. There is a similar increase in sheep (Macfarlane 1963, 1964) subjected to water deprivation in summer. In man and sheep, a standard heat exposure in summer is followed by a greater rise in ADH secretion than in winter (Macfarlane and Robinson, 1957). The injection of vasopressin into the sheep and camel, leads to an unexpected increase in urine flow and in the excretion of sodium and potassium. According to Schmidt-Neilsen (1964), this is probably because the vasopressin is given when urine flow is already low and therefore it causes an increase in the excretion of electrolytes, which carry water with them. According to Itoh (1954), antidiuretic substance in rat serum increases on exposure to heat. Raising the body temperature of rats by heating to 40 C for

2 hr produces little dehydration and no increase in anti-diuretic activity but when heating continues for 4 hr, plasma protein concentration increases and the ADH level is raised significantly (Robinson and Macfarlane, 1956).

d) Sex hormones

Experiments on rams and on small laboratory mammals have shown that exposure to high temperature less than an hour may cause damage to the sperm. In rams exposed to 40 C for between 6 hrs and 3 days, the decrease in semen quality is proportional to the length of exposure. The decrease first appears in semen ejaculated 13-21 days later and lasts for 35-39 days (Moule and Waites, 1963). Short exposure to high temperature is sufficient to reduce the fertility.

Macfarlane et al (1959), have reported that exposure of pregnant females to high temperature leads to fetal resorption. Exposure of rats to temperature as high as 39.5 C for 5 hr and 2 days supressed estrus for 9 days and only after 14 days was there successful mating (Chang and Fernandez-Cano, 1959).

(J) THERMOREGULATION IN YOUNG ANIMALS

The maintenance of constant body temperature requires the complete development of thermoregulatory system, which is partially developed in new born rats (Alain Korvrah et al, 1976).

It is a very well established fact that adult warm blooded animals can not usually stand a reduction of body temperature below 16-20 C (Girgolv, 1939; Sheinis, 1943; Starkov, 1947; and Kuznestsova, 1948).

Newly hatched domestic chicks are poor thermoregulator Wekstein et al (1969); Romjin (1954) and Wekstein et al (1967) have demonstrated that in chicks after oneweek of hatching the body temperature is independant of ambient temperature. Upon cold exposure (Freeman, 1966), the newly hatched chick increases oxygen consumption which is independent of shivering. Moore et al in 1962 have shown that the dependence of non shivering thermogenesis for mainte-nance of homeothermy during acute cold stress has also been observed in kittens, rabbits, rats, guinea pigs and human infants. As these mammals mature, their non-shivering thermogenesis is replaced gradually by shivering thermogenesis (Carlson, 1966 and Himms - Hagen, 1967). The early nonshivering heat production is dependent on sympathetic neural function since it can be blocked by the administration of adrenergic blocking drugs in guinea pig and rabbits (Heimet al, 1966) and by ganglionic blocking drugs in kittens and puppies (Moore et al, 1962).

Infant albino rats are unable to regulate their body temperature under cold stress until they are 18 days old. This was first reported by Hill (1947) and was corroborated by fairfield (1948); Adolph, (1948); and Holtkamp et al (1949).

Hill (1947), took measurements of body temperatures during cooling of rats at different ages and found that greatest resistance to lowering of body temperature occurred between 18 and 30 days of age.

Fairfield in 1948 showed that young rats could cease breathing movements, heart beats and all other detectable signs of life for 1 to 2 hours and still recover when warmed. There is a statement in a paper of Adolph (1948), that puppies overcooled to a body temperature of 10 C remained alive for 2 hours.

In rats, the adults were found to die at a body temperature of 14 C to 16 C, while the new borns can endure 1 C for at least one half hours. During the first three weeks of life (Adolph, 1948) the transition to the adult tolerance occurred. In cats the transition both in tolerance and heart beat frequencies is found to be slower. Prokop' Eva (1960), demonstrated that young animals are more resistant to excessive cooling and can withstand a more drastic reduction in their body temperature than can adult animals. It is possible to restore the vital functions of young dogs which had been cooled to a body temperature of 6-5 C.

Very young animals in which the full coordination and integeration of the nervous system is not yet developed, show an astonishing tolerance to changes of body temperature (Adolph, 1950). This tolerance is greater than in the adult of the same species.

Adolph in 1951 studied cat, golden hamster, rat and to some extent mouse, guinea pig and rabbit at diverse postnatal ages with respect to lower lethal temperature limits, and heart beat frequencies; lethal temperature that could be endured became higher with increased age of all species. In cat it rose from 7 C to about 18 C, and in hamster from 1 C to 4 C. Breath frequencies decreased as temperature decreased in new born infants.

Buchanan et al 1949 demonstrated that hamsters acquire the ability to effectively regulate their body temperature in a cold environment (5-8 C) at ages ranging from 30-44 days. Myelination in the dorsolateral areas of the hypothalamus, as determined photometrically reaches its height at the time thermoregulation becomes fully developed.

MATERIALS AND METHODS

MATERIALS

Animals

Normal healthy albino rats of Wistar strain were used for the experiments in present study. The body weight was 150-250 g for adult rats (age 4-6 months) and 40-70 g for young rats (age 20-30 days). The rats for the experiments were obtained from central animal house of the All India Institute of Medical Sciences, New Delhi-16 and were kept under controlled ambient conditions (temperature 27 ± 1 C; RH 50-60 %) in the animal house of School of Environmental Sciences, Jawaharlal Nehru University, New Delhi-57.

Diet of animals

The animals were fed ad libitum and had free access to water. The standard diet was obtained from the Hindustan Liver Limited, India. It had the following composition.

1.	Crude protein	24 percent
2.	Ether extract (fat)	4 percent
3.	Crude fibre	4 percent
4.	Ash	8 percent
5.	Calcium	1 percent
6.	Phosphorus	0. 6 percent
7.	Carbohydrates	50 percent
8.	Metabolizable energy content	3200 cal/kg.

METHODS

The details of the procedure employed for producing hypo and hyperglycemia, estimation of blood glucose levels, induction of thermal stress and the methods of recording and obtaining data on rectal temperature and survival time are described in the following paragraphs:

1. PRODUCTION OF HYPERGLYCEMIA

a) By administration of streptozotocin

Diabetic hyperglycemia was produced by streptozotocin (Sigma) regarded as a condensation product of a glucosamine and a nitrosourea molecule. Rats were injected intraperitoneally with streptozotocin in a single dose of 85 mg/kg body weight. The streptozotocin was freshly dissolved in citrate buffer, pH 4.5, and was injected within 5 minutes of preparation. The volume of administered solution did not exceed 0.5 ml. The drug is reported to selectively destroy islets of Langerhans (β- cells) of pancreas.

b) By administration of glucose

Glucose (300 mg) was dissolved in 2 ml of saline and was fed orally to all the rats irrespective of their weights. Oral feeding was done with the help of 2 ml syringe, the needle of which was attached to a thin, soft polythene tube, about 4 cm in length. The controls were fed with the same amount of saline. The glucose was fed

1 hr before the animals were exposed to cold and heat stress. No food or water was given to the animals during this period.

2. PRODUCTION OF HYPOGLYCEMIA

8 units per kg body weight of insulin (Boots Company, India Ltd.) was administered to make the experimental rats hypoglycemic. Stock solution was prepared with a concentration of .8 ml of insulin in ten ml of normal saline. The injection for rat was nearly 0.5 ml. The stock was stored in refri-gerator and away from light. Insulin was injected intraperitoneally to the experimental rats one hour before exposure to cold and heat stress. Control rats were treated with the same amount of normal saline.

3. INDUCTION OF THERMAL STRESS

Cold stress was induced by exposing the rats in deep-freezer (Kelvinator freezer K) maintained at a constant ambient temperature of -20 C. The desired temperature could be attained by adjusting the thermostat control. Air temperature was recorded both at the beginning and end of the experiment with the help of a standard alcohol thermometer. The recorded datum was the mean of the two observations. The rats were shaved before exposure to -20 C. The shaving was done in order to hasten the rate of fall of body temperature.

For exposure to low and high ambient temperatures of varying degrees viz., 15 C, 25 C, 32 C, 35 C and 38 C the rats were kept in a desiccator kept inside the BOD incubator (Scientific Equipment Works, Delhi). The temperature inside the desiccator could be obtained at any desired degree by adjusting the control knob of BOD incubator. The temperature inside the desiccator was read with the help of a mercury thermometer fitted into it.

In order to effect homogeneity in the experimental conditions and to avoid error due to high degree of variability, a separate control group of rats was chosen for each experiment.

4. RECORDING OF RECTAL TEMPERATURE

Rectal temperature was recorded with the help of telethermometer (Aplab) using a thermister probe (Yellow springs, Ohio USA). The latter was inserted about 6 to 7 cms deep in the rectum of adult conscious rats and 3 cm in the young rats. The thermistor probe was held in position by tying it to the tail by means of adhesive tape. The cable of the probe was encased in an iron shield that helped to prevent the rats from chewing the cable. The other end of the thermister was connected to the telethermometer for direct measurement of the rectal temperature. Calibration of telethermometer was made on every alternate day with the help of an accurate mercury thermometer.

5. MEASUREMENT OF SURVIVAL TIME

The time of death of the animal during exposure to heat or cold stress was indicated by the point of cessation of respiration.

6. WITHDRAWL OF BLOOD SAMPLES FOR ASSESSMENT OF HYPO- AND HYPERGLYCEMIA

The blood samples in streptozotocin treated rats were collected after 5 days to ensure that permanent diabetes had been produced. In insulin treated glucose fed and insulin treated plus glucose fed rats, the glucose estimation was carried at 1, 2 and 3 hrs after the treatment. Blood samples were also collected from streptozotocin and insulin treated, glucose fed and insulin plus glucose fed rats after 30 minutes of exposure to cold stress (-20 C) and after 60 minutes of exposure to heat stress (38 C). Similarly, blood was collected from the controls (normoglycemic rats) at room temperature and after exposure to heat and cold stress. The blood samples were collected in vials containing preservative (sodium fluoride and potassium oxalate) by inserting very thin glass capillaries into the inner canthus of rat. The blood glucose was estimated immediately after collection of blood.

7. ESTIMATION OF BLOOD GLUCOSE

Blood glucose was estimated by the method of Sharma and Sur (1966), which is a modification of Asatoor

and Kings (1954) method. This method omits potassium oxalate in alkaline reagent. Optical density of the solution obtained with arseno-phosphomolybdate reagent was read on the Elico-colorimeter. The optical density depends on the reducing power of the filtrate and gives an estimation of glucose only. The results obtained by these methods are similar to those obtained with the glucose oxidase method.

(a) Preparation of stock solution and working standard solution

i) Preparation of isotonic sodium sulphate copper sulphate solution

12.5 g of anhydrous sodium sulphate (Analar) and 5.1 g of crystalline copper sulphate (Analar) was dissolved in distilled water in a volumetric flask and volume was made to one litre.

ii) Preparation of sodium tungstate

This was prepared by dissolving 10 g of sodium tungstate in 100 ml of distilled water in a volumetric flask. The concentration of the solution was 10%.

iii) Preparation of alkaline reagent

168 g of anhydrous sodium sulphate (Analar) was dissolved in 600 ml of boiling water. The solution was then

cooled. In a beaker containing 100 ml of distilled water, 24 g of anhydrous sodium carbonate (Analar) and 12 g of Rochelle salt were dissolved. To the above reagent sodium bicarbonate (16 g)was added and dissolved. This solution was then added into the sodium sulphate solution and the volume made up to 1 litre by using distilled water. The solution was filtered after allowing to stand for 24 hours.

iv) Preparation of Arseno-molybdate reagent

100 g of ammonium molybdate was dissolved in 1900 ml of distilled water. To this 84 ml of concentrated sulphuric acid was added drop by drop while stirring continuously. 12 g of disodium orthoarsenate was dissolved in 100 ml of distilled water and added to the above solution. The solution was incubated at 37 C for 48 hours.

v) Preparation of glucose stock solution

It was prepared by dissolving 100 mg of glucose in 100 ml of saturated benzoic acid solution.

vi) Preparation of working standard

One ml of stock glucose solution was dissolved in 100 ml of isotonic sodium sulphate copper sulphate solution.

b) Standard curve for glucose

A set of six tubes of equal height and internal

diameter, 0.1 ml (10 ug), 0.2 ml (20 ug), 0.3 ml (30 ug), 0.4 ml (40 ug), 0.5 ml (50 ug) and 0.6 ml (60 ug) of working standard was taken. Volume was made to 2 ml in each tube by adding isotonic copper sulphate solution. For blank 2 ml of isotonic copper sulphate was taken in a separate test tube. Alkaline reagent (2 ml) was added into each tube. Test tubes were placed in a boiling water bath for exactly 10 minutes and cooled subsequently by keeping under running tap water. Colour was developed by adding 2 ml of arseno-molybdate solution. It was mixed thoroughly and kept standing for 10 minutes. Optical density was read in Elico-colorimeter at 540 nm after setting the blank at zero. The graph was plotted between glucose concentration and optical density.

c) Analytical procedure

In a 15 ml centrifuge tube containing 7.8 ml of isotonic sodium sulphate copper sulphate solution, 0.1 ml of blood was added. The contents were mixed by rotation in the palms and kept for 5 minutes to ensure complete diffusion of glucose from RBC. The non reducing substances (glutathionic etc) remained in the RBC. 0.1 ml of sodium tungstate was added and mixed thoroughly. After few minutes tube were centrifuged at 3000 rpm.

2 ml of centrifugate was taken in a separate test tube. To this 2 ml of alkaline reagent was added. The test

tube was covered with glass balls and suspended in boiling water bath exactly for 10 minutes. Tube was taken out and cooled to room temperature by running tap water.

To all the test tubes 2 ml of arsenomolybdate reagent was added and solution was mixed until the effervescence ceased. After allowing to stand for 5 minutes, the optical density was measured.

8. PROCEDURE EMPLOYED TO INDUCE FROST BITE

The method employed to induce frost bite was that designed by Fuhrman (1955), and Balasubrahmanyan et al (1963)

For production of the cold injury the rats were anaesthetized with anesthetic ether and hind limbs were immersed upto the ankle in a freezing mixture (ethylene glycol, water and alcohol, in the ratio of 2:1:1 and solid carbondioxide) to obtain the desired temperature. The immersion was continued for 5 minutes. Freezing was always indicated by sudden whitening of the skin. The animals were returned to the cages and no external dressing were applied to the injured feet. The percentage of cold injury were estimated in four groups of animals control, insulin treated, streptozotocin treated and glucose fed. All the animals were exposed to cold injury on the same day. The freezing temperature used was -19 C for studies on the effect of insulin and streptozotocin and -23 C for studies on the effect of glucose feeding.

9. STATISTICAL EVALUATION OF THE DATA

All the data presented in this dissertation have been statistically evaluated and given as mean and standard deviation, calculated by the following formulae.

$$S.D. = \sqrt{\frac{\sum (X - \bar{X})^2}{n - 1}}$$

where Σ = summation for all values of X

X = the individual value in the sample

$\bar{X}$ = the mean

n = number of animals

Student's t test

Gosset (pseudonym student) devised a test to evaluate the significance of the difference between two means.

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{S.E_1^2 + S.E_2^2}}$$

where t = a value used to determine probability

$\bar{X}_1$ = the mean of one group of data

$\bar{X}_2$ = the mean of second group of data

$S.E_1$ = the standard error of the mean of the first group

$S.E_2$ = the standard error of the mean second group

Using the t value in a table of student's distribution one determines the probability 'p'. The degree of freedom for obtaining the 'p' was $(N_1 + N_2 - 2)$ where N_1 and N_2 are the number of animals used in the two groups under test.

A 'p' less than .05 is usually considered to be significant; this means that there are less than five chances out of 100 that a difference between the two means of the indicated magnitude occurred by chance.

Chi square test

If the data fit into the yes and no category, the chisquare test of significance is used. The calculation is

$$\chi^2 = \frac{(X_1 - m_1)^2}{m_1} + \frac{(X_2 - m_2)^2}{m_2}$$

where X_1 = observed number of first group
m_1 = expected number of first group
X_2 = observed number of second group
m_2 = expected number of second group

The expected number is based on the null hypothesis that there is no difference between the two groups.

Regression line

The graph of the regression equation is the straight line. The general equation of a straight line with x as the independent variable is:

$$Y = ax + b$$

where a = represents the slope

b = the ordinate of the point where the line crosses the Y axis.

Y = denotes the dependent variable given by line.

The values of a and b were calculated by the method of least squares. If the smoothed curve is to be straight line then it has two parameters, a and b. The sum of the squared deviations from this line is to be as small as possible, hence the derrivative of this sum with respect to a and b equal zero. Thus we obtain two equations for determining parameters a and b.

$$\sum Y = a \sum x + bN$$

$$\sum XY = a \sum x^2 + b \sum x$$

Where N is the number of observation for the straight line a we obtain the equations:

$$a = \frac{N \sum XY - \sum X \sum Y}{N \sum (X^2) - (\sum X)^2}$$

$$b = \frac{\sum X \sum XY - \sum X^2 \sum Y}{(\sum X)^2 - N \sum (X^2)}$$

RESULTS

EFFECT OF HYPERGLYCEMIA ON RATE OF INCREASE OF RECTAL TEMPERATURE (T_{re}) ON EXPOSURE TO 38 C

a) Glucose Fed Rats

i) Adult rats

In normoglycemic rats the body temperature increased with time and levelled off to 43.64 ± 0.55 after 40 minutes at 38 C (Fig.1). After 60th minute there was a fall in body temperature and at the end of 80th minute it was 43.42 ± 1.01. In the glucose fed rats the rise in body temperature was at a higher rate than the normoglycemic controls. It stabilized at 44.42 ± 0.88 at the end of 40 minutes. There was no tendency for the body temperature to fall after the 60th minute. The body temperature after 80th minute was 44.89 ± 1.34. Difference in the body temperature between the control and glucose fed rats was statistically significant after 40th ($p < .01$) as well as after 80th minute ($p < .01$) of exposure at 38 C (Table 1,see p. 41).

ii) Young rats

During exposure to high ambient temperature of 38 C, both the control and glucose fed rats showed tendency to increase their rectal temperature (Fig. 2). There was no tendency for the Tre to fall in normoglycemic young rats as was the case with normoglycemic adult rats. Tre after 40th minute of exposure in control and glucose fed rats was

FIG. 1 RATE OF INCREASE OF RECTAL TEMPERATURE (Tre) IN NORMOGLYCEMIC (N) AND GLUCOSE FED (G) ADULT RATS FOLLOWING EXPOSURE TO 38 C.

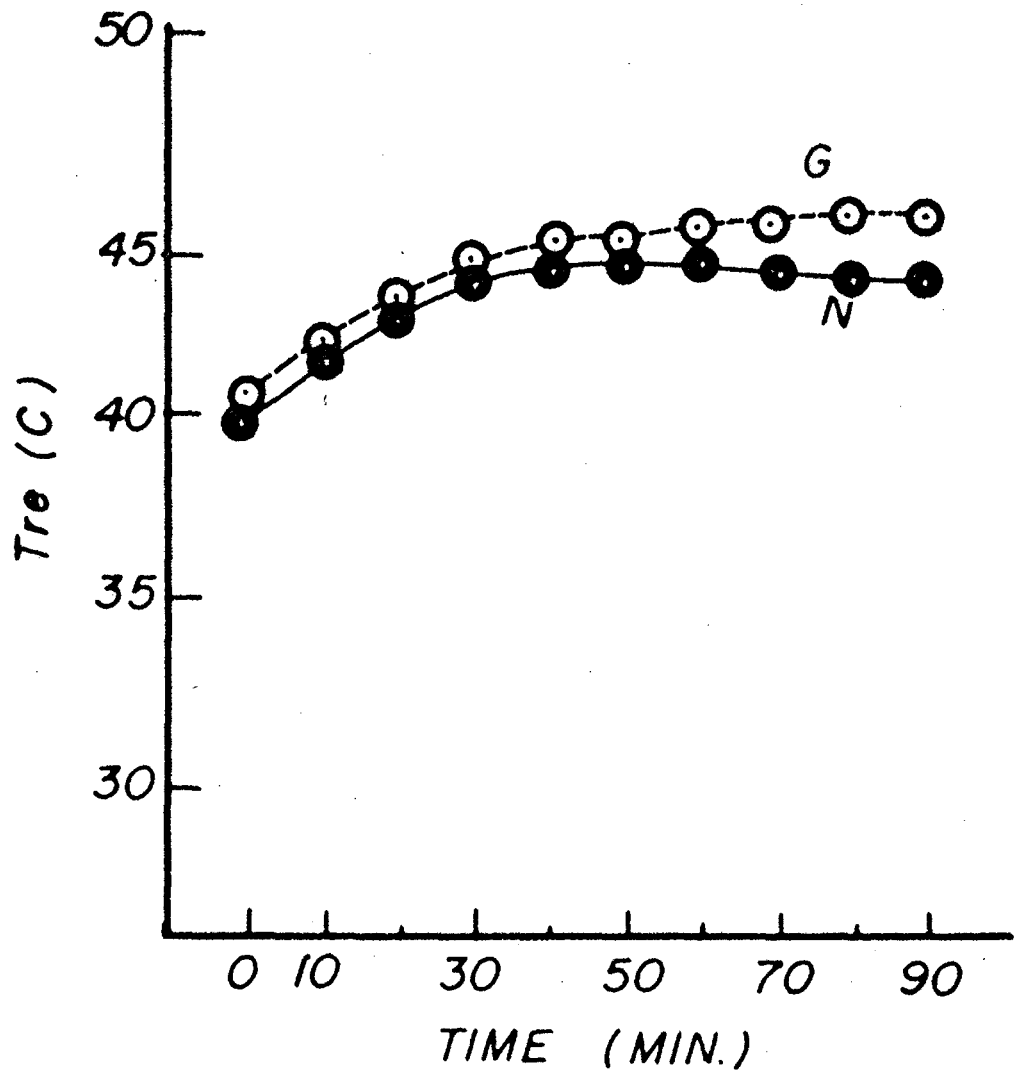
50
45
40
35
30
Tre (C)
G
N
0
10
30
50
70
90
TIME (MIN.)

FIG. 2 RATE OF INCREASE OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND GLUCOSE FED (G) YOUNG RATS FOLLOWING EXPOSURE TO 38 C.

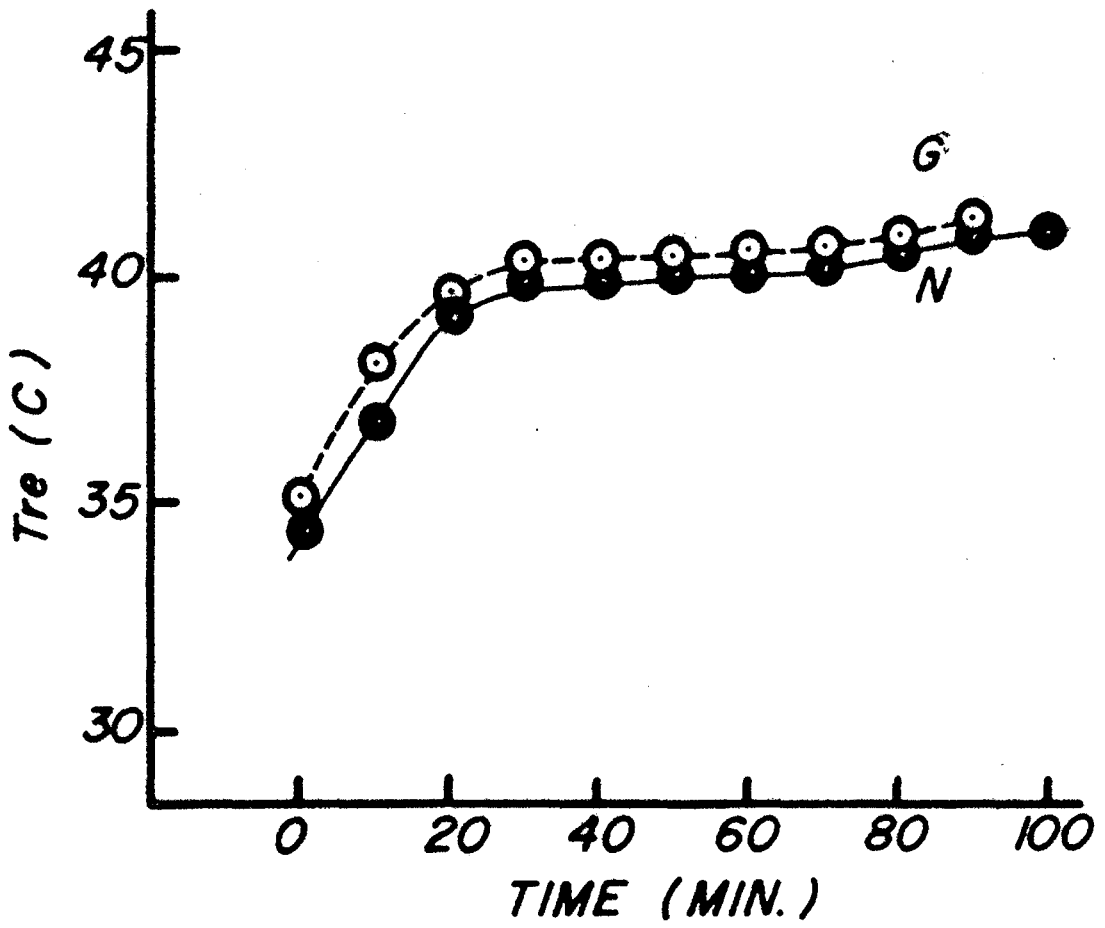
45
40
35
30
Tre (C)
G
N
0
20
40
60
80
100
TIME (MIN.)

TABLE 1. RECTAL TEMPERATURE (Tre) AT 40TH AND 90TH MINUTE OF EXPOSURE TO 38 C IN ADULT RATS FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	Tre at 40th min	Significance	Tre at 90th min	Significance
Normal	7	159.14± 8.34	43.54±1.51	p.< .01	44.92±1.79	p <.01
SZT	7	159.00±10.26	44.75±0.48		45.58±0.52	
Normal	12	167.80±13.59	42.0 ±0.57	NS	41.5 ±1.0	p <.001
Insulin	12	168.00±12.43	42.0 ±0.76		43.41±0.80	
Normal	9	183.39±11.82	43.64±0.55	p.< .01	43.42±1.01	p <.01
Glucose feeding	9	183.22± 9.42	44.42±0.83		44.89±1.34	

40.05 ± 0.93 and 39.90 ± 0.78 respectively. Tre after 80 minutes of exposure to 38 C in control and glucose fed rats was 40.60 ± 0.96 and 40.69 ± 1.29 respectively. The difference between two, however, was not statistically significant after 40th and 80th minute of exposure (Table 2, see p-43).

b) Streptozotocin treated rats

In normoglycemic rats the body temperature increased with time and levelled off to 43.54 ± 1.51 after 40 minutes at 38 C. The Tre in streptozotocin treated rats after 40 minutes of exposure was 44.75 ± 0.48. In control rats, Tre tended to decline after 80 minutes (Fig. 3). The rectal temperature after 80th minute of exposure in control and streptozotocin treated rats was 44.92 ± 1.79 and 45.58 ±0.52 respectively. The difference between the two was statistically significant after 40th ($p < .01$) and 80th ($p < .01$) minute of exposure to 38 C (Table 1, see p-41).

c) Insulin treated rats

i) Adult rats

In normoglycemic rats, the body temperature increased with time and continued upto 50 minutes of exposure. After that there was a decrease in rectal temperature (Fig. 4). Rectal temperature after 40th minute in control and insulin treated rats was 42.0 ± 0.57 and 42.0 ± 0.76 respectively. The difference was not statistically significant. Rectal

FIG. 3 RATE OF INCREASE OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND STREPTOZOTOCIN TREATED (SZC) ADULT RATS FOLLOWING EXPOSURE TO 38 C.

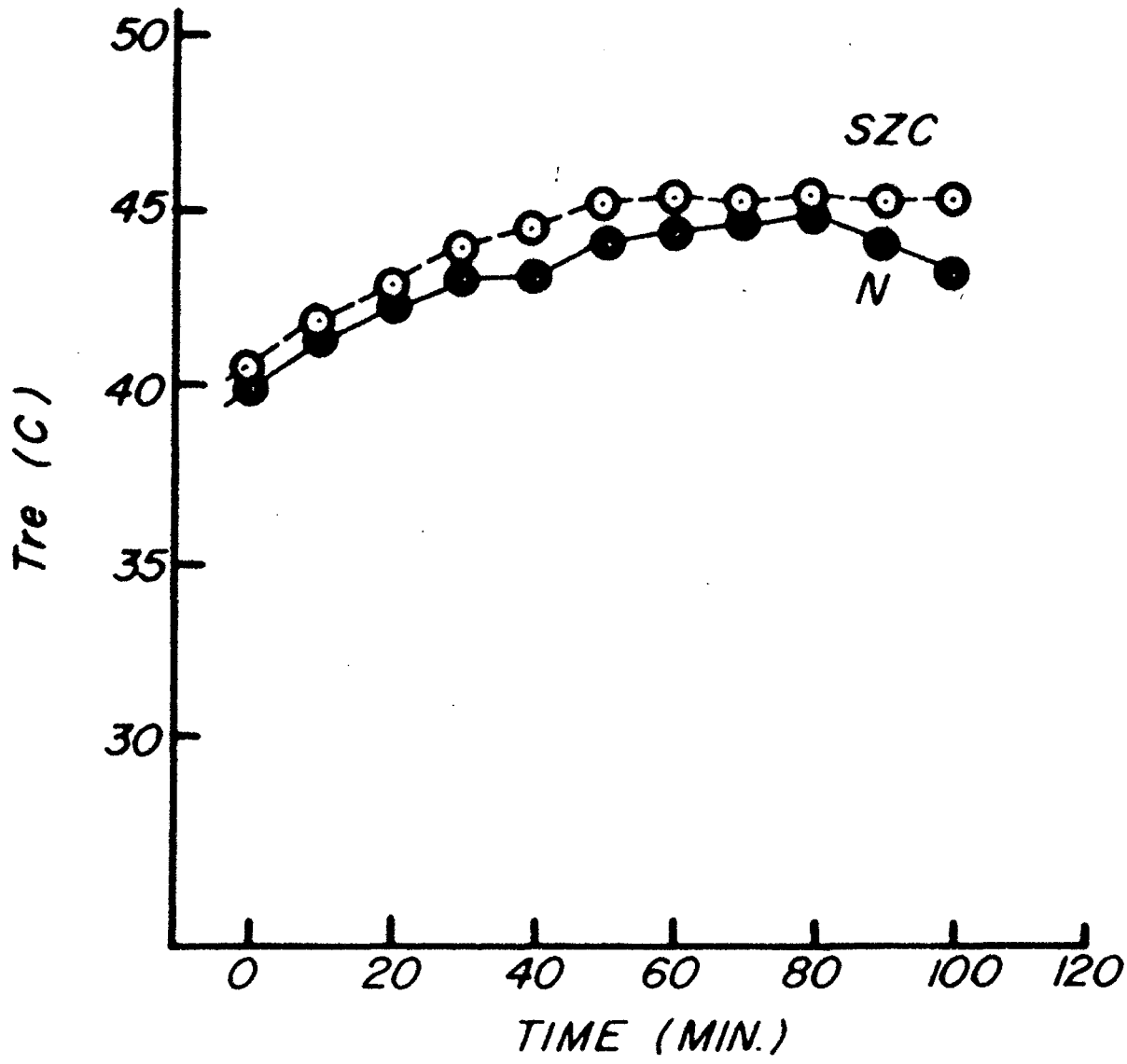
50
45
40
35
30
Tre (C)
SZC
N
0
20
40
60
80
100
120
TIME (MIN.)

FIG. 4 RATE OF INCREASE OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND INSULIN TREATED (I) ADULT RATS FOLLOWING EXPOSURE TO HEAT.

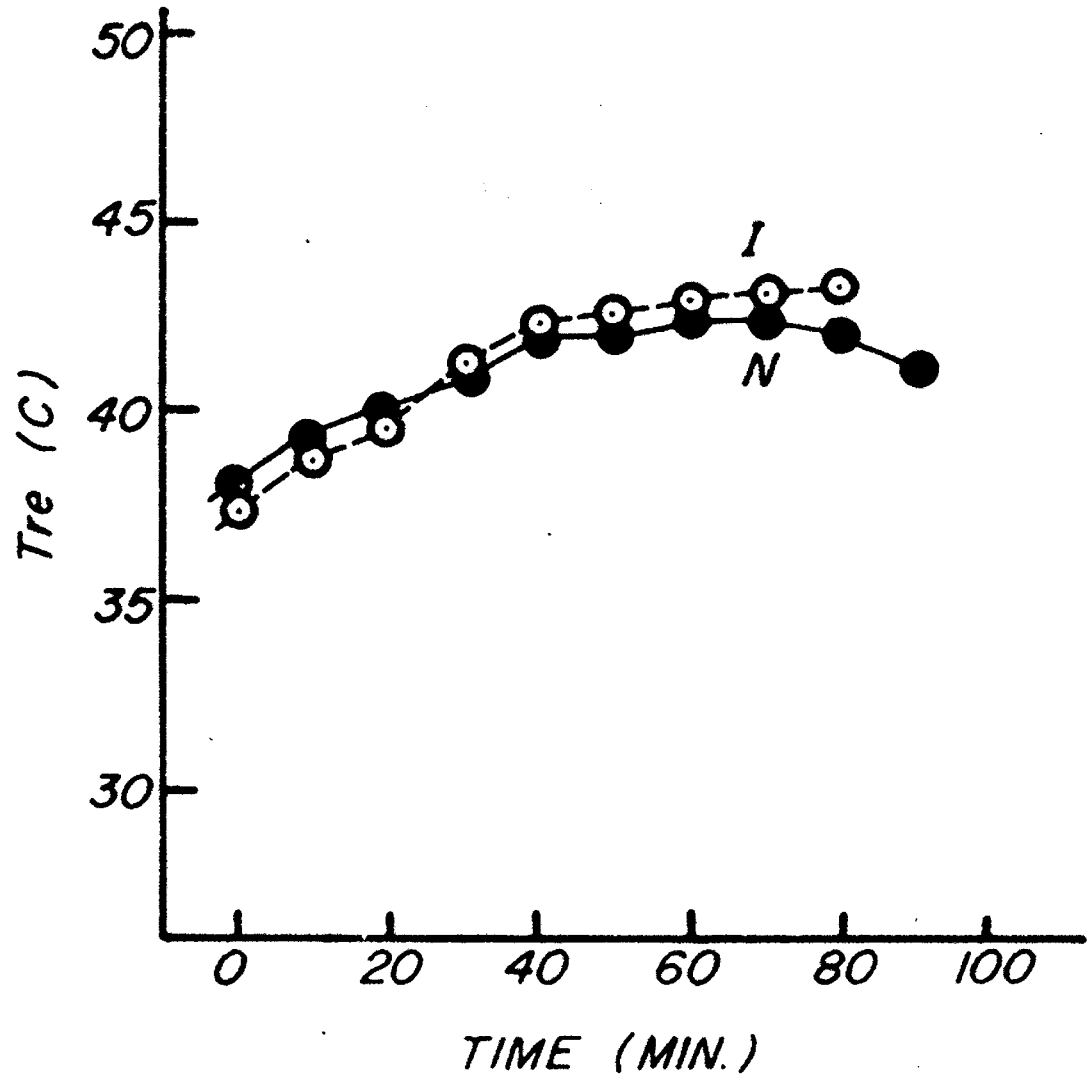
50
45
40
35
30
Tre (C)
I
N
0
20
40
60
80
100
TIME (MIN.)

TABLE 2. RECTAL TEMPERATURE AT 40TH AND 80TH MINUTE OF EXPOSURE TO 38 C IN YOUNG RATS FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	Tre at 40th min	Significance	Tre at 80th min	Significance
Normal	6	58.33 ± 5.16	41.5 ± 0.39	NS	-	-
Insulin	6	58.67 ± 5.54	42.0 ± 0.91			
Normal	5	48.8 ± 6.12	40.05 ± 0.93	NS	40.60 ± 0.96	NS
Glucose feeding	5	49.6 ± 6.24	39.90 ± 0.78		40.69 ± 1.25	

temperature after 80 th minute of exposure in control and insulin treated rats was 41.5 ± 1.0 and 43.41 ± 0.81 respectively (Table 1, see p-41). The difference between two was statistically significant ($p < .01$).

ii) Young rats

The rate of rise in Tre was about the same in insulin treated and the control rats (Fig. 5). The average Tre after 40 th minute of exposure in control and insulin treated rats was 41.5 ± 0.39 and 42.0 ± 0.91 respectively (Table 2, see p-43). The difference between two was not statistically significant.

d) Glucose fed plus insulin treated rats

On exposure to 38 C the rectal temperature of the control as well as experimental animals rose linearly with time (Fig. 6). The regression line of the variations of Tre against time, as determined by the method of least square, yielded a high coefficient of correlation. The values of the constants b and a and of the coefficient of correlation are given in Table 3 (see p-45). The slopes of the two lines was found to be statistically significant, with the line for normoglycemic animals occupying a lower position.

FIG. 5 RATE OF INCREASE OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND INSULIN TREATED (I) YOUNG RATS FOLLOWING EXPOSURE TO 38 C.

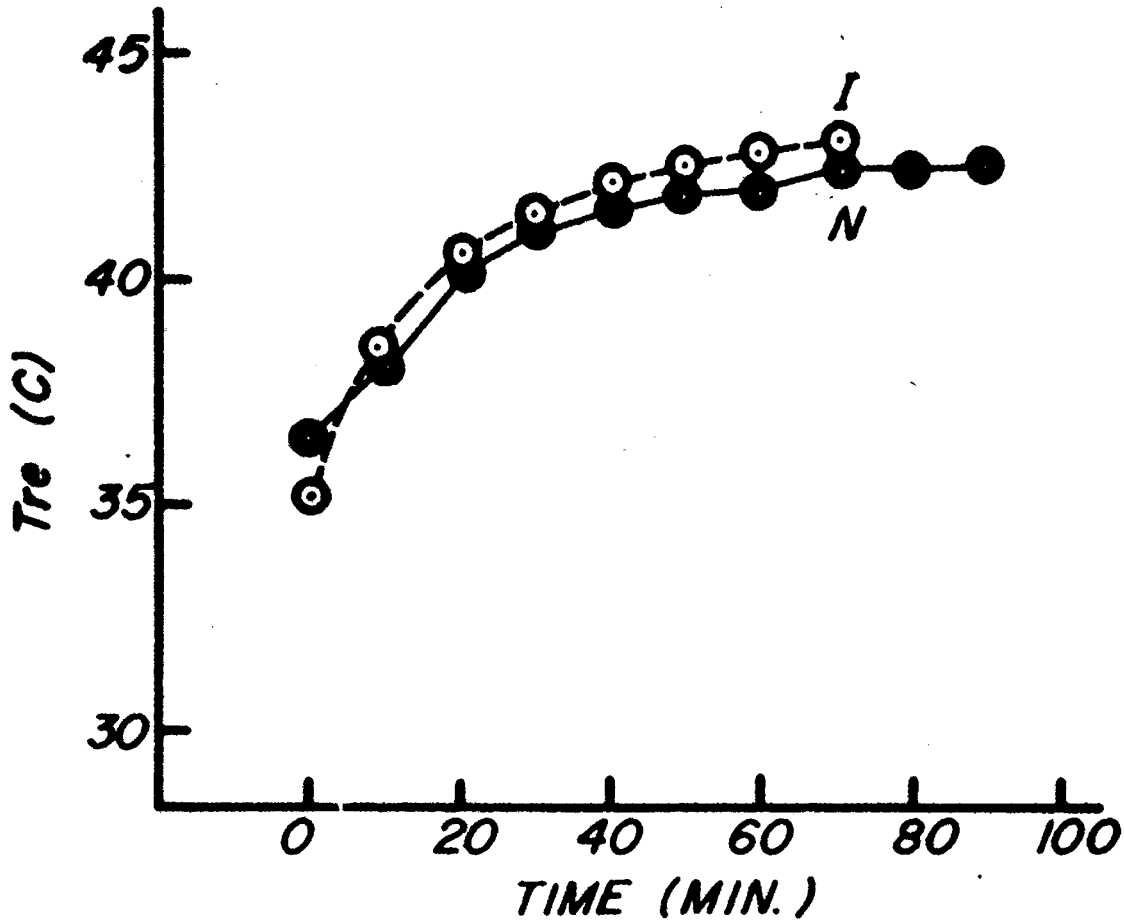
45
40
35
30
Tre (C)
I
N
0
20
40
60
80
100
TIME (MIN.)

FIG. 6 RATE OF INCREASE OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND INSULIN TREATED PLUS GLUCOSE FED (I + G) ADULT RATS FOLLOWING EXPOSURE TO 38 C. THE LINES ARE DRAWN FROM THE REGRESSION EQUATION, $y = b + ax$.

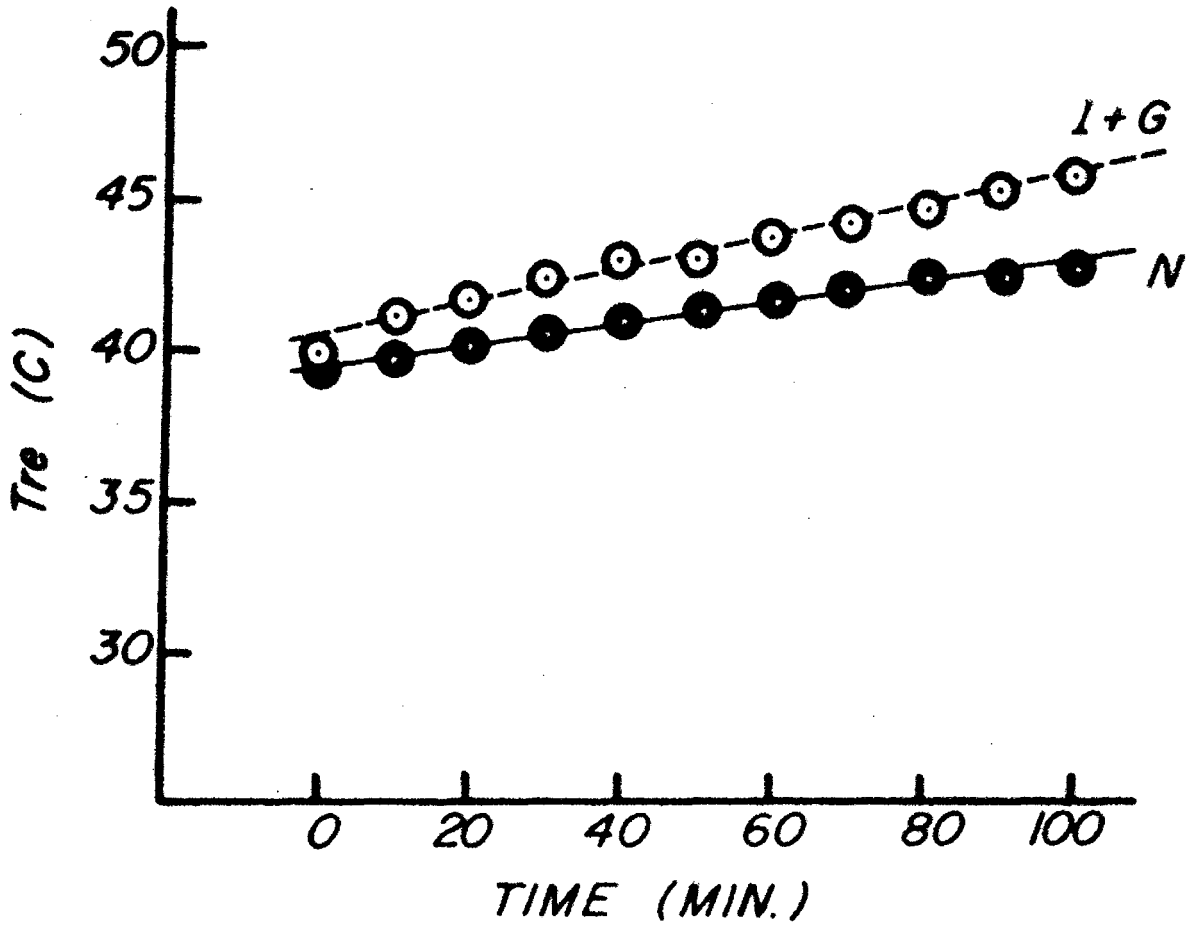
50
45
40
35
30
Tre (C)
I+G
N
0
20
40
60
80
100
TIME (MIN.)

TABLE 3. VALUES OF THE CONSTANTS a AND b, AND COEFFICIENT OF CORRELATION r, IN THE REGRESSION EQUATION $y = b + ax$ FOR CONTROL (C) AND INSULIN TREATED PLUS GLUCOSE FED (I+G) ADULT RATS EXPOSED TO AN AMBIENT TEMPERATURE OF 38 C. WHERE x IS THE TIME IN MINUTES AND y IS THE RECTAL TEMPERATURE IN C.

Treatment	b	a	r	Significance
C	39.5859	.0357		
			0.9738	$p < .05$
I + G	40.4843	.0566		

STEADY STATE RECTAL TEMPERATURES AT DIFFERENT AMBIENT TEMPERATURES IN NORMOGLYCEMIC HYPOGLYCEMIC AND HYPERGLYCEMIC RATS

The steady state temperatures of glucose fed, streptozotocin treated and insulin treated animals exposed to ambient temperatures of 15, 25, 32 and 35 C are given in Tables 4,5,6 and 7 (see p-47 to 50) along with values of the normoglycemic controls. The values of Tre were not significantly different in the hyperglycemic rats as compared to those of the controls at all the ambient temperatures. However, the insulin treated animals had significantly lower body temperature as compared to controls at all the four ambient temperatures.

EFFECT OF HYPERGLYCEMIA ON RATE OF FALL OF RECTAL TEMPERATURE (Tre) ON EXPOSURE TO -20 C

a) Glucose fed animals

i) Adult rats

The rectal temperature fell linearly with time in normoglycemic as well as in hyperglycemic animals (Fig.7). The regression lines of the values of Tre against time gave high coefficient of correlation in control and treated animals. The values of a and b and of the coefficient of correlation are shown in Table 8 (see p-51). The difference between the slopes of the two lines was statistically

FIG. 7 RATE OF FALL OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND GLUCOSE FED (G) ADULTS RATS FOLLOWING EXPOSURE TO -20 C. THE LINES ARE DRAWN FROM THE REGRESSION EQUATIONS $y = b - ax$.

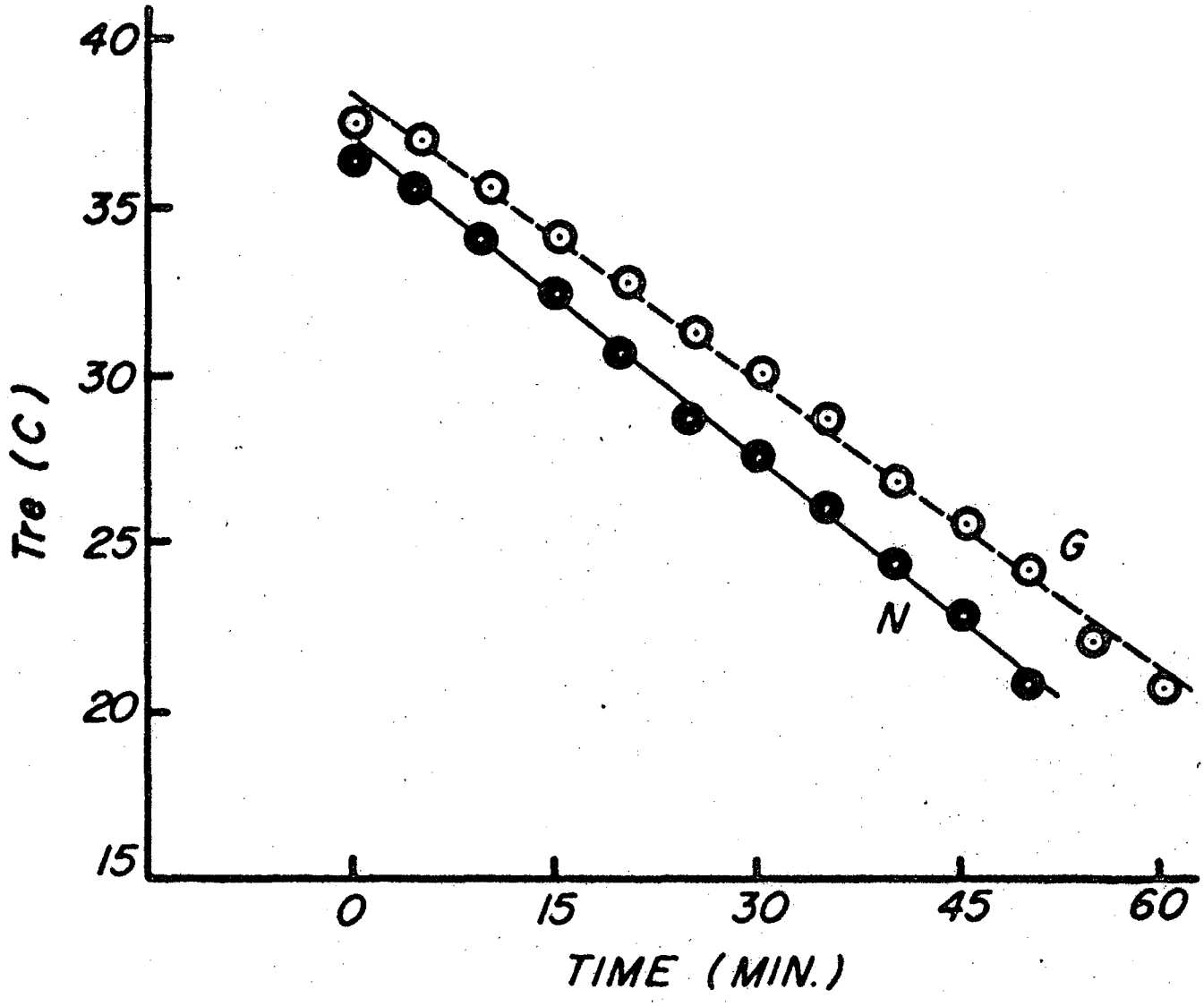
40
35
30
25
20
15
Tre (C)
0
15
30
45
60
TIME (MIN.)
G
N

TABLE 4. STEADY STATE RECTAL TEMPERATURE (Tre) AT Ta OF 15 C FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	Tre at 15°C	Significance
Control	5	151 ± 9.19	38.25 ± 0.53	NS
SZC	5	150.6 ± 8.47	37.55 ± 2.33	
Control	5	156.8 ± 15.22	38.15 ± 0.65	$p < .05$
Insulin	5	158.2 ± 14.41	34.75 ± 2.59	
Control	5	174.2 ± 12.50	37.25 ± 0.43	NS
Glucose fed	5	174.8 ± 15.79	37. 7 ± 1.71	

TABLE 5. STEADY STATE RECTAL TEMPERATURE (Tre) AT Ta OF 25 C FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	Tre at 25 C	Significance
Control	6	174. ± 11.64	37.70 ± 1.48	NS
SZC	6	173.60± 15.47	37.45 ± 1.59	
Control	6	155.00± 12.65	37.46 ± 0.43	p <.001
Insulin	6	159.00± 10.85	34.13 ± 1.73	
Control	5	145.60± 12.90	37.55 ± 1.30	NS
Glucose fed	5	145.20± 12.28	37.70 ± 2.03	

TABLE 6. STEADY STATE RECTAL TEMPERATURE (Tre) AT Ta OF 32 C FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	Tre at 32 C	Significance
Control	5	163.40 ± 14. 2	40.95 ± 1.08	Ns
SZC	5	162.00 ± 12.19	42.05 ± 0.65	
Control	6	168.67 ± 6.80	39.29 ± 0.25	p <.001
Insulin	6	168.67 ± 6.80	38.46 ± 0.25	
Control	5	172.20 ± 5.93	39.25 ± 0.59	NS
Glucose fed	5	172.20 ± 5.95	38.55 ± 0.54	

TABLE 7. STEADY STATE RECTAL TEMPERATURE (Tre) EXPOSED AT Ta OF 35 C FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	Tre at 35 C	Significance
Control	5	161.80 ± 5.02	42.85 ± 0.29	NS
SZC	5	162.00 ± 6.28	42.55 ± 0.54	
Control	5	180.20 ± 13.50	41.20 ± 0.21	$p < .05$
Insulin	5	182.60 ± 14.67	40.75 ± 0.35	
Control	5	176.00 ± 9.62	40.25 ± 0.47	NS
Glucose fed	5	176.20 ± 9.60	39.70 ± 0.40	

TABLE 8. VALUES OF THE CONSTANTS a AND b, AND COEFFICIENT OF CORRELATION, r IN THE REGRESSION EQUATION $y = b - ax$ FOR CONTROL (C) AND GLUCOSE FED (G) ADULT RATS EXPOSED TO AN AMBIENT TEMPERATURE OF -20 C WHERE x IS THE TIME IN MINUTES AND y IS THE RECTAL TEMPERATURE IN C.

Treatment	b	a	r	Significance
C	37.2205	-.3226		
			.9991	$p < .01$
G	38.2886	-.2874		

significant, the line for glucose fed animals occupying a higher position.

ii) Young rats

On exposure to -10 C the Tre fell with time in curvilinear manner in both the control and glucose fed rats (Fig. 8). The average time taken for Tre to reach 20 C was 39.17 ± 11.48 minutes in control rats and 26.16 ± 1.67 in glucose fed rats (Table 9, see p-53). The difference of 13.01 minutes was statistically significant ($p < .001$).

b) Streptozotocin treated rats

The rectal temperature fell linearly with time in normoglycemic as well as in diabetic animals (Fig. 9). The regression lines of the values of Tre against time gave high coefficient of correlation in control and treated animals. The values of a and b and of the coefficient of correlation are shown in Table 10 (see p- 54). The difference between the slopes of the two lines was statistically significant, the lines of streptozotocin treated animals occupying a lower position.

c) Effect of insulin hypoglycemia on rate of fall of rectal temperature (Tre) on exposure to -20 C

The linear fall in Tre was with time in normoglycemic as well as in hypoglycemic animals is shown in Fig. 10. The regresaion lines gave high coefficient of

FIG. 8 RATE OF FALL OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND GLUCOSE FED (G) YOUNG RATS FOLLOWING EXPOSURE TO -20 C.

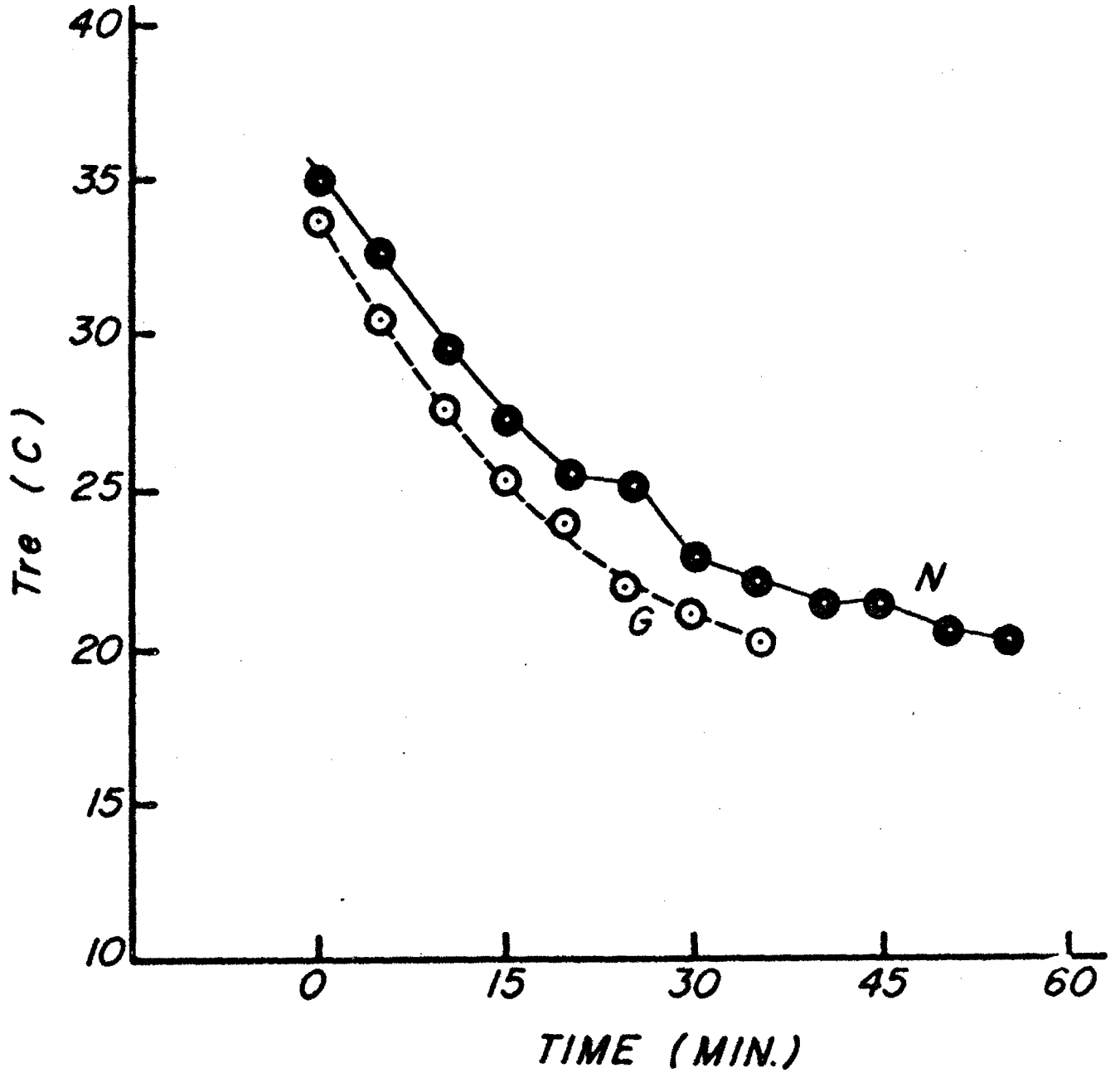
40
35
30
25
20
15
10
Tre (C)
0
15
30
45
60
TIME (MIN.)
N
G

FIG. 9 RATE OF FALL OF RECTAL TEMPERATURE (Tre) IN NORMOGLYCEMIC (N) AND STREPTOZOTOCIN TREATED (SZC) ADULT RATS FOLLOWING EXPOSURE TO -20 C. THE LINES ARE DRAWN FROM THE REGRESSION EQUATIONS $y = b - ax$.

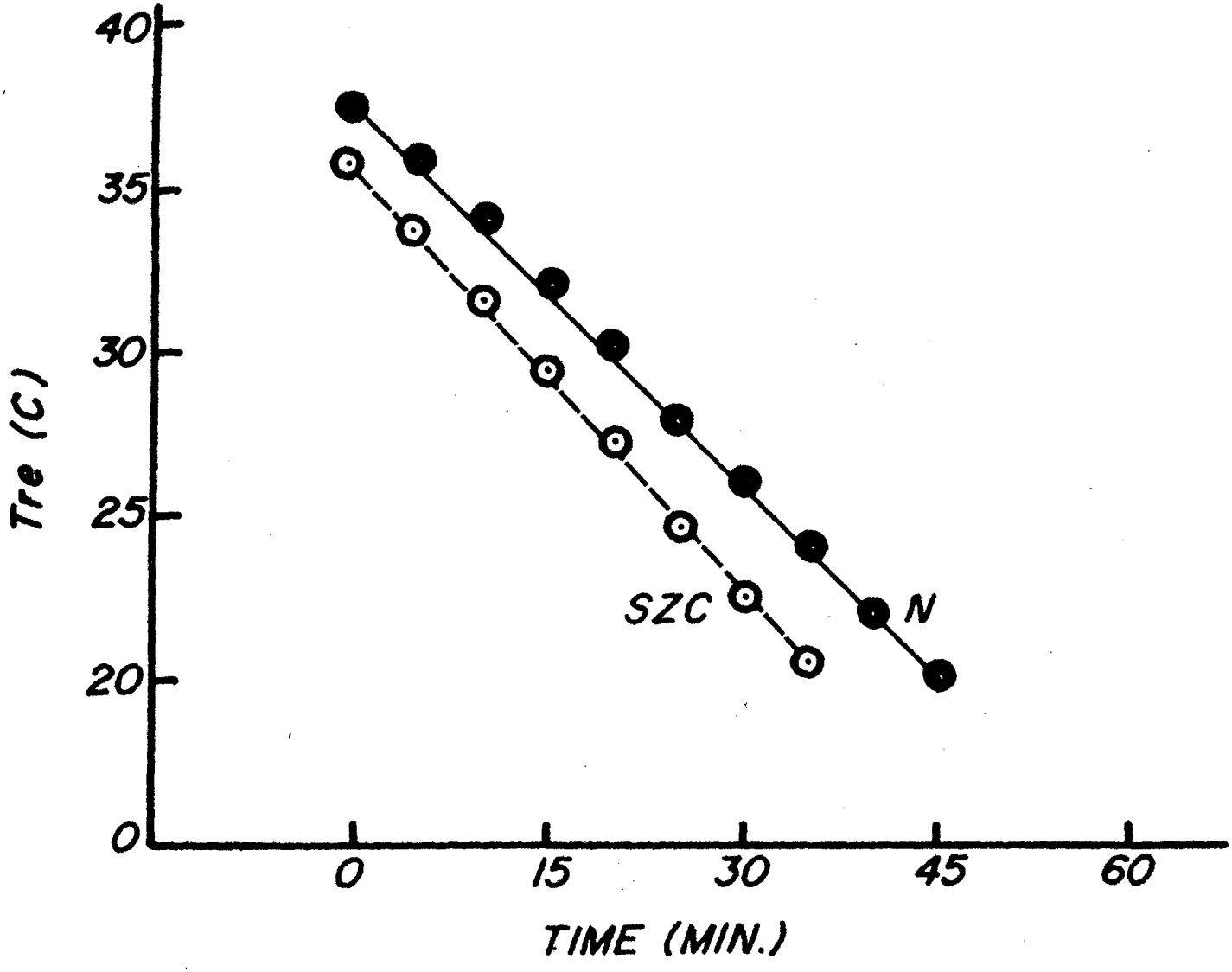
40
35
30
25
20
0
Tre (C)
0
15
30
45
60
TIME (MIN.)
SZC
N

FIG. 10 RATE OF FALL OF RECTAL TEMPERATURE (T_{re}) IN NORMOGLYCEMIC (N) AND INSULIN TREATED (I) ADULT RATS FOLLOWING EXPOSURE TO -20 C. THE LINES ARE DRAWN FROM THE REGRESSION EQUATION $y = b - ax$.

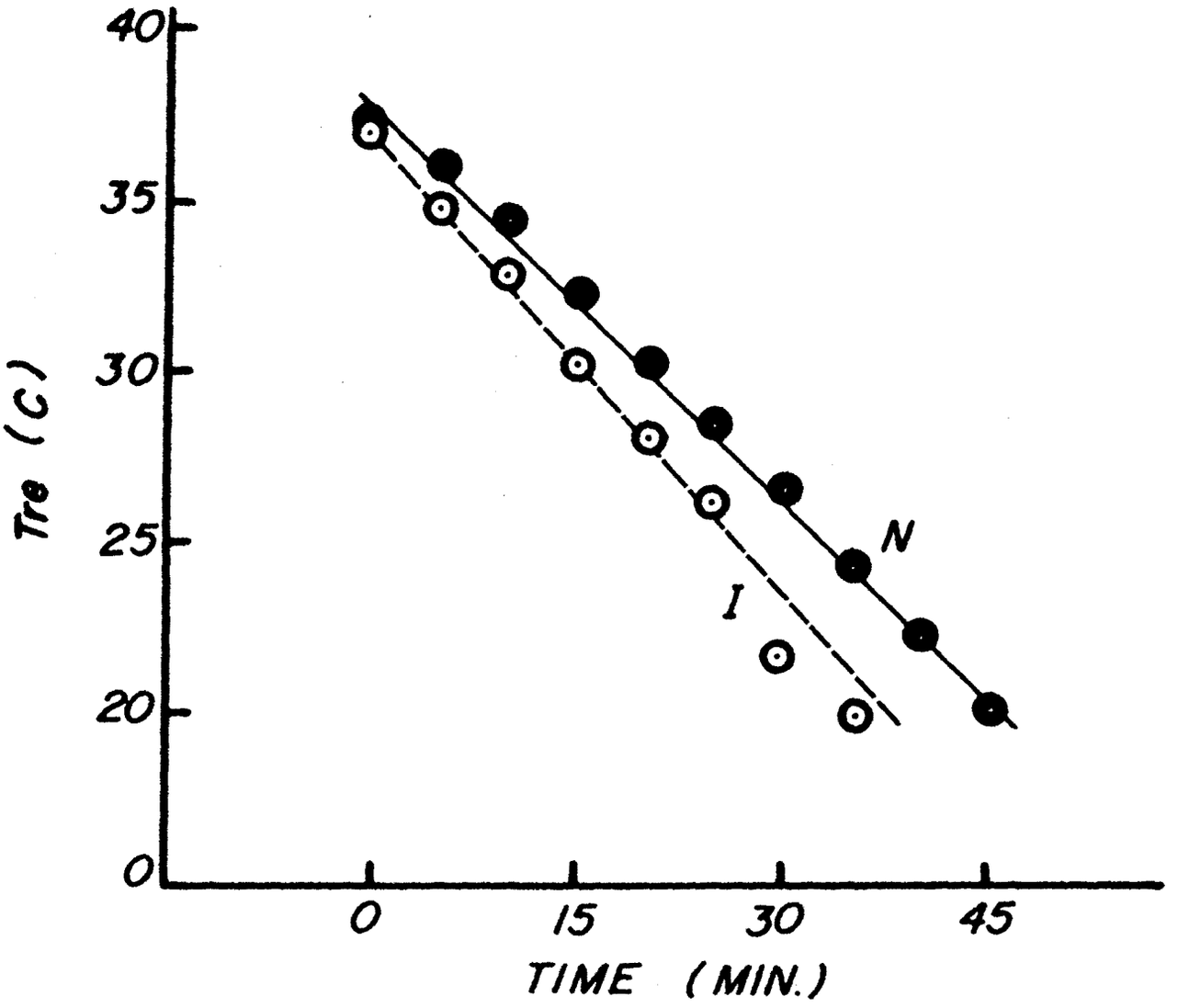
40
35
30
25
20
0
Tre (C)
0
15
30
45
TIME (MIN.)
N
I

TABLE 9. TIME TAKEN TO REACH T_{re} TO 20 C IN YOUNG RATS EXPOSED AT T_a OF -20 C

Treatment	N	B.W.	Time	Significance
Young rats (Control)	6	40.33 ± 2.33	39.17 ± 11.28	$p < .001$
Glucose fed	6	40. 0 ± 2.12	26.16 ± 8.67	

TABLE 10. VALUES OF THE CONSTANTS a AND b, AND COEFFICIENT OF CORRELATION, r IN THE REGRESSION EQUATION $y = b - ax$ FOR CONTROL (C) AND STREPTOZOTOCIN TREATED (SZC) ADULT RATS EXPOSED TO AN AMBIENT TEMPERATURE OF -20 C WHERE x IS THE TIME IN MINUTES AND y IS THE RECTAL TEMPERATURE IN C.

Treatment	b	a	r	Significance
C	37.9514	-.3964		
			.9998	$p < .001$
SZC	36.0192	-.4495		

correlation in normoglycemic controls and hypoglycemic animals. The values of a and b and of the coefficient of correlation are shown in Table 11 (see p-56). The line for insulin treated animals was steeper than that for the controls, and the difference between the two slopes was significant.

d) Effect of glucose feeding plus insulin treatment on rate of fall of rectal temperature (Tre) on exposure to -20 C

The rectal temperature (Tre) was linearly related to time in controls as well as in glucose fed plus insulin treated animals (Fig. 11). The regression lines of the values of Tre against time gave high coefficient of correlation in control and treated animals. The values of a and b and of the coefficient of correlation are shown in Table 12 (see p-57). The difference between the slopes of the two lines was statistically significant. The line of glucose fed plus insulin treated animals occupyied higher position as compared to the controls.

MEAN CRITICAL RECTAL TEMPERATURE AT THE TIME OF DEATH FOLLOWING EXPOSURE TO -20 C

Mean critical rectal temperature (C Tre) is the rectal temperature at which death occured was estimated for control and treated animals by the following equation:

$$C\ Tre = b - a\ t$$

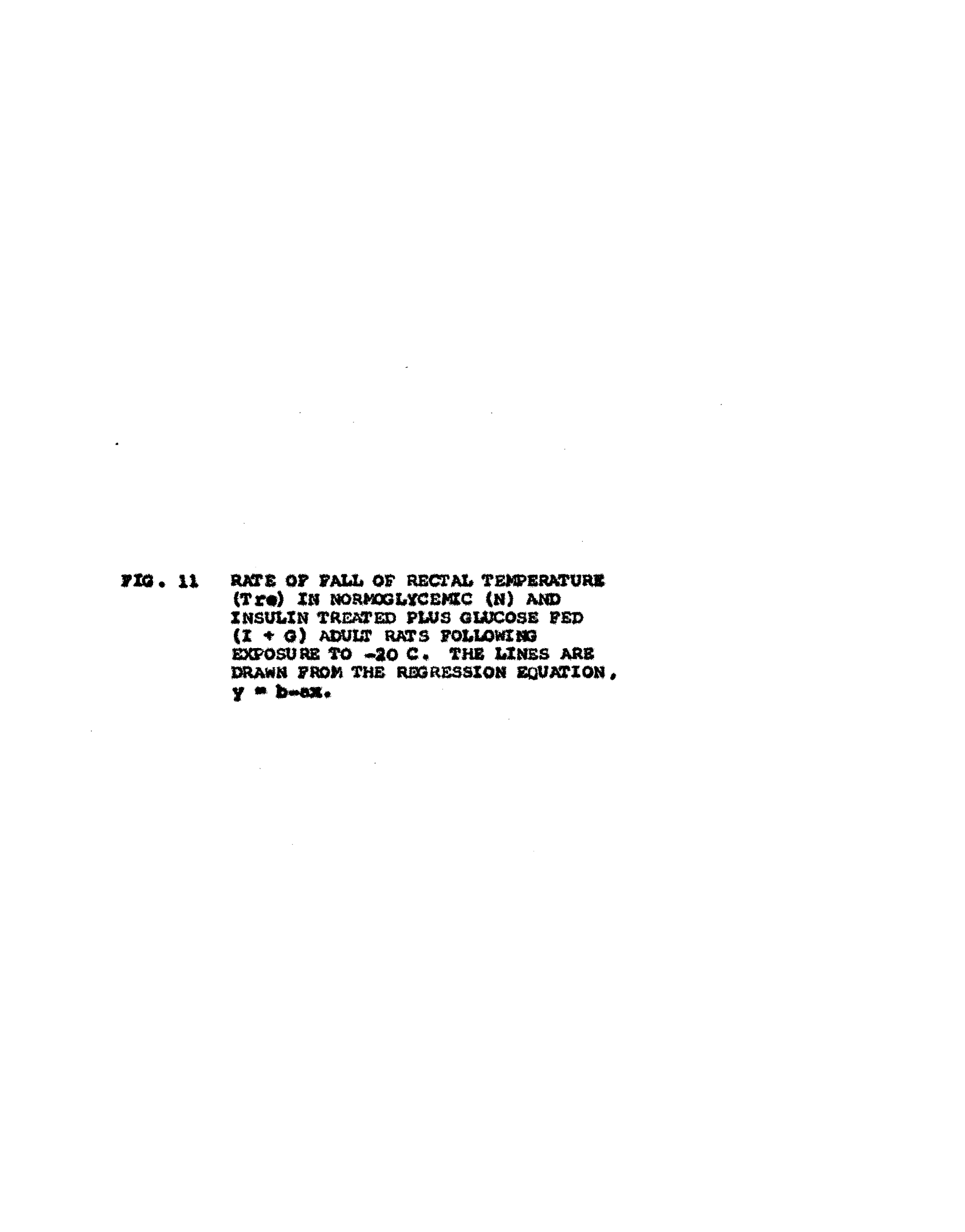

FIG. 11 RATE OF FALL OF RECTAL TEMPERATURE (Tre) IN NORMOGLYCEMIC (N) AND INSULIN TREATED PLUS GLUCOSE FED (I + G) ADULT RATS FOLLOWING EXPOSURE TO -20 C. THE LINES ARE DRAWN FROM THE REGRESSION EQUATION, $y = b - ax$.

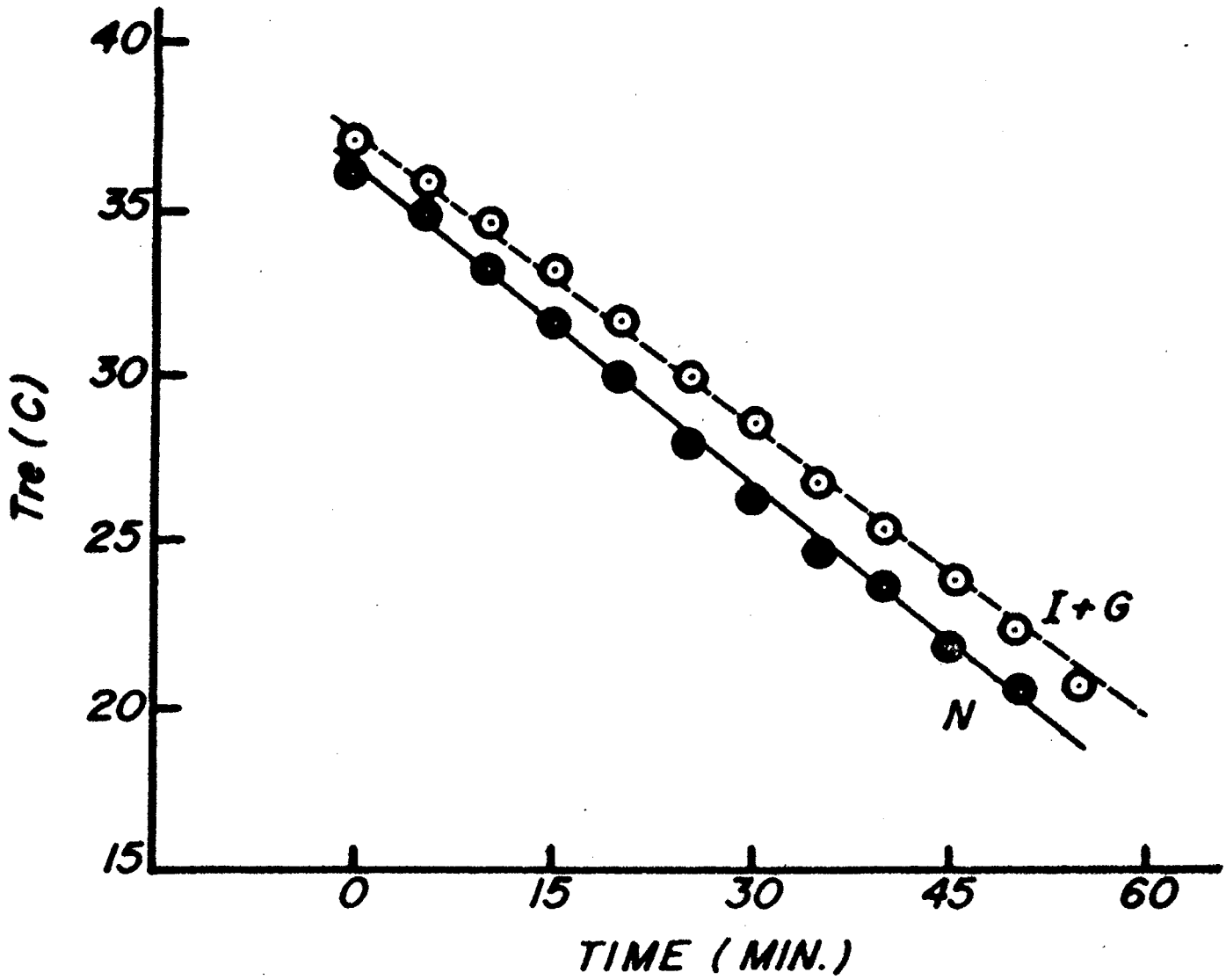
40
35
30
25
20
15
Tre (C)
0
15
30
45
60
TIME (MIN.)
I+G
N

TABLE 11. VALUES OF THE CONSTANTS a AND b, AND COEFFICIENT OF CORRELATION, r, IN THE REGRESSION EQUATION $y = b - ax$ FOR CONTROL (C) AND INSULIN TREATED (I) ADULT RATS EXPOSED TO AN AMBIENT TEMPERATURE OF -20 C. WHERE x IS THE TIME IN MINUTES AND y IS THE RECTAL TEMPERATURE IN C.

Treatment	b	a	r	Significance
C	38.1437	-.3909		
			.9951	$p < .05$
I	37.1325	-.4518		

TABLE 12. VALUES OF THE CONSTANTS a AND b, AND COEFFICIENT OF CORRELATION, r, IN THE REGRESSION EQUATION $y = b - ax$ FOR CONTROL (C) AND INSULIN TREATED AND GLUCOSE FED (I + G) ADULT RATS EXPOSED TO AN AMBIENT TEMPERATURE -20 C. WHERE x IS THE TIME IN MINUTES AND y IS THE RECTAL TEMPERATURE IN C.

Treatment	b	a	r	Significance
C	36.4641	-.3226		
			.9983	$p < .05$
I + G	37.4352	-.2996		

Where t is the mean survival time and a and b are constants in the regression line relating Tre to time. The values of C Tre for normoglycemic, glucose fed, streptozotocin treated, insulin treated and glucose fed plus insulin treated rats are given in Table 13 (see p-59).

EFFECT OF HYPERGLYCEMIA ON THERMAL TOLERANCE

a) Glucose fed rats

i) Adult rats

Mean survival time under cold stress (-20 C) was 72 ± 2.00 in glucose fed rats and 61 ± 2.14 minutes in controls (Table 14, see p-60). The increase of 10.83 in survival time of glucose fed rats was statistically significant ($p < .001$). Hyperglycemia produced by glucose feeding therefore, increases tolerance to cold.

Mean survival time was 90.22 ± 14.35 minutes in glucose fed rats exposed to heat stress (38 C). On the other hand, none of the control rats died during the 150 minutes of observation (Table 15, see p-61). The difference between the two was statistically significant ($p < .001$).

ii) Young rats

Mean survival time was 50.16 ± 11.67 minutes in glucose fed young rats exposed to cold stress (-10 C). The control rats survived for 66.17 ± 10.40 minutes (Table 16, see p-62). The decrease in survival time of glucose fed rats by

TABLE 13. MEAN CRITICAL RECTAL TEMPERATURE (C Tre) AT THE TIME OF DEATH FOLLOWING EXPOSURE TO -20 C.

Treatment	C Tre
Control	13.80
S2C	14.82
Control	17.42
Glucose feeding	17.59
Control	15.58
Insulin	16.65
Control	16.98
Glucose plus Insulin	16.12

TABLE 14. SURVIVAL TIME (ST) IN ADULT RATS AT -20 C FOLLOWING DIFFERENT TREATMENTS

Treatment	N	B.W.	ST	Significance
Control	6	150.40 ± 2.54	60.67 ± 1.75	p <.001
S2C	6	149.56 ± 2.32	47.17 ± 1.94	
Control	10	155.20 ± 3.49	57.70 ± 2.11	p <.001
Insulin	10	154.80 ± 3.71	45.30 ± 2.87	
Control	7	196.71 ± 17.58	61.17 ± 2.14	p <.001
Glucose fed	7	196.64 ± 17.26	72.00 ± 2.00	
Control	8	199.50 ± 17.36	60.38 ± 2.50	p <.001
Glucose plus insulin	8	202.00 ± 18.85	71.13 ± 1.89	

TABLE 15. SURVIVAL TIME IN ADULT RATS DURING EXPOSURE TO 38 C

Treatment	N	B.W.	ST	Significance
Normoglycemic	12	167.80 ± 13.58	150 min	p <.001
Insulin	12	168.00 ± 12.43	74.25 ± 11.73 min	
Normoglycemic	9	183.38 ± 11.82	150 min	p <.001
Glucose feeding	9	183.22 ± 9.42	90.22 ± 14.35 min	
Normoglycemic	6	166.38 ± 4.56	150 min	p <.001
Insulin plus Glucose	6	166.56 ± 4.48	97.83 ± 18.28 min	

TABLE 16. SHOWING SURVIVAL TIME (ST) IN YOUNG RATS AT -10 C

Treatment	N	B.W.	ST	Significance
Control	6	40.33 ± 2.33	66.17 ± 10.40	$p < .001$
Glucose feeding	6	40. 0 ± 2.12	50.16 ± 11.67	

16.01 minutes was statistically significant ($p < .001$). Thus, glucose feeding in young animals decreases tolerance to cold.

At an ambient temperature of 38 C, the mean survival time of control and glucose fed rats was 112.60 ± 24.40 and 101.80 ± 21.41 minutes respectively (Table 17, see p-64). The difference between two was statistically significant ($p < .001$).

b) Streptozotocin treated rats

Mean survival time under cold stress (-20 C) was 47.17 ± 1.94 in streptozotocin treated rats and 60.67 ± 1.75 minutes in control rats (Table 14, see p-60). The decrease in survival time of streptozotocin treated rats by 13.5 minutes was statistically significant ($p < .001$). Thus, streptozotocin treated rats showed less tolerance.

Mean survival time was 75.29 ± 13.64 minutes in streptozotocin treated rats exposed to heat stress (38 C) and 86 ± 9.54 minutes in controls (Table 18, see p-65). The difference of 10.71 minutes was significant statistically ($p < .05$). All the streptozotocin treated rats died. In controls five out of seven animals died and the other two survived during the 150 minutes of observation.

EFFECT OF INSULIN HYPOGLYCEMIA ON THERMAL TOLERANCE

a) Adult rats

Mean survival time under cold stress (-20 C) was

TABLE 17. SHOWING SURVIVAL TIME IN YOUNG RATS AT 38 C

Treatment	N	B.W.	Survival time at 38 C	Significance
Normoglycemic	6	58.33 ± 5.16	86.17 ± 14.14 min	p ∠.001
Insulin treatment	6	58.67 ± 5.56	58.67 ± 11.64 min	
Normoglycemic	5	48. 8 ± 6.12	112.60 ± 24.24 min	p ∠.001
Glucose feeding	5	49. 6 ± 6.24	101.80 ± 21.41 min	

TABLE 18 SHOWING SURVIVAL TIME (ST) IN STREPTOZOTOCIN TREATED ADULTS RATS AT 38 C

Treatment	N	B.W.	St at 38 C	Significance
Normoglycemic	7	159.14 ± 8.34	86.00 ± 9.54	$p < .05$
S2C Treatment	7	159.00 ± 10.26	75.29 ± 13.64	

57.70 ± 2.11 minutes in controls and 45.30 ± 2.87 minutes in insulin treated rats (Table 14, see-p-60). The decrease of 12.40 minutes in survival time of insulin treated rats was statistically significant ($p < .001$). Hypoglycemia produced by insulin thus, decreases tolerance to cold.

Mean survival time was 74.25 ± 11.73 minutes in insulin treated rats exposed to heat stress (38 C). On the other hand, none of the control rats died during the 150 minutes of observation (Table 15, see p-61). The difference was statistically significant ($p < .001$).

b) Young rats

Mean survival time of control and insulin treated young rats exposed to heat stress (38 C) was 86.17 ± 14.44 minutes and 58.67 ± 11.64 minutes respectively (Table 17, see p-64). The decrease in survival time of insulin treated rats by 27.4 minutes was statistically significant ($p < .001$).

EFFECT OF INSULIN TREATMENT PLUS GLUCOSE FEEDING ON THERMAL TOLERANCE

Mean survival time under cold stress (-20 C) was 71.13 ± 1.89 minutes in glucose fed rats treated with insulin and 60.38 ± 2.50 minutes in controls treated with saline (Table 14, see p-60). The increase of 10.75 minutes in survival time of glucose fed plus insulin treated rats was statistically significant ($p < .001$).

Mean survival time was 97.83 ± 18.28 minutes in insulin treated rats plus glucos fed rats exposed to heat stress (38 C). On the other hand, none of the controls died during the 150 minutes of observation (Table 15). The difference between the two was statistically significant ($p < .001$).

SUSCEPTIBILITY OF NORMOGLYCEMIC, GLUCOSE FED, STREPTOZOTOCIN TREATED AND INSULIN TREATED ANIMALS TO LOCAL COLD INJURY

On exposure of the limbs to -23 C, nine out of the ten normoglycemic animals and five out of ten the glucose fed animals developed frost bite. The lower incidence of frost bite in glucose fed animals as compared to the normoglycemic controls was statistically significant (Table 19, see p-68).

On exposure of animals to -19 C three out of ten normoglycemic animals sustained cold injury. On the other hand, in the case of insulin treated and streptozotocin treated animals eight of ten animals developed cold injury (Table 20, see p-69). The difference was statistically significant.

CHANGES IN BLOOD GLUCOSE LEVELS OF NORMOGLYCEMIC, HYPOGLYCEMIC AND HYPERGLYCEMIC ANIMALS ON EXPOSURE TO -20 C

a) Normoglycemic rats

The mean blood glucose levels in normoglycemic rats

TABLE 19. INCIDENCE OF FROSTBITE IN THE GROUPS OF CONTROL (C) AND GLUCOSE FED (G) ADULT RATS ON EXPOSURE OF LIMBS TO FREEZING MIXTURE (TEMPERATURE - 2° C). SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE TWO GROUPS WAS DETERMINED BY CHISQUARE METHOD (FISCHER'S EXAT-TEST).

Treatment	No. with frostbite	No. without frostbite	Significance
C	9	1	
			$p < 0.07$
G	5	5	

TABLE 20. INCIDENCE OF FROSTBITE IN INSULIN TREATED (I) AND STREPTOZOTOCIN TREATED (SZC) AS COMPARED TO THE CONTROL (C) ON EXPOSURE OF THE LIMBS TO FREEZING MIXTURE (TEMPERATURE -19 C). SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE TWO GROUPS WAS DETERMINED BY CHISQUARE METHOD (FISCHER'S EXAT-TEST).

Treatment	No. with frostbite	No. without frostbite	Significance
C	3	7	
I	8	2	$p < .0.035$
SZC	8	2	$p < .0.035$

was found to be 96.78 ± 7.40 mg/100 ml of blood at a neutral temperature of 27 ± 1 C. It increased to 150.33 ± 7.33 mg/100 ml on exposure to cold stress (-20 C) for 30 minutes (Table 21, see p-71 and Fig.12). The change in blood glucose level was statistically significant ($p < .001$).

b) Hypoglycemic rats

A mean blood glucose level of 96.78 ± 7.40 mg/100 ml at a neutral temperature of 27 ± 1 C fell to 26 ± 2.24 one hour after insulin treatment and subsequently rose to 46.67 ± 13.29 and 91.67 ± 19.66 at the end of second and third hour respectively (Table 22, see p-72). In animals exposed to -20 C one hour after insulin injection the mean blood glucose level rose from 26 ± 2.24 to 67.09 ± 13.39 mg % after exposure to cold for 30 minutes (Table 21 and Fig. 12). Although, in insulin treated animals the mean blood glucose level after the first hour rose at a much higher rate at -20 C as compared to that at 27 ± 1 C the value at the end of 30 minutes exposure to cold is much less than that of the normoglycemic rats exposed to the cold. The value at the end of cold exposure are 150.33 ± 7.33 and 67.09 ± 13.39 mg/100 ml of blood in normoglycemic and hypoglycemic animals respectively. The difference was highly significant (Table 23, see p-73).

c) Hyperglycemic rats

1) Glucose feeding

A mean blood glucose level of 96.78 ± 7.40 mg/100 ml

FIG. 12 BLOOD GLUCOSE LEVELS IN NORMOGLYCEMIC (N), GLUCOSE FED (G), INSULIN TREATED (I) GLUCOSE FED PLUS INSULIN TREATED (I + G) AND STREPTOZOTOCIN TREATED (SZC) ADULT RATS BEFORE AND AFTER EXPOSURE TO -20 C.

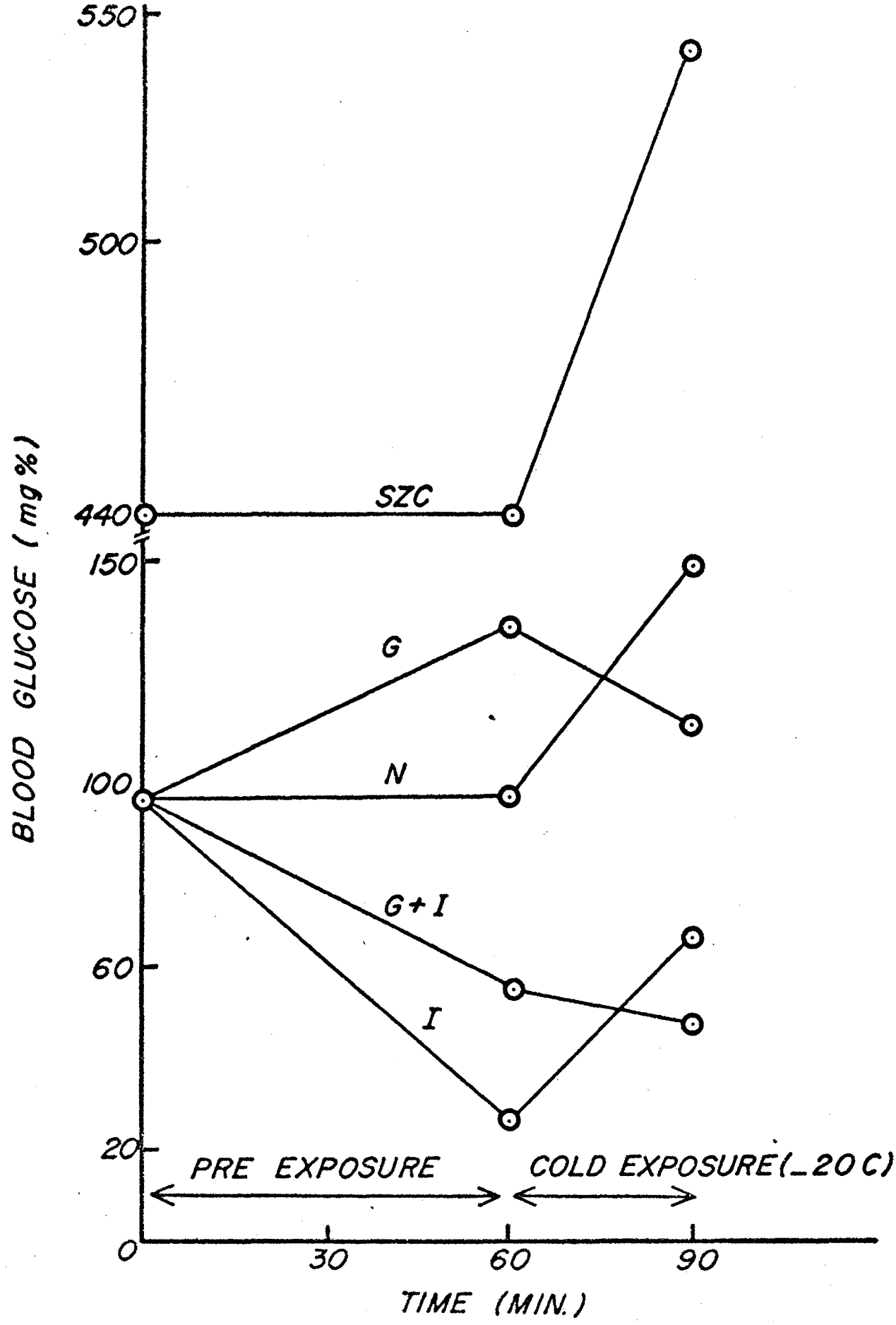
550
500
440
150
100
60
20
0
30
60
90
SZC
G
N
G+I
I
BLOOD GLUCOSE (mg%)
PRE EXPOSURE
COLD EXPOSURE(-20C)
TIME (MIN.)

TABLE 21. SHOWING BLOOD GLUCOSE LEVELS IN ADULT RATS BEFORE AND AFTER EXPOSURE TO -20 C FOR 30 MINUTES

Treatment	N	Blood Glucose Levels		Significance
		Before	After	
Normoglycemic	6	96.78 ± 7.40	150.33 ± 7.33	$p < .001$
SZC	6	441.00 ± 31.29	542.60 ± 42.24	$p < .001$
Insulin	6	26.00 ± 2.24	67.09 ± 13.39	$p < .001$
Glucose	6	135.75 ± 10.10	114.17 ± 70.44	$p < .001$
Glucose plus Insulin	6	54.49 ± 15.06	47.70 ± 12.05	$p < .01$

Note:- Glucose feeding as well as insulin treatment was given one hour before treatment.

TABLE 22. SHOWING BLOOD GLUCOSE LEVELS AT ONE HOUR INTERVALS AT Ta OF 27 ± 1 C

Treatment	N	Blood Glucose Levels (mg/100 ml)			
		0 Hr	1Hr.	2 Hr.	3 Hr.
Control	6	96.78 ± 7.40	-	-	-
SZC	5	441.00 ± 11.29	-	-	-
Insulin	6	-	26.00 ± 2.24	46.67 ± 13.29	91.67 ± 19.66
Glucose fed	6	-	133.75 ± 10.10	110.00 ± 7.74	74.51 ± 14.31
Glucose fed young rats	5	110.42 ± 3.54	138.12 ± 8.37	-	-
Insulin plus glucose	6	-	54.49 ± 15.06	61.33 ± 9.42	74.11 ± 12.83

TABLE 23. SHOWING BLOOD GLUCOSE LEVELS IN ADULT RATS EXPOSED AT Ta OF -20 C FOR 30 MINUTES

Treatment	N	B.W.	Blood Glucose Leves	Significance
Normoglycemic	6	186.31 ± 16.48	154.17 ± 12.81	p <.001
S2C treated	6	189.67 ± 16.65	542.60 ± 42.24	
Normoglycemic	5	155.40 ± 3.71	150.33 ± 7.33	p <.001
Insulin treated	5	155.30 ± 3.49	67.09 ± 13.39	
Normoglycemic	5	149.20 ± 2.54	149.66 ± 7.88	p <.001
Glucose fed	6	150.31 ± 2.04	114.17 ± 7.04	
Normoglycemic	5	165.60 ± 3.58	150.33 ± 7.33	p <.001
Glucose plus insulin	7	162.31 ± 2.62	47.70 ± 12.05	

Note:- Glucose feeding as well as insulin treatment was given one hour before cold exposure.

at neutral temperature of 27 ± 1 C increased to 135.75 ± 10.10 mg/100 ml of blood one hour after glucose feeding and subsequently fell to 110 ± 7.74 and 74.51 ± 14.31 mg at the end of second and third hour respectively (Table 22, see p-72). In animals exposed to cold one hour after glucose feeding the mean blood glucose fell from 135 ± 10.10 to 114.17 ± 7.044 mg/100 ml of blood following 30 minutes of exposure to cold (Table 21 and Fig. 12). The rate of fall of blood glucose at -20 C was about the same as at 27 ± 1 C. At the end of cold exposure the value of blood glucose were 149.66 ± 7.88 and 114.17 ± 7.04 respectively in normoglycemic and hyperglycemic animals. The difference was highly significant (Table 23).

ii) Streptozotocin treatment

Streptozotocin treated rats had a mean blood glucose levels of 441.00 ± 11.29 and increased to 542.60 ± 42.24 mg % (Table 21 and Fig 12) when exposed to cold stress. The difference was statistically significant ($p < .001$).

d) Glucose feeding plus insulin treatment

A mean of blood glucose level of 96.78 ± 7.40 mg/100 ml at ambient temperature of 27 ± 1 C fell to 54.49 ± 15.06 one hour after glucose feeding and insulin treatment and subsequently rose to 61.33 ± 9.42 and 74.11 ± 12.83 at the end of second and third hour respectively (Table 22). In animals exposed to -20 C one hour after glu-

cose feeding plus insulin treatment, the mean blood glucose level fell from 54.49 *± 15.06 to 47.70 ± 12.05 mg after exposure to cold (Table 21 and Fig. 12). The difference is statistically significant. In glucose fed plus insulin treated animals the mean blood glucose level at end of 30 minutes exposure to cold is significantly lower than that in normoglycemic rats exposed to cold. The values at the end of cold exposure are 150.33 ± 7.33 and 47.70 ± 12.05 in normoglycemic and treated animals respectively. The difference is highly significant (Table 23).

CHANGES IN BLOOD GLUCOSE LEVELS OF NORMOGLYCEMIC, HYPOGLYCEMIC AND HYPERGLYCEMIC ANIMALS ON EXPOSURE TO 38 C

a) Normoglycemic rats

In normoglycemic rats exposed to heat stress (39 C for 60 minutes), the mean blood glucose level increased to 140.82 ± 30.96 from 96.78 ± 7.40 mg/100 ml of blood at 27 ± 1 C. The increase of 44.04 mg in rats exposed to 38 C was statistically significant (Table 24, see p-76 and Fig 13).

b) Hypoglycemic rats

The mean blood glucose of insulin treated animals at 27 ± 1 C was 46.67 ± 13.29 mg and 26 ± 2.24 mg one hour after insulin treatment. When the animals were exposed to 38 C during the second hour of insulin administration the mean blood glucose rose from 26 ± 2.24 mg/100 ml

FIG. 13 BLOOD GLUCOSE LEVELS IN NORMOGLYCEMIC (N) GLUCOSE FED (G) INSULIN TREATED (I) GLUCOSE FED PLUS INSULIN TREATED (G+I) AND STREPTOZOTOCIN TREATED (SZC) ADULT RATS BEFORE AND AFTER EXPOSURE TO 38 C.

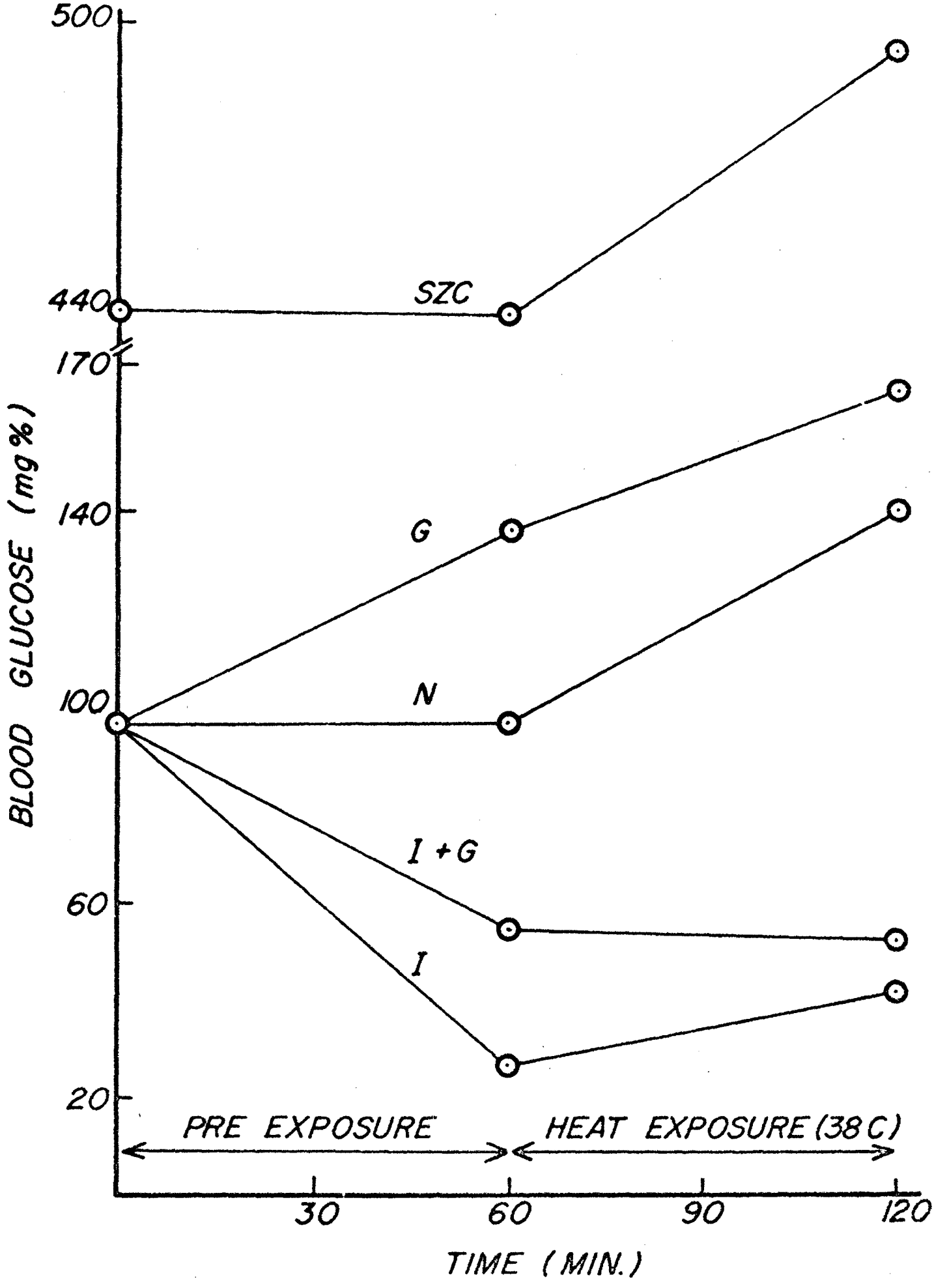
500
440
170
140
100
60
20
BLOOD GLUCOSE (mg%)
SZC
G
N
I + G
I
PRE EXPOSURE
HEAT EXPOSURE (38 C)
30
60
90
120
TIME (MIN.)

TABLE 24. SHOWING BLOOD GLUCOSE LEVELS IN ADULT RATS BEFORE AND AFTER EXPOSURE TO 38 C FOR 60 MINUTES

Treatment	N	Blood Glucose Levels		Significance
		Before	After	
Normoglycemic	6	96.78 ± 7.40	140.82 ± 30.96	$p < .001$
SZC	6	441.00 ± 31.29	496.36 ± 50.09	$p < .001$
Insulin	6	26.00 ± 2.24	41.26 ± 5.24	$p < .001$
Glucose	6	135.75 ± 10.10	165 .45 ± 13.49	$p < .001$
Glucose plus Insulin	6	54.49 ± 15.06	53.26 ± 6.45	NS

Note:- Glucose feeding as well as insulin treatment was given one hour before heat exposure.

of blood to 41.26 ± 5.24 (Fig 13 and Table 24). Thus the rate of rise of glucose one hour following insulin administration is about the same at 27 ± 1 C and 38 C.

c) Hyperglycemic rats

i) Glucose fed rats

The mean blood glucose value of 135 ± 10.10 mg one hour following glucose feeding at 27 ± 1 C fell to 110.00 ± 7.74 mg/100 ml of blood at the end of second hour (Table 22). When the animal was exposed to 38 C during the second hour of glucose feeding the mean blood glucose of 135 ± 10.10 mg rose to 165.45 ± 13.49 following one hour of exposure to heat (Table 24 and Fig. 13). Thus during the first and second hour of glucose feeding the blood glucose falls in animals maintained at 27 ± 1 C and rises in animals exposed to heat during this period.

ii) Streptozotocin treated rats

A mean glucose level of 441 ± 11.29 in streptozotocin treated rats at 27 ± 1 C increased to 496.36 ±50.09 after exposure to 38 C for one hour (Table 24 and Fig. 13). The difference was statistically significant ($p < .001$).

d) Glucose fed plus insulin treated rats

The mean blood glucose level of animals after one and two hour following glucose feeding plus insulin treatment

at 27 ± 1 C was 54.49 ± 15.06 and 61.33 ± 9.42 respectively (Table 22, see p-72). When the animals were exposed to 38 C during the second hour of glucose feeding plus insulin treatment, there was no significant change in the value of blood glucose. Thus the normal rise of blood glucose during the second hour following treatment at 27 ± 1 C was not observed when the animal was exposed to 38 C during the second hour.

CHANGES IN BLOOD GLUCOSE LEVELS OF NORMOGLYCEMIC AND HYPERGLYCEMIC YOUNG RATS ON COLD EXPOSURE (-10 C)

a) Normoglycemic young rats

The mean blood glucose level of 102.53 ± 6.17 mg/100 ml of blood in normoglycemic rats at 27 ± 1 C increased to 139.00 ± 23.40 mg/100 ml of blood on exposure to -10 C for 30 minutes (Fig. 14 and Table 25, see p-79). The change was statistically significant ($p < .001$).

b) Glucose fed young rats

The mean blood glucose level of 138.12 ± 8.37 mg/100 ml of blood at the end of one hour following glucose feeding (Table 22, see p-72) rose to 205.00 ± 9.50 on exposure to cold (-10 C) for 30 minutes (Fig. 14 and Table 25). The difference was statistically significant ($p < .001$).

FIG. 14 BLOOD GLUCOSE LEVELS IN NORMOGLYCEMIC (N) AND GLUCOSE FED (G) YOUNG RATS BEFORE AND AFTER EXPOSURE TO -10 C.

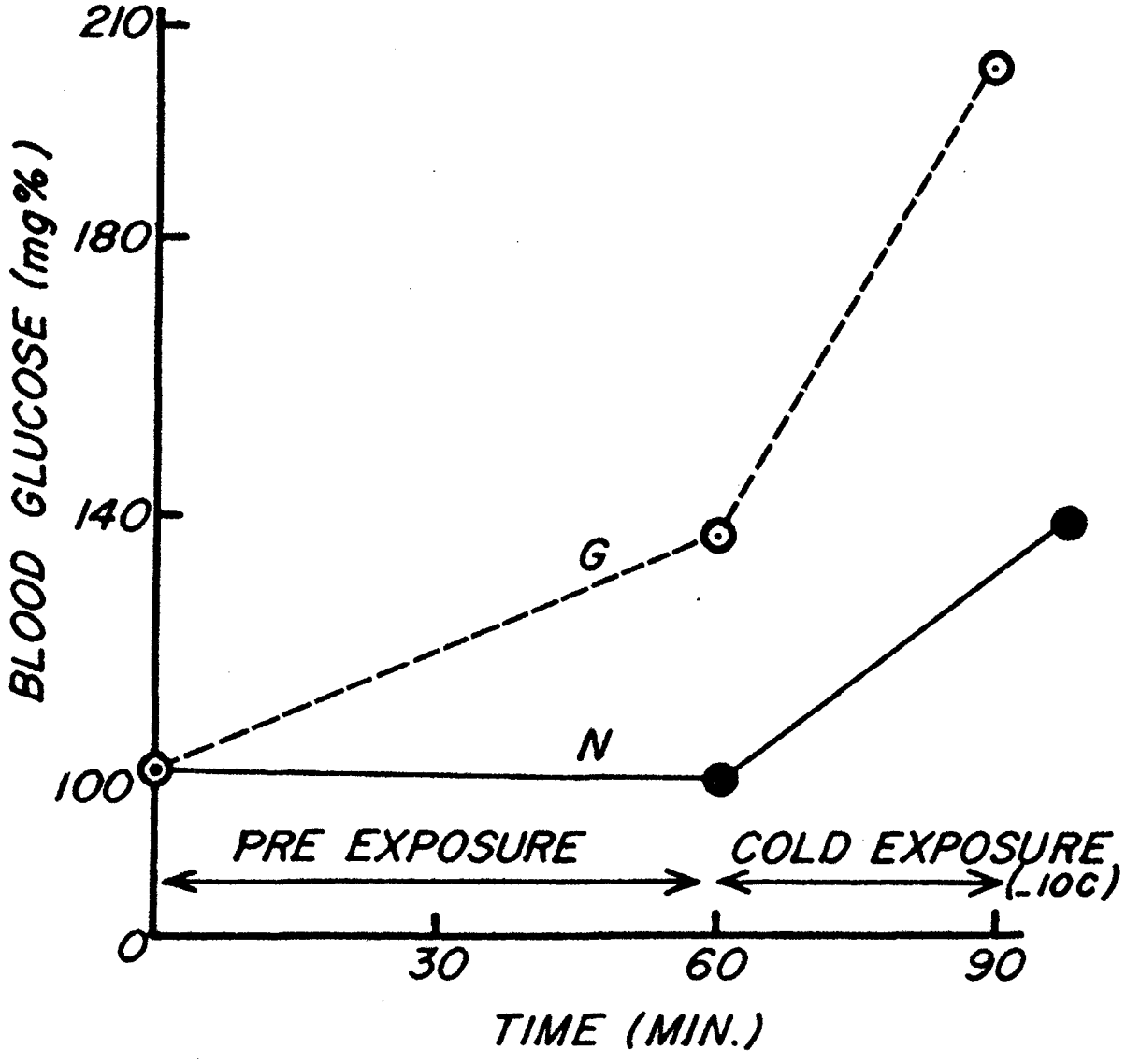
210
180
140
100
0
BLOOD GLUCOSE (mg%)
G
N
PRE EXPOSURE
COLD EXPOSURE
(-10C)
30
60
90
TIME (MIN.)

TABLE 24. SHOWING BLOOD GLUCOSE LEVELS IN YOUNG RATS BEFORE AND AFTER EXPOSURE TO -10 C FOR 30 MINUTES

Treatment	N	Blood Glucose Levels		Significance
		Before	After	
Normoglycemic	8	102.53 ± 6.17	139.00 ± 23.40	$p < .01$
Glucose feeding	8	138.12 ± 8.37	205.00 ± 9.50	$p < .001$

Note:- Glucose feeding was done one hour before exposure.

CHANGES IN BLOOD GLUCOSE LEVELS OF NORMOGLYCEMIC AND HYPERGLYCEMIC RATS ON HEAT EXPOSURE (38 C)

a) Normoglycemic young rats

The mean blood glucose level of 102.53 ± 6.17 mg/100 ml in normoglycemic rats at 27 ± 1 C decreased to 79.00 ± 7.01 mg/100 ml on exposure to 38 C for 60 minutes (Fig.15, and Table 26, see p-81). The difference was statistically significant ($p < .001$).

b) Glucose fed young rats

The mean blood glucose level of 138.12 ± 8.37 one hour following glucose feeding at 27 ± 1 C decreased to 92.00 ± 12.07 mg on exposure to 38 C for 60 minutes. The difference between the two was statistically significant (Fig. 15 and Table 26, see p-81).

FIG. 15 BLOOD GLUCOSE LEVELS IN NORMOGLYCEMIC (N) AND GLUCOSE FED (G) YOUNG RATS BEFORE AND AFTER EXPOSURE TO 38 C.

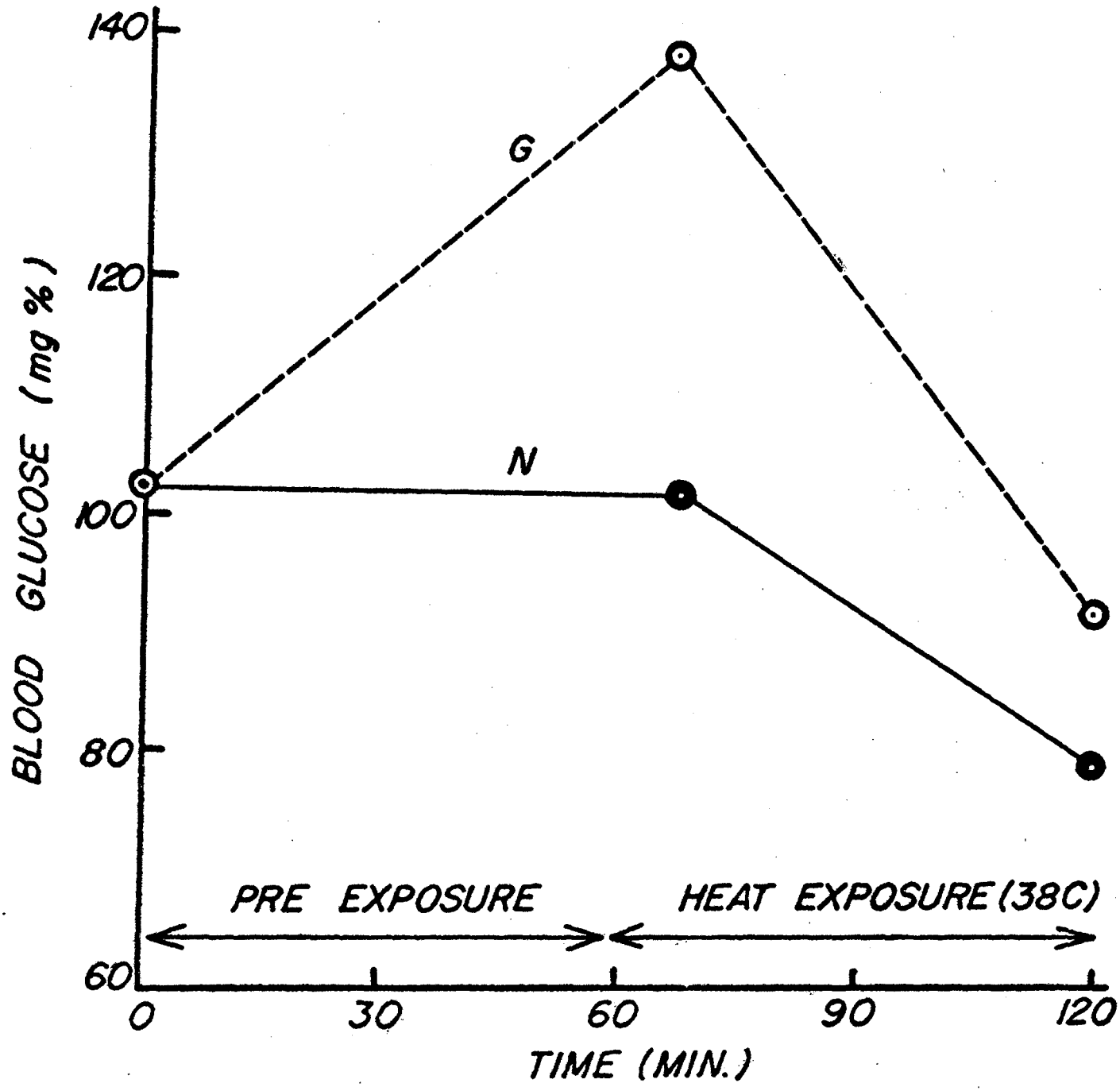
140
120
100
80
60
BLOOD GLUCOSE (mg %)
G
N
PRE EXPOSURE
HEAT EXPOSURE (38C)
0
30
60
90
120
TIME (MIN.)

TABLE 26. SHOWING BLOOD GLUCOSE LEVELS IN YOUNG RATS BEFORE AND AFTER EXPOSURE TO 38 C FOR 60 MINUTES

Treatment	N	Blood Glucose Levels		Significance
		Before	After	
Normoglycemic	8	102.53 ± 6.17	79.00 ± 7.01	$p < .001$
Glucose feeding	8	138.12 ± 8.37	92.00 ± 12.07	$p < .001$

Note:- Glucose feeding was done one hour before exposure.

DISCUSSION

Glucose increases tolerance to cold in adult rats, and decreases the tolerance in young rats. Insulin and streptozotocin reduce the tolerance to cold. When glucose and insulin are administered together, tolerance to cold is better than in the case of normoglycemic rats. Thus, effect of glucose dominates that of insulin on cold tolerance, when the two are administered simultaneously. The differences between the responses of adult and young animals on exposure to cold can not be explained on the basis of relatively higher glucose load per unit body weight in young animals when the same amount of glucose (300 mg) is given to both, since higher cold tolerance as compared to that of the normoglycemic animals was still obtained when the adult animals were given a glucose load of 600 mg.

The heat tolerance of adult as well as young animals who were fed with glucose was less than that of the normoglycemic controls. The same was true in respect of animals administered insulin, streptozotocin or insulin plus glucose. The changes in cold and heat tolerance by the different treatments are related to the alterations in the rate of fall or rise of body temperature on exposure to cold or heat respectively. Thus, the rate of fall in body temperature on cold exposure is less in glucose fed than in the normoglycemic controls. On the other hand, in insulin and streptozotocin treated animals and in young animals treated with glucose the rate of fall of body temperature is more as compared to normoglycemic controls.

The rate of fall of body temperature was found to be linear with time in the adult normoglycemic rats as well as in rats subjected to different treatments.

The mean rectal temperature at which death occurred as calculated from the regression equation gave different values for different groups of controls. It ranged from 13.80 C to 17.59. Since the experiments on different groups were conducted on different days it is possible that some uncontrolled factors were involved in the variations of CTre from time to time. Each experimental group had its own control group and since the exposure to cold was carried out simultaneously on the control and experimental group, any effect of uncontrolled variable was eliminated. It was observed that for each treatment the CTre of experimental group did not vary significantly from the control group. This suggests that the effect of different treatments was mediated through an alteration of the rate of fall of body temperature and not due to change in the CTre. In young animals, the rate of fall in Tre is curvilinear. This may be due to the fact that the temperature for cold stress was -10 C instead of -20 C. The CTre as judged from the plot of Tre against time is higher (above 20 C) than in the case of adult animals (13-17 C). It is surprising that the response of glucose fed young animals is opposite to that of glucose fed adult animals.

The changes in cold tolerance with different treatments are also reflected in the incidence of frostbite. The incidence of frostbite is less in glucose fed animals as compared to the normoglycemic controls, although statistically the results do not fall within the 5 percent probability level. The incidence of frostbite in insulin and diabetic animals (Poe, 1963) is significantly higher than that of the normoglycemic controls. It is possible that the difference in the incidence of frostbite with different treatments resulted from variations in the rate of fall of the limb temperatures.

In normoglycemic animals exposed to heat, the body temperature rises and levels off after some time; with further exposure the body temperature tends to decline. In experiments with glucose, insulin and streptozotocin, the rise of temperature was not linear with time in control as well as treated animals. In insulin plus glucose treated animals as well as in the normo - glycemic controls the rectal temperature increased linearly with time. The glucose fed and insulin treated animals did not survive for more than ninety minutes, whereas the respective controls were still alive at the end of 150 minutes at 38 C. This may be due to the lack of fall of body temperature after 50 to 60 minutes of exposure as displayed by the normoglycemic controls. Although, the streptozotocin animals had a significantly lower survival time than the normoglycemic controls which showed a fall in body temperature after 60th minute, all the animals in the latter group did not survive for 150 minutes

as was the case with controls in other experiments. This can be explained by the fact that the experiments on streptozotocin were carried out in the winter months whereas all the other experiments were conducted in summer months. The insulin plus glucose treated animals did not survive for more than about 98 minutes, whereas their normoglycemic controls were alive at the end of 150 minutes. The CTre in the case of insulin plus glucose treated animals, as calculated from the regression equation was 46.2 C. Although, no clear fall of body temperature in the normoglycemic controls was evident, the rate of rise of body temperature was sufficiently low in the normoglycemic animals so that it did not reach the CTre of 46 C within 150 minutes.

As in the case of adult rats, survival time at 38 C is lower in glucose fed and insulin treated rats as compared to their normoglycemic controls. However, unlike in the adult rats the rectal temperature at 40th and 80th minute of exposure is not significantly different in glucose fed and insulin treated rats as compared to their respective controls. Considering the results of experiments on adult and young rats, it is difficult to say whether the low survival time in the treated animals is due to their earlier attainment of CTre or reduced tolerance of the vital organs to tolerate a high body temperature.

Except in the case of insulin hypoglycemia the effect of various treatments on thermoregulation is evident only at very low and at very high ambient temperatures. Thus, in rats treated with insulin, glucose feeding and streptozotocin the body temperature on exposure to 15 C, 25 C, 32 C and 35 C are not significantly different from that of their normoglycemic controls. In the case of insulin treatment, the body temperatures are lower than the normoglycemic controls at ambient temperatures of 15 C, 25 C, 32 C and 35 C. A higher body temperature than that in the normoglycemic animals is obtained in the insulin treated animals only when the ambient temperature is 38 C. This suggests that the neutral temperature in these rats was between 35 and 38 C. Since, the experiments were carried out in the summer, the results are consistent with the findings of Bhatia et al (1969), and Bhatia (1977), that the neutral temperature of 32 C obtained in winter rises to a higher level during the summer.

As already stated alterations in tolerance to thermal stress with different treatments are caused largely by changes

in the rate of rise or fall of body temperature. How the latter is related to the changes in blood glucose levels with associated metabolic effects is more difficult to explain. As regards the changes in tolerance to cold stress in adult animals is concerned, the availability of sufficient glucose in the blood and of the adequate amount of insulin for utilization of blood glucose to meet the extra-metabolic demands for substrate in the thermogenic tissues may be the determinant factor. In normoglycemic animals increase in the blood glucose level brought about by stimulation of neoglucogenesis by catecholamines may help the thermogenic tissues to meet their extra demand for glucose (Bickford et al, 1960 and Fuhrman, 1947). A simular increase in neoglucogenesis would be expected in the diabetic animals, but without a proportional increase in glucose utilization in the absence of insulin (Van Itallie, 1960). The present experiments therefore revealed a much greater rise in blood glucose in diabetic animals as compared to normoglycemic rats exposed to cold stress. This would also explain the greater fall in body temperature in the streptozotocin treated animals.

An increased level of insulin stimulated by hyperglycemia after glucose feeding is known to increase the rate of glucose utilization (Blecher, 1966; Rodbell, 1966; and Renold, 1964). Any effect of catecholamines in these animals exposed to cold to increase neoglucogenesis would be counter acted by raised levels of blood insulin. For this reason no rise

of blood glucose on cold stress is evident in animals fed with glucose and exposed to cold after one hour. The lower rate in fall of body temperature in glucose fed animals as compared to the normoglycemic animals could then be explained by the higher rate of utilization of glucose by the thermogenic tissues.

In contrast to the response of the adult animals to cold, the rate of fall of body temperature in the glucose fed young rats is higher than in their normoglycemic controls. In these animals the blood glucose levels rise during cold stress instead of falling as in the case of adult animals (Alain Kervrah, 1976). The increase in blood glucose of young rats fed with glucose and exposed to cold is about twice that of the normoglycemic controls. This suggests a decreased glucose utilization in glucose fed young rats. Since, the insulin secretion in the young rats is believed to be as sensitive to blood glucose levels as in adult rats, it is possible that a decreased utilization of glucose in glucose fed animals exposed to cold may be due to some specific effect of high blood glucose levels in supressing shivering in young rats. The consequent reduction in the rate of thermogenesis could then explain the greater fall in the body temperature in glucose fed animals.

It seems that in mild and moderate degrees of cold stress, the thermogenic tissues are able to meet their increased

demands for glucose and that it is only under severe degree of cold stress that the blood glucose in sufficient quantities is not available to these tissues. This is evident from the observations that at a temperature between the neutral temperature and 15 C, the normoglycemic and the glucose fed animals had the same degree of fall in body temperature.

Administration of insulin to the normal animals results in increased utilization of glucose by the tissue (Debodo, 1959), increased glycogenesis (Larner and Villarpalasi, 1959) and increased lipogenesis (Mahler et al, 1963 and Ball et al, 1964). This results in rapid fall in blood glucose, thereby decreasing the availability of glucose to the tissues. After about one hour the blood glucose begins to rise, and this rise is accelerated if the animal is exposed to cold, as seen in the present experiments. The lower availability of glucose to the tissues may possibly be responsible for the greater fall of body temperature under cold stress in the hypoglycemic as compared to normoglycemic animals. The insulin treated animals were observed to have a greater fall in body temperature as compared to normoglycemic animals even at mild degree of cold stress suggesting that during cold exposure animals were very sensitive to low blood glucose levels.

The animals which were fed with glucose and simultaneously administered insulin and exposed to cold behaved very much like the glucose fed animals as regards their rate of fall of body temperature and survival in cold is concerned.

However, the values of the blood glucose at the end of one hour was only slightly higher than that of insulin treated animals, and at the end of exposure to cold, it was even lower than in the case of insulin treated animals. These animals must therefore have a higher rate of utilization of glucose as compared to the normoglycemic animals, and the low values of blood glucose must be due to a higher rate of turnover of glucose in blood.

In normoglycemic adult animals exposed to heat there is a rise of blood glucose as in the case of cold stress, though of much less magnitude. This rise is likely to be more due to reduction in glucose utilization than due to stimulation of catecholamine secretion by heat stress, when the ambient temperature is changed from 27 to 38 C. In the glucose fed adult animals exposed to heat the fall in blood glucose during the second hour as seen at neutral temperature was not observed. This suggests that the increase in glucose utilization and glycogenesis one hour after glucose feeding, when the animal is exposed to heat stress is of smaller magnitude than when the animal is exposed to neutral or low ambient temperature. The higher rate of rise of body temperature could be due to increased metabolism resulting from greater rate of glucose utilization. As in the case of cold stress, the responses of the young animals to heat stress were opposite to those in the case of adult animals. Heat exposure caused a significant fall in blood glucose in normo-

glycemic as well as glucose fed young animals. The fall in blood glucose levels in glucose fed young animals exposed to heat is of higher magnitude than in the case of normoglycemic animals. A higher rate of rise of body temperature under heat stress in glucose fed young animals can be explained on the assumption of a higher rate of glucose utilization associated with accelerated metabolism.

In insulin treated adult animals exposed to heat during second hour of insulin administration, the blood glucose levels recover at a much lower rate than in the case of animals exposed to neutral temperature. Since, the blood glucose levels were very low the glucose utilization must have been subnormal. Inspite of this, the body temperature in insulin treated animals was higher following heat stress than in normoglycemic animals. In streptozotocin treated animals also the body temperature after heat stress was higher than in the case of normoglycemic animals, although, one would expect a lower rate of glucose utilization by the tissues. A greater fall of body temperature under cold stress and a greater rise of body temperature under heat stress in streptozotocin treated and insulin treated animals as compared to normoglycemic animals points to the possibility of breakdown of thermoregulatory centers by factors which interfere with glucose utilization. Insulin and streptozotocin treatment, therefore reduces the tolerance to high as well as low ambient temperatures. On the other hand the glucose fed animals have

a higher tolerance to cold and the lower tolerance to heat than that of the normoglycemic controls. The higher body temperatures of the glucose treated animals exposed to cold or heat stress as compared to that of normoglycemic animals indicates that the effect is due to increased production of metabolic heat.

The observation that animals fed with glucose and administered insulin respond to thermal stress like the glucose fed animals although the blood glucose levels are only slightly higher than those insulin treated animals would tend to be inconsistent with the hypothesis that factors reducing glucose utilization disturb the thermoregulatory centers. However, it is possible that although in glucose fed and insulin administered animals the turnover rate of glucose is higher than in the case of normoglycemic animals.

The above conclusion is regarding the significance of changes in blood glucose of animals subjected to different treatments and exposed to thermal stress, and the relation between these changes and body temperature are only tentative. Studies on glucose utilization and on the enzymes of the carbohydrate metabolic pathway are necessary to confirm the hypothesis.

SUMMARY AND CONCLUSIONS

Responses of rats one hour after feeding with glucose, treatment with insulin, streptozotocin and glucose fed plus insulin, were compared with those of normoglycemic animals by

a) exposing them to cold stress (-20 C) and heat stress (38 C).
b) measuring the survival time and
c) estimations of blood glucose levels in cold and heat stress.

In addition susceptibility of rats to cold injury was determined in normoglycemic, insulin and streptozotocin treated animals.

The rats were exposed to -20 C in deep freezer and to various degree of ambient temperatures (15 C, 25 C, 32 C, 35 C and 38 C) in BOD incubator. For cold injury the limbs of the animals were exposed to freezing mixture with temperature ranging from -23 to -19 C.

The following results were obtained:

a) The rate of fall of Tre at -20 C was more in insulin and streptozotocin treated rats as compared to their normoglycemic controls. It was less in glucose fed as well as insulin treated plus glucose fed animals as compared to their normoglycemic controls. In contrast to this glucose fed young rats showed greater fall in Tre as compared to their normogly-

cemic controls following exposure to -10 C.

When the rats were exposed to heat stress (38 C), the rate of increase of body temperature was more in glucose fed, glucose fed plus insulin treated, streptozotocin and insulin treated adult rats as compared to their normoglycemic controls. The same was true with the insulin and glucose fed young rats.

b) Streptozotocin and insulin treated rats showed a less tolerance to -20 C as compared to their normoglycemic controls. Glucose fed and glucose fed plus insulin treated animals survived for longer time as compared to their controls. Young rats fed with glucose had less survival time than that of normoglycemic controls.

During exposure to 38 C, streptozotocin, insulin treated, glucose fed and insulin treated plus glucose fed rats had a lower tolerance than their respective controls.

c) There was increase in levels of blood glucose in normoglycemic and streptozotocin treated rats following exposure to -20 C. In insulin treated animals the rise of blood glucose on exposure of animals to -20 C during second hour following insulin administration was higher as compared to that at neutral temperature. On the other hand, glucose fed adult rats showed a fall in glucose levels after exposure to cold in the second hour of glucose feeding which was comparable to the fall at neutral temperature. In glucose fed plus insulin admin-

istered rats the blood glucose levels following exposure to cold during second hour of treatment were the same as at neutral temperature. Normoglycemic and glucose fed young rats showed a significant increase in blood glucose levels following exposure to -10 C. During exposure to heat stress of 38 C normoglycemic adult rats showed an increase in glucose levels. Glucose fed animals exposed to heat in the second hour after glucose feeding showed a rise instead of a a fall in blood glucose observed at neutral temperature. In contrast to this normoglycemic and glucose fed young rats showed a fall in glucose levels following heat exposure. Insulin treated and insulin plus glucose treated animals exposed to heat one hour following the treatment displayed a rise of blood glucose which was comparable to that at neutral temperature.

Incidence of cold injury was more in normoglycemic rats as compared to the glucose fed animals, when the limbs were exposed to freezing mixture at -23 C. Insulin treated and streptozotocin rats showed a higher incidence of frostbite than that of their respective normoglycemic controls when exposed at -19 C. The following conclusions can be drawn from the above results :

(1) The alterations in cold tolerance by various treatments is caused through their effect on the rate of cooling of the body and not by change in the critical body temperature at which death occurs.

(2) The changes in heat tolerance by various treatments is largerly due to the alterations in the rate of rise of body temperature, although, there is some evidence for an alteration in critical body temperature at which death occurs.

(3) Alterations in the rate of change of body temperature by different treatments seems to be mediated through changes in glucose utilization.

(4) Insulin and streptozotocin treatment appears to influence the thermal responses of the animal through the disturbance of the thermoregulatory centre by fall in glucose utilization.

(5) Glucose and glucose plus insulin treatment seems to alter the responses to thermal stress to increased metabolic heat production associated with higher utilization of glucose.

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