INTERNAL BODY TEMPERATURE CHANGES IN THE RAT IN RESPONSE TO FEEDING

by

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

It is an everyday observation that healthy men and adult animals maintain their weight with remarkable consistency over long periods of time. They adjust food intake to energy requirements with such precision that body stores of fat vary only slightly. This is the most easily appreciated evidence of a physiologic mechanism which regulates food intake. Such a regulatory device must integrate information derived from the volume of each meal, the number of meals eaten daily, and the nutritive value of the mixed diet consumed.

The problem of the regulation of food intake, in spite of the great attention it has received in the past, has not been resolved. A recent symposium on the regulation of hunger and appetite (43) revealed little agreement among the experts on the basic mechanism of hunger -- a physiologic state resulting from deficits of nutrients which manifests itself in a disagreeable complex of sensations including the epigastric hunger pang, and behavioristically in activated feeding reflexes and increased motor activity. Nor was there any uniformity of opinion as to the state which resulted in satiety -- lack of desire to eat or absence of the desire to eat which is associated with repletion of the nutrient deficits.

At present, the common conception is that food intake is regulated by a "center" in the brain sensitive to a certain as yet unknown change in the body. Four major and separate states have been advanced as being

that vital change necessary for the initiation and cessation of feeding. These theories will be considered in more detail as well as the evidences establishing the existence of a central regulatory mechanism.

REVIEW OF THE LITERATURE

The hypothalamus and the neural basis of regulation.

Since the discovery in 1940 by Hetherington and Ranson (27) that bilateral ventromedial hypothalamic lesions resulted in obesity in rats, focus has been on that part of the brain, and subsequent investigations have confirmed the importance of hypothalamic function in the regulation of food intake. Brobeck, Tepperman and Long (10) made the observation that the obesity resulting in rats with ventromedial hypothalamic lesions was due to hyperphagia and the resultant increase in deposition of body fat. In 1951 Anand and Brobeck (2) established the role of two areas in the hypothalamus dealing with food intake behavior. They made three observations on rats and cats: 1) lesions of the hypothalamus at the level of the ventromedial nucleus induced obesity by increasing food intake, 2) lesions of the lateral area at this level of the hypothalamus abolished or markedly diminished food intake, and 3) destruction of both of these areas resulted in a failure of feeding as had been noted after lateral lesions. A dual mechanism of regulation was proposed. The lateral hypothalamus was referred to as the "appetite center" responsible when activated for the food seeking and feeding reflexes. Identified as the "satiety center" was the medial hypothalamus which inhibited feeding reflexes and the "appetite center" as well.

Subsequent investigations on the hypothalamic control of food intake have largely been extensions on this "brake-accelerator" concept. Delgado and Anand (16) reported in 1953 that they could provoke an increase of

food intake in cats by electrical stimulation of the lateral hypothalamus.

Brobeck, Larsson and Reyes(9) placed recording electrodes in the hypothalamus of cats and found that amphetamine produced obvious increased electrical activity in the medial region of the "satiety center" of these anesthetized animals but no change in the lateral area. Their findings supported the earlier interpretation of Harris and his group (25) that the anorexia experienced by their human subjects and the reduction of food intake in their dogs following amphetamine administration resulted from the effect of the drug on the central satiety mechanism.

A reciprocal effect on feeding behavior was noted in 1960 by Epstein (17) who used chemicals to stimulate and depress the hypothalamic "feeding centers" as described by Brobeck et al (10). By injecting procaine (a neuro-depressant) into the medial hypothalamus through a chronically implanted cannula in that area, Epstein found that rats increased their food intake. A similar effect was noted after injection of hypertonic saline (a neuro-stimulant) into the lateral hypothalamic region. Conversely, procaine into the lateral area and hypertonic saline into the medial "satiety center" decreased food consumption levels.

While the central mechanism regulating food intake has been defined and localized, its peripheral component is less well established. As a result, current research is being directed toward determining the factor or factors which govern the activity of the central mechanism. Changes in the organism after food has been eaten must directly or indirectly affect the hypothalamus. The emphasis has been on the mechanism by which

animals and men avoid overeating, and therefore, the search has been for the signals which suppress the activity of the lateral hypothalamus and stimulate the medial hypothalamus.

Four major theories have been proposed to explain variations in hunger--satiety balance. They are: 1) the mechanical effect of food in the gastrointestinal tract, 2) the "glucostatic" theory, 3) the changes in cellular hydration, and 4) the "thermostatic" theory. Although these proposals are considered separately, it should be regarded that theoretically there is the possibility that no single factor but rather a combination or an interaction of factors is responsible for bringing about the end result of satiation.

The role of the gastrointestinal tract.

The role of the stomach in the regulation of food intake was investigated as early as 1915 by Cannon and Washburn (13) and in 1916 by Carlson (14) who reported that sensations of hunger described by human subjects as "feelings of emptiness, a somewhat disagreeable or painful sensation of tension, or hunger pang" localized in the epigastrium coincided with hunger contractions of an empty stomach. Usually associated with these epigastric sensations were increased nervous excitability, restlessness and sometimes weakness, nausea and headaches.

Acceptance of this original idea that gastric contractions are the prime stimuli for food intake warrants evidence that hunger is experienced and food intake occurs only after gastric contractions and that satiety

is brought about and food intake ceases when these contractions cease.

Carlson concluded that in the normal individual, chemical changes of the blood as well as nervous impulses from the brain and spinal cord augmented or decreased the gastric hunger mechanism in a way to correlate it with the needs of the organism. He suggested that hypoglycemia, mediated by its effect on the stomach, might be responsible for inducing these hunger sensations.

Bulatao and Carlson (11) reported that the intravenous infusion of five and ten grams of glucose in the form of 50% glucose solutions markedly or completely suppressed gastric contractions in fasting dogs. Control injections of hypertonic saline and lactose did not produce this effect. In studies on human subjects, Stunkard and Wolff (64) in 1954 reported the similar finding that intravenous injections of 50 cc of 50% glucose promptly abolished gastric contractions and the subjective sensation of hunger in normal subjects.

On the other hand, Quigley and Hallaran (49) and Mulinos (45) (following their experiments of glucose infusion in human subjects) found that the fasting gastric motility was not influenced by blood glucose alterations. They also cited cases of diabetic individuals with high glucose levels who nevertheless experienced hunger sensations.

There is, however, evidence that the upper gastrointestinal tract does have a regulatory function in metering the amount of food eaten on a meal-to-meal basis. Adolph (1) reported in 1947 that, in the dog, prefeeding a portion of the regular diet shortly before ad libitum feeding reduced intake by a corresponding amount. Gastric distension by the

ingested food acting as a brake on further food intake was suggested by Janowitz and Grossman (32). They found that, in esophagostomized dogs, the duration of sham feeding was reduced by the effect of gastric distention either with food or with nutritionally inert materials such as gum arabic and water-filled balloons. This was later confirmed by Share, Martyniuk and Grossman (56) who noted that a water-filled balloon placed in the stomach of dogs with esophagostomies and gastric fistulas depressed oral food intake, with the degree of reduction being inversely related to the size of the balloon.

Metering by gastric distention is probably mediated by vagal afferent fibers arising from the gastric stretch receptors described by Paintal (46) in 1954. Using anesthetized cats, he recorded the electrical activity in the vagal afferents in response to gastric distention with water-filled balloons. He found the frequency of discharge and the degree of distention to be linearly related, and the discharges started 0.1 to 0.5 sec. after the beginning of distention. The conclusion drawn from his experiment was that stretch receptors were located in the smooth muscle of the stomach, principally in the pyloric region, which functioned to signal the state of distention to the "satiety center" of the hypothalamus. Thus, gastric receptors were the peripheral mechanism for the immediate satiation following food intake.

Support of Paintal's proposal came in 1961 when Sharma and his group (57) recorded electrical activity from the region of the "satiety center" in response to gastric distention. Inflation of intragastric balloons with water or air produced high voltage irregular waves in the ventromedial

hypothalamus. The response occurred selectively in the "satiety center" with no such change being observed in the "appetite center" or in other hypothalamic regions. On the other hand, it was found that gastric hunger contractions did not change the electrical activity of either the "feeding" or "satiety centers".

The influence of the activity of the stomach as an important determinant of food intake regulation has pretty much been ruled out by the works of Ingelfinger (31) and Grossman and Stein (24). Patients who had bilateral vagotomies continued to experience sensations of hunger, and those with total gastrectomies maintained normal food intake patterns in spite of the obvious absence of gastric contractions and distentions. Animals with denervated gastrointestinal tracts also showed normal regulation of food intake (23). The conclusion drawn is that the gastric mechanism is at most only one component of the entire complex of factors regulating eating behavior and appears to be a dispensable one.

The "glucostatic" theory

The relationship of glucose metabolism and food intake has been an area of much controversy. The non-controversial fact is that marked hypoglycemia, whether occurring spontaneously or insulin-induced, is associated with hunger sensations in man, and increased food intake in men and animals (19, 23, 35, 39, 44, 58). In view of the limited carbohydrate stores of the body and the fact that the essential, if not the exclusive source of energy for the central nervous system is blood glucose, it seemed reasonable to propose that the central nervous system should maintain centers sensitive to variations in this vital metabolite. Hunger

and food intake would then be, in hypoglycemic states, mechanisms through which the central nervous system ensures homeostasis.

However, the apparent paradoxes afforded by the hyperphagia seen in diabetes mellitus, in which a person will continue to eat in spite of a blood glucose reaching abnormally high levels, and by the hyperphagia accompanying tendency to higher glucose levels in the obese, had to be resolved before it could be concluded that blood glucose level was the prime regulator of food intake.

In attempting to conciliate contrasting observations, Mayer (38) presented his "glucostatic" theory in 1952. He postulated that there were "glucoreceptors" in the central nervous system (in the ventromedial hypothalamus) which were sensitive to the rate at which glucose was being utilized by them. Low utilization rates excited neural activity leading to hunger sensations and food-taking activity. High utilization rates produced the opposite effect. Arteriovenous glucose differences served as an index of utilization rate and, for most purposes, peripheral arteriovenous differences as measured from finger blood (arterial) and antecubital vein blood served as an index of rate of utilization by the "glucoreceptors" in the central nervous system.

The previously unexplained hyperphagia in the diabetic and obese individuals becomes acceptable under the terms of the "glucostatic" theory. It appears that those two conditions have one factor in common--namely that whereas absolute levels of blood glucose are increased, utilization as measured by arteriovenous differences in peripheral circulation is decreased (38).

The assumption that the ventromedial region of the hypothalamus incorporates specialized cells sensitive to glucose utilization rates is based upon and has received support from the works dealing with goldthioglucose. It was noted in 1950 by Waxler and Brecher (69) that following administration of toxic doses of goldthioglucose to albino mice, those that survived became obese. Over a seven month period, those treated had gained an average of 45 gms as compared to a control group which had gained an average of 5 gms. The weight gain was largely a result of increased food intake which amounted to 45-75 gms/10 day period/mouse whereas the control animal ate 25-40 gms of food over the same period. Marshall, Barrnett and Mayer (37) in 1955 used goldthiomalate with equal gold content as a control agent to the goldthioglucose they injected into mice. They produced obese animals with the glucose preparation but none with the malate. A study of the sections of the mice brain 24-72 hours after injection in the thioglucose group showed lesions in the hypothalamus always and only involving the ventromedial nuclei. No lesions could be found in the control animals. It should be recalled that previous experiments had demonstrated that damage to the ventromedial nuclei resulted in the production of obesity in rats and mice (2). The interpretation from the experiment was that the ventromedial area in the hypothalamus effectively concentrates radioglucose on the basis of increased permeability to compounds containing glucose. This selective sensitivity of the "satiety center" to glucose supports the postulated presence of "glucoreceptors" basic to Mayer's theory.

The concept of arteriovenous glucose difference as applied to the "glucostatic" theory is less well established. Because of the inaccessibility of the vessels, studies based on changes in blood glucose levels in vessels to and from the hypothalamus and its relationship to regulation of food intake are lacking. Supporters of this theory have been content to assume that peripheral changes are reflections of similar fluctuations within the brain, and no attempt has been made to test the validity of this assumption. At the same time, the results of Rowe and his group (50), demonstrating that there is no change in the arteriovenous glucose difference as measured across the cranial vessels in the fasted or satiated state, detract little from the theory. The minute amount of glucose that would be utilized by the ventromedial nuclei might be physiologically important, yet not demonstrable in such a gross measurement as the glucose consumption of the brain as a whole.

There are numerous and conflicting reports on the relationship of blood glucose levels (spontaneous variations, glucose-induced hyperglycemia, or insulin-induced hypoglycemia) and their effects on hunger sensations and gastric hunger contractions. These have been reviewed by Grossman (22).

The critical evidence in the last analysis of the "glucostatic" theory must relate to arteriovenous glucose differences and their effect on food intake. Experimentally induced elevation of arteriovenous difference should bring about a decrease or cessation of food intake. Conversely, if in a satiated individual or animal the arteriovenous difference could be narrowed, excessive food intake should occur. Unfortunately

there are few studies reported, and here again, the evidence is contradictory.

Van Itallie, Beaudoin, and Mayer (67) tested the hypothesis on human subjects. They reported that arteriovenous glucose differences correlated closely with the caloric intake of the subject. Moreover, there was a quantitative relationship between the arteriovenous difference values and the incidence of hunger feelings; that differences of more than 15 mg/100 ml were never associated with hunger. However, close scrutiny of the data reveals that hunger was not always experienced when the arteriovenous difference was less than 15 mg/100 ml. In fact, some subjects failed to experience hunger even when the arteriovenous differences were negative values. The authors failed to recognize this obvious contradiction to the "glucostatic" theory. Fryer et al (20) repeated the study and found their results not in accordance with the theory. Complete lack of hunger did occur in the presence of negligible or even negative arteriovenous differences, and conversely, in two subjects who experienced marked hunger, the arteriovenous glucose difference was found to be greater than 15 mg/100ml.

The results from a study by Bernstein and Grossman (6) on normal male subjects also failed to support the "glucostatic" theory. Glucose or saline was administered intragastrically or intravenously just prior to a test meal which the subjects could consume ad libitum. Two saline controls and two glucose tests were performed on each subject by each route. The dose of glucose was 200 ml of 10% solution intravenously and 200 ml of 25% solution intragastrically. The control was 200 ml of 0.9% saline.

The subjects did not know what the test substances were, and they did not know that the purposes of the study was to measure food intake. Despite the marked hyperglycemia and elevation of arteriovenous glucose differences with the glucose treatments, no significant depression of food consumption occurred.

Other investigators have used glucagon instead of glucose in their studies on the "glucostatic" theory (48, 53, 63, 65). They stressed that the rapid administration of a markedly hypertonic glucose solution with its resultant abnormally elevated blood levels is not physiological. On the other hand, Van Itallie, Morgan, and Dotti (68) have shown that glucagon is a more appropriate test agent because the pattern of hyperglycemia induced is similar to that occurring under natural conditions following ingestion of meals. Glucagon by its glycolytic action would be expected to increase arteriovenous differences. Some of the results thus far noted after intravenous and intramuscular administration of glucagon have been consistent with the "glucostatic" theory. Increases in arteriovenous differences were associated with inhibition of gastric contractions (65), decrease in hunger sensations (63), and depression of calorie intake (53).

However, the only test of any significance, that done by Penick and Hinkle (48), fails to support the theory. They found that glucagon did produce a depression of food intake but this occurred between two and four hours after the drug had been administered when the arteriovenous glucose differences had returned to fasting levels (3-5 mg/100 ml). The intake measured at the 30 minute point of the experiment when the arteriovenous difference was elevated (greater than 15 mg/100 ml) showed no

significant difference from control values. It appeared that the action of glucagon on food intake was independent of its effect upon the peripheral blood glucose concentration. The mechanism of the effect needs clarification.

The influence of water on food intake.

The possible relationship of food intake levels to the availability of water was noted by Strominger (59) in 1947 when he observed that restriction of water in normal rats caused a marked depression of food intake. In rats made hyperphagic by hypothalamic lesions, he noted polydipsia and polyuria. The striking thing was that the daily water intake in milliliters was approximately 200% of the average food intake in grams, the same quantitative ratio that he found among the normal rats.

Crampton and Lloyd (15) had previously reported that food intake levels in rats could be markedly reduced by restricting water supply to half the volume usually consumed.

Adolph (1) has commented that in dogs the thirst exhibited during and after periods of eating is a state of dehydration from the withdrawal of fluids from the body for the digestive juices.

These reports suggest the presence of a mechanism operating to relate quantitatively the intake of water to food intake, possibly as a means by which the animal maintains osmotic and ionic equilibrium.

The problem of osmotic factors in the regulation of food intake has received the attention of Schwartzbaum and Ward (55). Food-deprived rats

were stomach-loaded with different osmotic concentrations of either glucose, NaCl, or sodium saccharine which were isosmotic with respect to each other. They found that hypertonic pre-loads reduced food intake by as much as 50%, whereas hypotonic pre-loads tended to increase intake above the control levels. These results were interpreted to suggest that food intake was regulated to maintain a certain tonicity of the gastrointestinal contents. The similarity of effects (food intake levels) produced by isosmotic concentrations of glucose and sodium chloride was an indication that the caloric properties of loads was not involved in the immediate regulation of food intake. The saccharine was used as a control for the taste effects.

The physiological mechanism by which tonicity of stomach loads effects food intake presumably involves either or both cellular dehydration and gastric distention. Leprovsky et al (33) found that in addition to a lowered food intake in rats fed without water, the gastric contents of all animals, fed with or without water was approximately 49% water. They postulated that rats deprived of water regulated their food intake level so as to match the amount of water they were able to mobilise from their own tissues to maintain a constant water:food ratio. They added that in rats it is possible that the temporary withdrawal of fluid from selected tissues and the consequent dehydration may be one of the factors causing cessation of eating. These authors declined to speculate as to which tissues were involved or by what pathway this change at the cellular level was transmitted to the "satiety center". Stomach distention might be expected to result from loading with hypertonic fluid because of

the reduced stomach motility thereby decreasing the rate of stomach emptying (28). It has been discussed previously that distention of the stomach has a depressing effect on further food intake (32, 56). However, later experiments with denervated gastrointestinal tracts indicated that this is a minor and dispensable factor.

In a preliminary study on the neural control of thirst, Anand and Dua (3) produced hypodipsia in rats by electrolytic lesions in an area just rostral to the "feeding center" of the hypothalamus. Future investigations of the hypothalamus may reveal a functional as well as an anatomical interplay of the centers controlling food and water intake.

The "thermostatic" theory.

Another factor considered as a possible influence on the regulation of food intake is the body temperature changes which are associated with the ingestion of food.

Booth and Strang (7) published a report 27 years ago on changes in skin temperatures after eating. In normal persons, there was a consistent rise in the skin temperature of the palm within 10 minutes after onset of eating a protein meal, and that these rises averaged 2.0°C one hour after onset of eating. In obese subjects, the skin temperature rose significantly later (24 minutes) and to a significantly lesser degree (0.5°C). The attainment of satiety, as evidenced by the cessation of eating, was associated with a sensation of warmth and comfort in most cases and by the appearance of perspiration in some. These observations

were interpreted as resulting from a production and dissipation of heat in response to the ingestion of the food, and suggested to the authors that an increase in skin temperature might be a part of the satiety mechanism. The slower and smaller increase in obese people would thus lead to a greater food intake before the signal of satiety reached a threshold value.

No work was done on this subject until Brobeck in 1948 (8), using the experimental results of Booth and Strang as evidence, proposed the "thermostatic" theory of the regulation of food intake. He postulated that heat production was an important signal to the "satiety center" and that "animals eat to keep warm and stop eating to prevent hyperthermia". Two experiments, one dealing with environmental temperature, the other with body temperature, served as the basis for his theory.

Brobeck (8) exposed adult male rats to varying environmental temperatures and recorded food intake and body temperatures. From the results, it appeared that food intake fell with rising environmental temperature to the point where rats did not eat when the temperature was so warm that they experienced hyperthermia. The environmental temperature at which this occurred was not always the same (range of 34.4-36.1°C) and it varied from one rat to another. The rectal temperatures recorded when food intake was inhibited was in the neighborhood of 40.0°C. This inverse relationship of environmental temperatures and food intake levels had been previously reported by Gasnier and Mayer (21). Rabbits kept at temperature ranges of -3 to 30°C ate more during cold than during warm exposure.

The experiment done by Strominger and Brobeck (61) led to the proposal that increased heat production after food intake had an important influence on the satiety mechanism. They noted that animals ate different amounts of different diets, and inferred from that that the animals had some ability to recognize some quality in food so as to change their intake when the composition of the food was altered. Rats kept in a constant environmental temperature were fed diets with varying amounts of fat, carbohydrate and protein. There was no consistency in the number of calories eaten, in the level of intake of any particular constituent of the diet, or in the total amount of food eaten as the composition of the diets were changed. The only variable that remained constant was the estimated specific dynamic action (SDA) value of the food ingested. From these data, the authors suggested that the extra heat released by the assimilation of food (SDA) acted upon hypothalamic centers sensitive to changes in temperature. When a certain critical level was reached, a "thermostat" was activated and initiated impulses bringing about satiety. The skin temperature rise in the postprandial period reported by Booth and Strang was, according to the "thermostatic" theory, the peripheral manifestation of SDA acting centrally to evoke cutaneous vasodilation which accompanied a central inhibition of appetite and induction of satiety that was not recognized by the earlier investigators.

This view was also expressed by Stunkard et al (62) who confirmed the original finding of a significant rise in skin temperature after

a meal. A mean rise of 1.5°C occurred between 15 and 30 minutes after ingestion of 120 grams of protein. The values at 30 minutes were significantly higher than the control temperatures.

On the other hand, Passmore and Ritchie (47) were unable to demonstrate any significant changes in skin temperatures over the abdomen, chest, palm and in the rectum. Their subjects took in a high protein meal sufficient to produce satiety. The maximum change recorded by thermistors was 0.2 °C increase in the rectum one hour after completion of the meal. The skin temperature changes were inconsistent, rising in some areas and falling in others. They felt that measuring skin temperature was unsatisfactory as a technique of trying to assess the effects of heat production on satiety.

Although these two were not able to verify the supposed effect of SDA peripherally, they did succeed in showing a relationship between SDA and satiety. By indirect calorimetry, heat production was noted to begin within the first three minutes after ingestion of a protein-rich liquid preparation. The gradual rise in heat production reached a peak in 30-40 minutes and was followed by a gradual fall. The significance of this experiment is attested to by the absence of any expressions of hunger during the period in which heat production was rising, the peak SDA coinciding approximately to onset of satiety, and to the absence of any latency period before there was an increase in energy expenditure. The fact that there is no latency period suggests strongly that SDA could have an important role in the normal satiety mechanism.

Brobeck, in formulating his "thermostatic" theory, made no statements as to how the food regulatory center in the hypothalamus appreciates the SDA effect. His vaguely-defined "thermostat" has been assumed to be localized in the preoptic area which Magoun et al (36) had previously designated as a "heat loss center" concerned with mobilization of various heat loss mechanisms in response to hyperthermia.

While reports defining pathways between the thermoregulatory and food regulatory centers are lacking, Andersson and Larsson (4) have shown a functional relationship of these two areas. Using an ingenuously designed apparatus, they were able to heat or cool discrete areas of the preoptic area and rostral hypothalamus in unanesthetized goats. A thermode was incorporated into the apparatus which allowed recording of temperature changes of the brain when hot and cold water was perfused. Local cooling, with a decrease in brain temperature from a control of 39°C to 29°C, induced eating and shivering in fed goats. Raising the brain temperature to 48°C completely inhibited eating in a previously hungry animal and stimulated drinking.

STATEMENT OF THE PROBLEM

The preceeding review of the major proposals thus far alluded to as having an important role in the mechanisms of hunger and satiety emphasize the point that there is no universal acceptance of any single one.

The earlier concept that gastric distention is the cause of satiety and that gastric contractions bring about hunger lost much of its luster after surgeons proved the stomach not to be essential for maintanence of normal eating patterns.

The "glucostatic" theory, subjected to much investigative work, has remained unproven. The experiment of Van Itallie et al (67) which has served as the basis for correlating high arteriovenous glucose difference and hunger fails to explain why there were subjects who felt no hunger when the differences were near zero. Furthermore, many investigators have been reporting contradictory findings of no correlation between high arteriovenous differences and hunger sensations (20) and no correlation of arteriovenous differences and food intake levels (48) as proposed by the theory. Criticism can also be directed at the assumptions relied upon by the proponents. A study of arteriovenous glucose differences across the ventromedial hypothalamus is needed before the "glucostatic" theory can be seriously considered.

The "osmoreceptor" or "water-food balance" proposal was never clearly defined and has failed to arouse much interest.

Brobeck's "thermostatic" theory has not been above criticism either. Mayer argues that this theory is unable to explain well-known phenomena such as the hyperphagia caused by diabetes mellitus or hypoglycemia. The theory, according to Mayer, also runs contrary to the clinical observation that hyperthermic agents such as thyroxin enhance appetite rather than the expected opposite effect. The experimental observation made by Mayer and Greenberg (40) that hypothalamic hyperphagic rats had a significantly higher rectal temperature than either operated non-hyperphagic or non-operated control animals is interpreted as evidence against the idea that "animals eat to keep warm".

In reference to the effect of environmental temperatures on food intake, Iampietro et al (29) found that caloric intake did not differ significantly over a two week period in men whether they were exposed to cold (15.6°C) or the heat (26.7°C).

However, the theory has failed to gain prominence not because of contradicting evidence against it, but rather from sparsity of accounts substantiating its original contentions. For example, no one has attempted to duplicate Strominger and Brobeck's experiment (60) in which the constancy of the SDA of food ingested was first recorded. The data of Andersson and Larsson (4) is strong support of the hypothesis that thermosensitive cells in or ahead of the hypothalamus are affected by heat to evoke inhibition of appetite and induction of satiety. Presumably this heat might be derived from the SDA of food. However, the question that remains unanswered from their study is the role the thermoregulatory centers play in controlling

appetite under normal conditions. The temperature changes induced by their local cooling and heating in and around the hypothalamus were drastic (10°C below and above resting temperature). It is difficult to imagine that changes of such magnitude would occur normally.

It is the purpose of the study, therefore, to examine the "thermostatic" theory under more normal conditions. Internal body temperature changes will be recorded under conditions of normal food intake. If the specific dynamic action of food raises the temperature as postulated by Brobeck, the effect of this more physiologic temperature change on the level of food intake will be evaluated.

MATERIAL AND METHODS

ANIMALS: Adult Sprague-Dawley male rats weighing between 400 and 600 grams were used. As judged from standard growth curves (54), these animals would be three months of age or older and past the stage of active growth and rapid weight gain.

These animals were trained to consume their daily food intake during a one-hour period. This was accomplished by fasting them for 23 hours, then offering them food for an hour. All rats lost weight during this initial training period which took between five and nine days. An animal was regarded as "trained" when its daily food intake did not vary by more than plus or minus one gram and its body weight returned to within ten grams of its initial weight.

ENVIRONMENT: All experiments were conducted in a six feet by six feet windowless room equipped with adequate ventilation and a single overhead light. The light was kept on at all times so as to minimize the effect of their nocturnal activities on food intake. However, the day-night differences in the noise from other animals housed on the same floor was unavoidable.

The temperature of the room was not controlled mechanically. All experiments were conducted between 10 a.m. and 1 p.m. when room temperature differences, as recorded by a thermometer having an accuracy to the closest 0.5°C, were in the range of 24.5 and 29.0°C. There was no change

in temperature greater than 0.5°C during any one experiment.

The animals were housed in groups of six except during the experiment when they were placed in individual cages. These separate cages were constructed from chicken wire and measured 20 cm in length and six cm in height and width. An animal placed in such a cage was allowed forward and backward movement of a few centimeters, but could not make complete turns or roll on its back without great difficulty. The cage was designed to restrict the activity of the animal and facilitate the handling of the temperature recording devices.

Each cage had a detachable food bin at one end from which the rat ate, either by poking its head into the bin, or by scooping a portion with its paws. There was only a minimal spillage problem. The food bin was weighed at the beginning and end of each eating period. Weighing was taken on a triple-beam balance, accurate to 0.1 gm.

METHOD OF RECORDING TEMPERATURE CHANGES: Intracranial temperature was measured by a thermistor bead (Fenwal GB 32J2; glass coated; 2000 ohms at 25°C plus or minus 20%) coated over with vinyl and mounted on a plastic frame.

Calibration of the thermistor was done using a constant-temperature water bath equipped with a mercury thermoregulator, an infra-red lamp, and a water fan. The thermistor was fixed in place in the bath at the tip of a thermometer certified by the National Bureau of Standards.

Utilizing a Wheatstone bridge (constructed by the Research Instrument

Service, UOMS) with a 1.35 voltage power source from a mercury battery, and a Grass (Model 5) Polygraph, calibration of the thermistor for the temperature range between 30.0 and 41.0°C was made (Fig. 1). The thermistor proved sensitive to 0.01°C changes. There were no drifts in the calibration curve during the course of the use of the thermistor.

The thermistor was chronically implanted intracranially in the following manner: the animal was anesthetized with veterinary nembutal at the dosage of 4 mg/100 gm of body weight administered intraperitoneally. The head was immobilized with a clamp and the skull exposed through an incision to the right of the midline. A burr hole less than 2 mm was made with a dental drill slightly posterior to the coronal suture and avoiding the superior sagittal sinus. With the plastic mount fixed to the skull with fine screws, the tip of the thermistor extended 7 mm into the cranial cavity (Fig. 2). No histological study was done to determine the exact location of the tip. The skin was then sutured, and each animal was given 300,000 units of procaine penicillin intramuscularly.

The animal was used in the experiment as soon as food intake returned to the pre-operative level.

For recording rectal temperature changes, a thermistor probe was used. This consisted of a similar thermistor bead coated with vinyl which was then taped to a stiff electrical wire and inserted into the rectum to a distance of 2.5 cm. A strip of adhesive tape was laid across the anal orifice to prevent the animal from expelling it. The calibration of the thermistor, and the use of a Wheatstone bridge and Grass polygraph were

in the manner similar to that employed with the cranial thermistor.

Each experiment covered a two hour period. The animal was placed in the individual cage with the thermistors recording fluctuations in intracranial and rectal temperatures over a 30 minute control period. Food was then made available for the next one-hour period. Temperature changes were also recorded over a 30 minute post-feeding period after the food was removed.

DIET: The variable in the experiment was the diet. The diets were made different from the basal by changing the amounts of protein (casein), carbohydrate (sucrose and corn starch), fat (safflower seed oil) and cellulose (alphacel) used. The amount of vitamin mixture and Salt Mixture USP XIV in each diet was constant. The composition, and the caloric and SDA values of the basal (control) and the different diets used are listed in Table 1.

Varying amounts of water were added to the diets to make them nearly equal to the pasty consistency of the high fat diet.

The basal diet was used during the training and recovery periods. After that, the animal was fed different diets alternating with the basal (e.g., day one--high protein, day two--basal, day three--high carbohydrate and so on). There was no set order in which the different diets were used. Temperature changes and the food intake levels were recorded for the different diets as well as the control diet.

Water was not made available during the experimental period except when the temperature change after water ingestion was being recorded.

FIGURE 1

Calibration of intracranial and rectal temperature recording thermistors. Technique described in text.

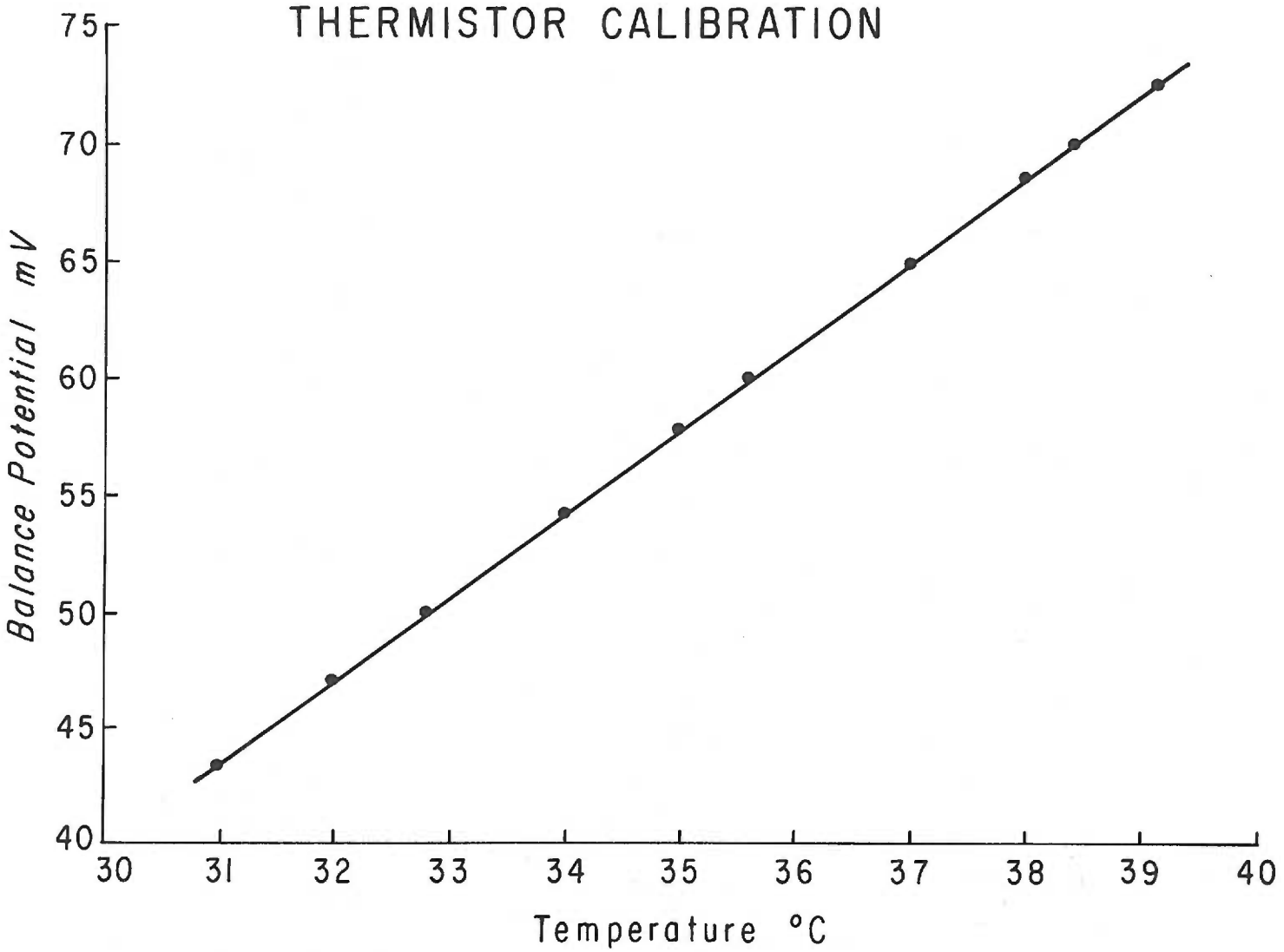
THERMISTOR CALIBRATION
Balance Potential mV
75
70
65
60
55
50
45
40
30
31
32
33
34
35
36
37
38
39
40
Temperature °C

FIGURE 2

Photographic copy of an X-ray of rat skull, posterior-anterior and lateral views, illustrating the position of the thermistor tip within the cranium of a decapitated rat. Leads connected to the thermistor under temperature recording conditions are not included. Enlarged 1.6 times actual size.

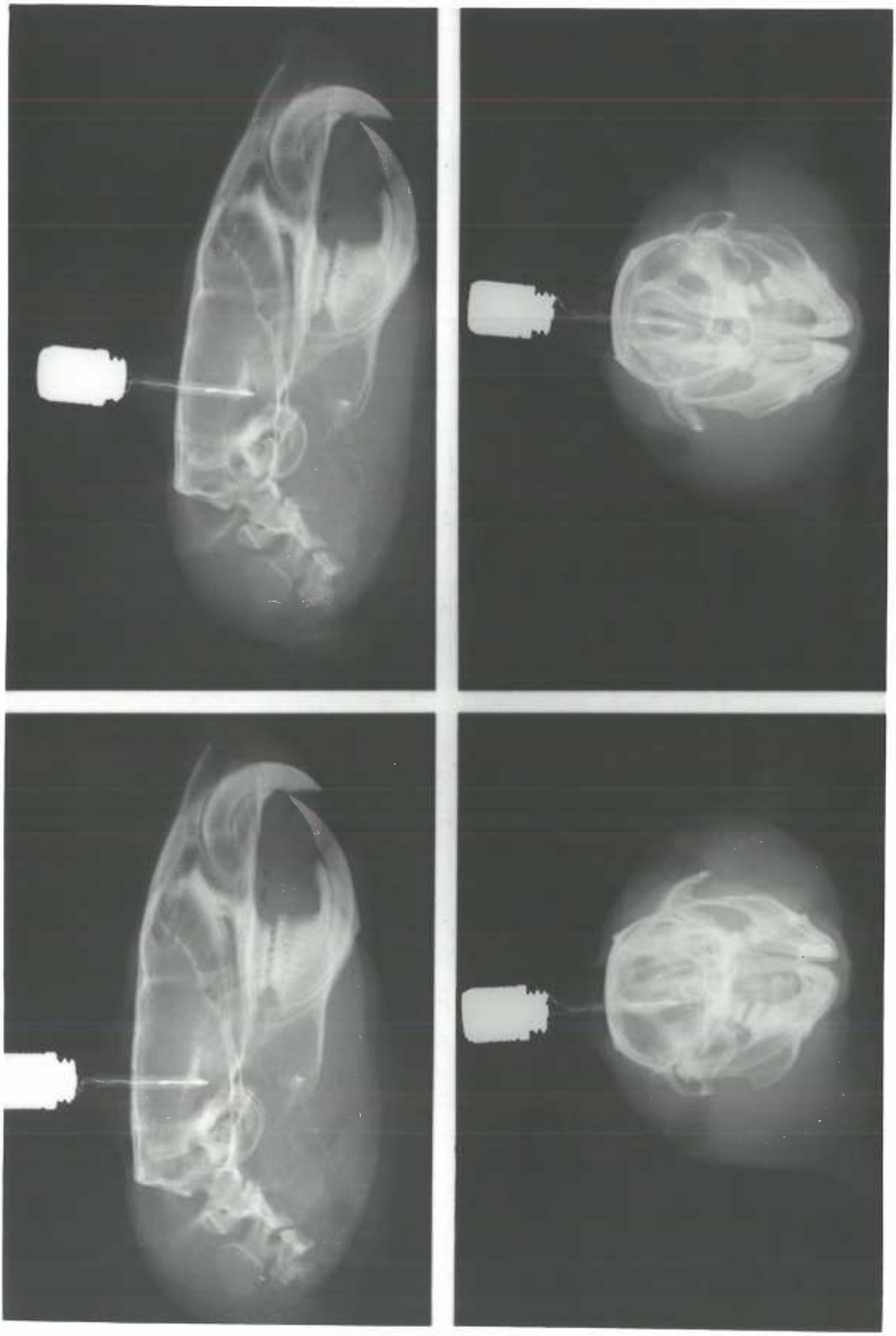

TABLE I

COMPOSITION OF THE VARIOUS DIETS USED IN THE EXPERIMENTS

	Basal				High Protein			
	%Wt	Cal	%Cal	SDA*	%Wt	Cal	%Cal	SDA*
Casein	20	80	27.5	24.0	65	260	66.5	78.0
Sucrose	35	140	48.1	6.9	20	80	20.5	3.9
Corn Starch	11	44	15.1	2.2	6	24	6.1	1.2
Corn Oil	3	27	9.3	1.1	3	27	6.9	1.2
Salt	4				4			
Vitamin	2				2			
Cellulose	25				0			
	100	291	100.0	34.2	100	391	100.0	84.3
	High Carbohydrate				High Fat			
Casein	20	80	20.5	24.0	20	80	15.5	24.0
Sucrose	54	216	55.2	10.6	35	140	27.1	6.9
Corn Starch	17	68	17.4	3.3	11	44	8.5	2.2
Corn Oil	3	27	6.9	1.1	28	252	48.9	10.3
Salt	4				4			
Vitamin	2				2			
Cellulose	0				0			
	100	391	100.0	39.0	100	516	100.0	43.4
	Cellulose							
Cellulose	100	0	0	0				

*After Lusk (quoted by Strominger and Brobeck, Yale J. Biol. Med., 25:383, 1953)

SDA Values

Protein: 30.0% of Caloric intake; Carbohydrate: 4.9% of Caloric intake; Fat: 4.1% of Caloric intake.

RESULTS

The changes in intracranial and rectal temperatures associated with food intake are shown in Figures 3 and 4.

The results are indicated as degrees centigrade change from the temperature recorded just at the onset of feeding. The mean intracranial temperature in the fasted rat was 38.08°C with a range between 37.1 and 38.9°C. The rectal temperatures noted before the onset of feeding was higher, the range being 38.5 to 40.0°C with a mean of 39.43.

The first arrow (at time zero) indicates the time when the food was made available to the animals. Rats which were fasted for 23 hours were noted to exhibit a consistent pattern of eating with the introduction of food. They ate steadily without stopping for a period ranging from 18 to 39 minutes with an average of 24.5 minutes as indicated by the second arrow on Figures 3 and 4. While all rats ate an additional amount after this initial period of vigorous activity, there was a wide variation in the duration of the periods devoted to eating and resting. In those experiments dealing with ingestion of a cellulose diet, ingestion of water, and in the experiments where the food was covered, the inconsistent pattern of behavior was present throughout the feeding period with no initial period of vigorous activity.

The temperature changes recorded in the period prior to the onset of eating are fluctuations in the resting temperature after the animals were handled in order to connect the leads to the intracranial thermistor,

introduce the rectal thermistor probe, and place the animals in the individual cages. During this control period, neither the intracranial nor the rectal temperature showed any trend as they both fluctuated above and below the reference temperature.

The increase in intracranial temperature and the decrease in rectal temperature which accompanied the onset of food intake is well demonstrated in Figure 3. The curve combines the mean values obtained with the basal, high carbohydrate, high fat and high protein diets. The intracranial temperature changes represent the mean of 23 experiments while an average of 14 experiments comprises the rectal temperature curve. There were noticable changes within a matter of seconds after the animals started to eat. The rapid changes during the first five minutes are further emphasized by the plotting of the minute-to-minute change that occurred during that initial period. A surprising observation was the near mirror image pattern created by the direction of change in the intracranial and rectal temperatures. The rise in intracranial temperature reached a peak approximately 15 minutes after the onset of eating, then gradually fell after a plateau of 10 to 15 minutes. In the opposite direction, the greatest rectal temperature change was recorded at the 15 minute point followed by a gradual return to control temperature. It is difficult to avoid noticing the coincidence of the phase of rapid and vigorous eating and the changes in temperature that occur during the first 15 minutes.

The changes in the intracranial temperature which followed eating are broken down in Figure 4 to show the differences in the degree of response to the various diets. The values plotted on the curve represent the mean of 13 experiments for the basal diet, four for the high protein diet, three for the high carbohydrate diet and three for the high fat diet. A Duncan test was performed on a set of correlated data. The results show that the mean temperature increase for any one nutrient diet differs significantly from all other nutrient diets taken individually. In three rats in which all dietary test procedures were carried out, there were no significant differences which could be attributed to biological variability among the animals.

The intracranial and rectal temperature responses to a pure cellulose diet (non-nutritive) are shown in Figure 5. An interesting comparison can be made by examining Figures 4 and 5 together. It will be noted that the increase in the intracranial temperature with the cellulose diet (Figure 5) is not significantly different from that obtained with the high fat diet (Figure 4), and if the two curves are superimposed, they appear to be closely overlapping. The rectal temperature response with the cellulose diet was not different from the fluctuations noted during the control period, and was in contrast to the significant fall noted with the nutritive diets.

Also included in Figure 5 are intracranial temperature changes observed with the ingestion of water (four experiments) and that associated with feeding activity per se (three experiments). Prior to re-

cording their responses to water, the animals were deprived of water for 23 hours. A prompt fall in intracranial temperature was recorded almost simultaneously with the onset of drinking of water at room temperature (26°C). Three experiments were done in which the intracranial temperature changes observed were not attributable to actual ingestion of food. The animals were fasted and placed in the individual cages in the usual manner. In this case, however, the food bin placed into the cage was covered by a watch glass. The food was clearly visible to the animals which exhibited mouth and paw movements in an attempt to get at the food. The mean increase in intracranial temperature was significantly lower than that following ingestion of any diet or cellulose.

Data on the intake levels of the different diets are summarized in Table 2. The set of values in parentheses is that obtained from matched rats. The size of the sample included in this set of data is limited by the few (four) animals that tolerated the cellulose diet. A comparison (by the t test) of the data obtained from this small sample and the data derived from the entire population shows no significant difference in the mean values listed in the Table.

To correct for variations in body weight among the animals, all values are expressed in terms of 100 gms of body weight. The "bulk" values indicate the level of intake of the diet-water mixture while the "dry weight" is an expression of only that fraction of the "bulk" constituting the diet. The "Caloric Intake" and "Calculated SDA"

values were calculated from the "dry weight" intake, having previously determined the Calories and SDA expected from one gram of each of the diets (see Table 1).

Examination of the data was directed to answering the pertinent questions raised and outlined in the statement of the problem. First of all, which, if any, of the variables within the diets is the determining factor as to the amount of that diet eaten? Secondly, do the data show any correlation between the temperature changes observed and the values of any of the dietary factors examined?

It can be seen by glancing through Table 2 that the animals apparently did not monitor their level of intake of the different diets to maintain any one factor constant. The bulk intake ranged from 3.60 to 9.20 gms/100 gms of body weight. Dry weight intake varied widely from a low of 2.30 for cellulose to a high of 5.37 gms/100 gms body weight for the high carbohydrate diet. Total Caloric intake and the SDA values of the ingested food also differed depending on the type of diet.

Attempts to express the degree of change in intracranial temperature as a function of a) the amount of bulk, b) the dry weight, c) number of Calories, and d) the SDA value all proved futile. The points were widely scattered and the slopes of the regression lines drawn through these points were not significant. Nor was any significance applicable to regression lines through points in graphs expressing the amount of bulk and dry weight ingested as a function of the Caloric or SDA values of the diets tested.

These findings will be discussed as they relate to the "thermostatic" theory and the problem of food intake regulation.

FIGURE 3

Changes in the intracranial and rectal temperatures in response to ingestion of nutritive diets. Combined data obtained with basal, high carbohydrate, high fat and high protein diets. The intracranial temperature curve represents mean values of responses obtained from 23 experiments. The rectal temperature changes are based on 14 experiments. The first arrow (at time zero) indicates the onset of eating which continued uninterrupted for an average time of 24.5 minutes indicated by the second arrow.

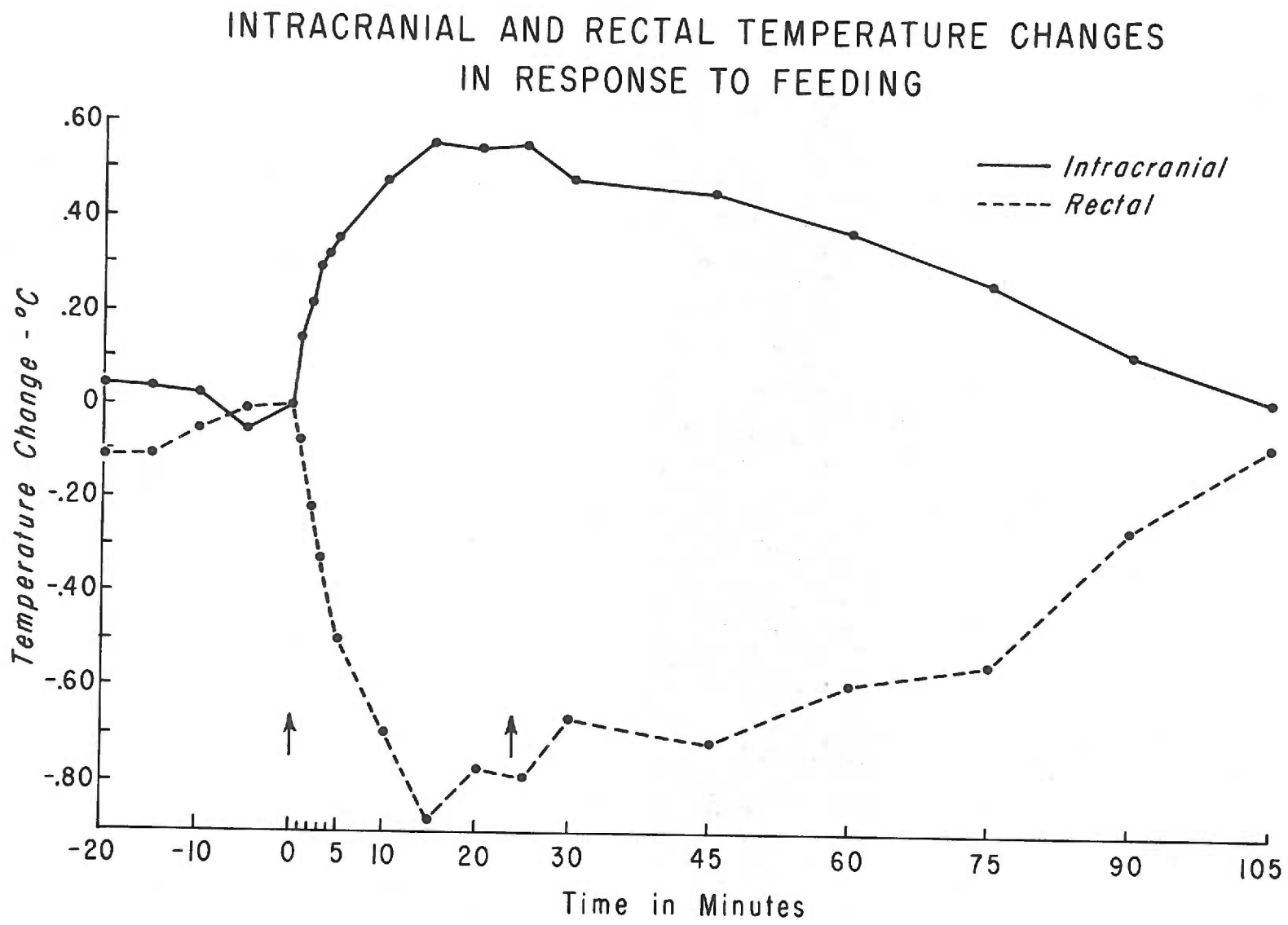
INTRACRANIAL AND RECTAL TEMPERATURE CHANGES
IN RESPONSE TO FEEDING
Intracranial
Rectal
Temperature Change - °C
.60
.40
.20
0
-.20
-.40
-.60
-.80
-20
-10
0
5
10
20
30
45
60
75
90
105
Time in Minutes

FIGURE 4

Changes in the intracranial temperature in response to ingestion of different nutritive diets. The basal diet curve represents the mean of 13 experiments; high protein, the mean of four; and both the high fat and high carbohydrate, the mean of three experiments.

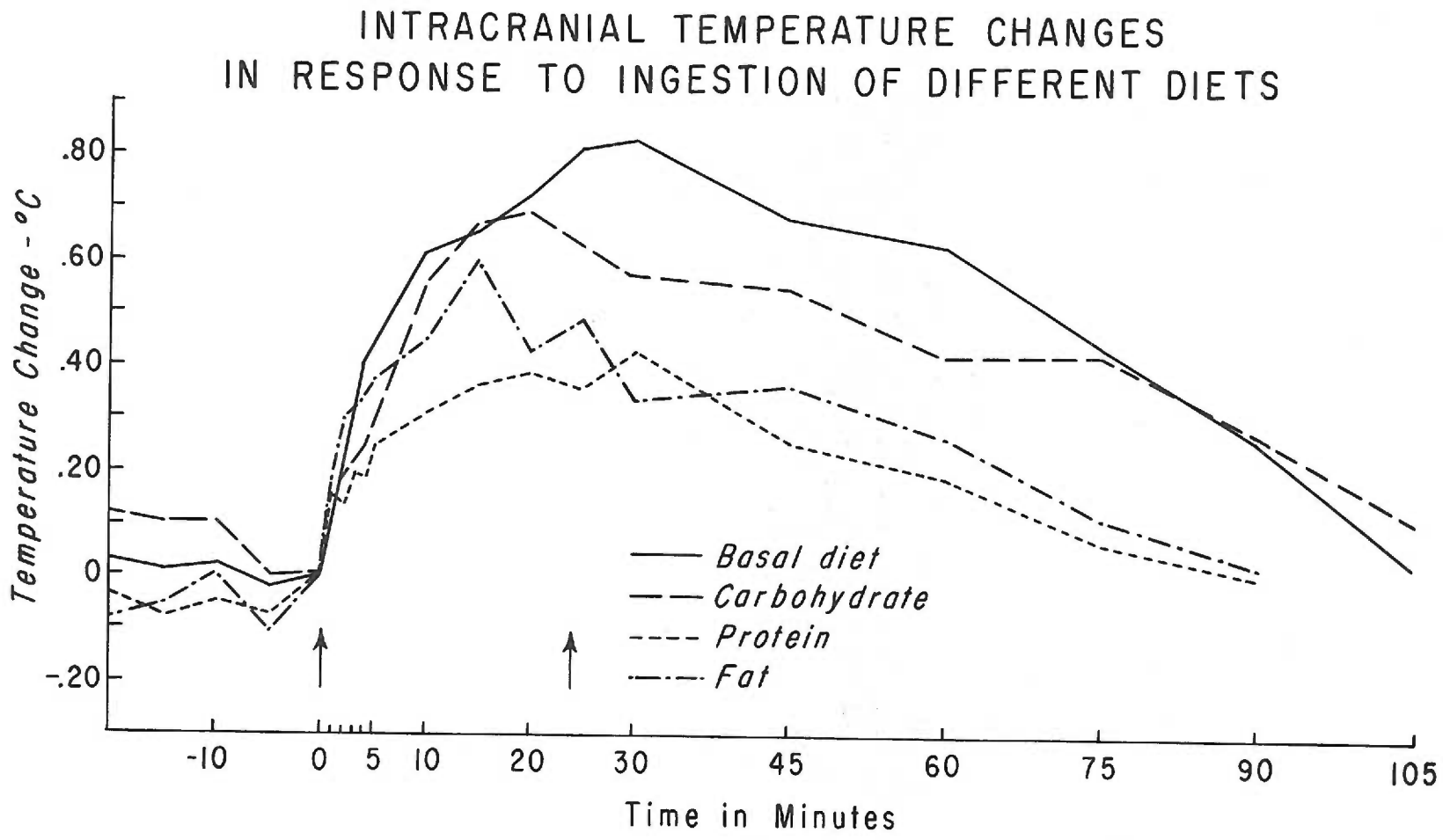
INTRACRANIAL TEMPERATURE CHANGES
IN RESPONSE TO INGESTION OF DIFFERENT DIETS
Temperature Change - °C
.80
.60
.40
.20
0
-.20
Basal diet
Carbohydrate
Protein
Fat
-10
0
5
10
20
30
45
60
75
90
105
Time in Minutes

FIGURE 5

Changes in the intracranial and rectal temperatures associated with ingestion of non-nutrient material (pure cellulose diet), mean of three experiments; ingestion of water, mean of four experiments; and association with food-seeking activity, mean of three experiments. The arrow indicates start of experiment.

INTRACRANIAL AND RECTAL TEMPERATURE CHANGES ASSOCIATED WITH INGESTION OF NON-NUTRIENT, WATER AND FEEDING ACTIVITY

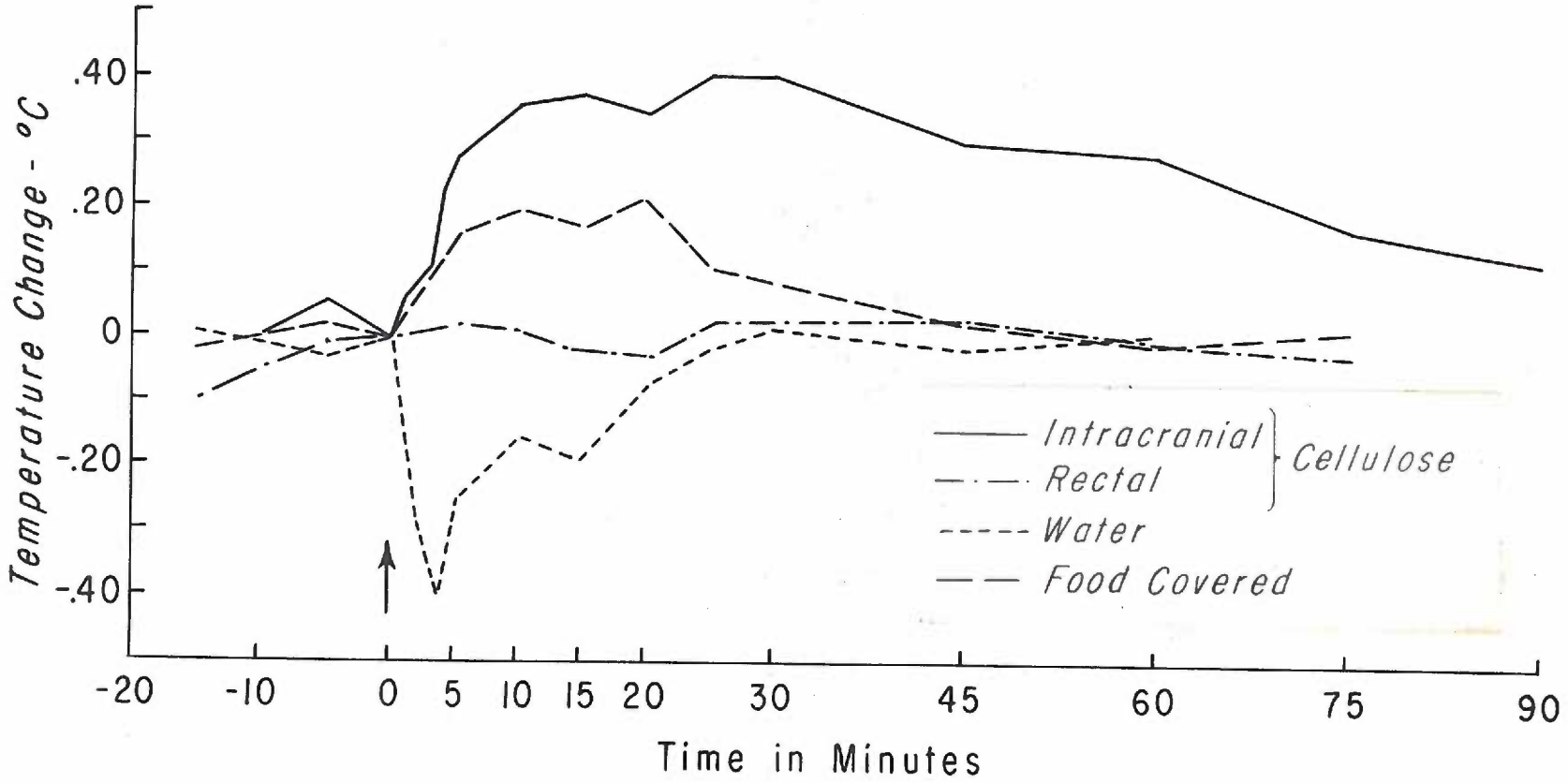

TABLE 2

MEAN DAILY FOOD INTAKE VALUES

DIETS	NUMBER OF ANIMALS TESTED	BULK Gms/100 gms body weight	DRY WEIGHT Gms/100 gms body weight	CALORIC INTAKE Cal/100 gms body weight	CALCULATED SDA of DRY WEIGHT INTAKE Cal/100 gms body weight
Basal	16 (4)	6.46 (6.57)	3.80 (3.87)	11.06 (11.25)	1.30 (1.32)
High Protein	12 (4)	5.46 (5.48)	3.28 (3.29)	12.80 (12.86)	2.76 (2.78)
High Fat	13 (4)	3.60 (3.36)	3.60 (3.36)	18.48 (17.34)	1.56 (1.46)
High Carbohydrate	13 (4)	6.25 (6.19)	5.37 (5.30)	21.01 (20.28)	2.10 (2.07)
Cellulose	4 (4)	9.20 (9.20)	2.30 (2.30)	- - - - - - -	- - - - - - -

( ):data from matched animals (N=4)

DISCUSSION

Methodology

Before entering into a discussion of the experimental results, an evaluation of the methods will be made, emphasizing the rationale for their use as well as pointing out the limitations as applied to the experiments.

Earlier reports on the temperature changes in response to eating have been limited to measurements of skin (7, 62) and rectal (30, 40) temperatures. These changes have been interpreted as the peripheral response reflecting changes in internal temperature, and as the internal temperature changes per se, respectively.

The inconsistency of the response of skin temperature to the ingestion of food sufficient to cause satiety has been a criticism directed at this technique by Passmore and Ritchie (47). They have pointed out that the changes, if any, would be too small to be accurately measured without rigorous control of the environment. The results of Benzinger (5) further stress the important role that environmental conditions play in determining the changes in skin temperature. Human subjects were placed in a constant hot environment of 45°C. Internal temperatures were recorded by thermocouples applied to the anterior ethmoidal region, to the nasopharyngeal recess, and to the tympanic membrane.

These areas receive their blood supply from the internal carotid artery. Skin temperature was measured in ten places. The subjects then ingested a substantial quantity of ice which produced a peculiar effect of cooling internal temperature (decrease of 0.5 to 0.7°C) while, under the conditions of the experiment, raised skin temperature as much as 0.6°C. The conclusion that can be drawn from the results is that a rise in skin temperature does not necessarily reflect a rise occurring in the internal temperature.

His results dealing with rectal temperatures were also of interest, and point out inadequacies of this particular technique. In the first place, as was reported here, rectal temperature was found to be higher than the cranial temperature. More significant however, was the discovery that the rectal temperature changes subsequent to ingestion of ice or warming both arms by immersion in water at 40°C did not approach the magnitude of change seen with cranial temperature recordings. Furthermore, the abruptness of the rise and fall in cranial temperature was not reflected in the rectum where there was a longer latency before a noticeable change occurred and a more gradual return to normal. Rectal temperatures have also been noted to be rather poorly reproducible even in the resting state (42). This apparently relates to the exact location of the recording device with the variability depending upon the differences in vascularity of the different parts.

The differences in temperature of one part of the body from other parts raises the question as to which temperature measurement is the

important index of internal body temperature. It is conceivable that in studying the temperature response to feeding, one might get widely divergent results depending on the organ or region chosen for the temperature measurement. However, in view of the work done in the past localizing the feeding centers, the pertinent temperature change in this experiment would be that recorded from the hypothalamus, and ideally, the thermistor should be placed there.

The technique for placement of thermosensitive devices in the hypothalamus of the rat had not been previously described. Without the benefit of past experience or the knowledge of what direct effect the presence of the thermistor in the hypothalamus might have on the thermal response and food intake levels, it was decided that the thermistor tip could be placed in the cerebrum instead. The temperature recorded has been designated as the intracranial temperature, and is regarded as inclusive of the hypothalamic temperature. The assumption that intracranial temperature reflects a uniform change within the entire cranium, including the hypothalamus, is based on the work done by Benzinger. His cranial temperature measurements have been equated to changes occurring in the internal carotid arterial tree, a branch of which supplies the hypothalamic area. The parallel response of cranial temperature and sudomotor activity (a rise in one and increased activity in the other and the converse) have been sufficient for him to assume that the probes placed in various parts of the cranium are also making observations of hypothalamic temperature.

The concept of specific dynamic action of food originated with Rubner in 1902 and was primarily of academic interest until the "thermostatic" theory identified this phenomenon as that intrinsic factor of food that animals recognise and quantitatively regulate when composition of the diets was altered (61). Specific dynamic action has been defined as that increment of heat produced by the body in excess of the basal metabolic rate following food ingestion. The nature of the mechanisms involved in the production of this extra heat has not been resolved. Other aspects of this subject, equally confusing, will not be discussed here.

Relevant to the "thermostatic" theory are the data which are utilized in the calculation of the SDA of diets. It is well to recall that the SDA of a diet is not the same as the sum of the SDA of the individual constituents of the diet, but depends, rather, upon the relative proportions of protein, carbohydrate and fat. Thus, the SDA of protein when fed alone is different from its contribution to the total SDA when fed in a mixture with other food stuffs. Rubner's original values, referred to by Lusk (34) and since corrected, were obtained by feeding pure cane sugar, protein and fat diets to dogs. He reported increases in metabolism after the protein meal of 30 Calories, after carbohydrate of 5.8 Calories, and after fat of 12.0 Calories.

Protein has been regarded as that food component in the diet exhibiting the greatest SDA and therefore, in the "thermostatic" theory, would be the food most effective in inducing satiety. This interpretation would probably be correct if the subjects were compared on the basis of equicaloric diets of pure protein, fat or carbohydrate, but may be

erroneous if applied to mixed diets. Swift et al (66) have tested two diets, one high in protein (128.6 gms/day) the other low (38.0 gms/day) but equicaloric, on college students who had approximately equal basal metabolic rates, body weights, and acceptance of the test diets. No difference was found in the measurements of heat production with these two diets, markedly differing in protein content, which served to emphasize the insignificant dynamic effects of high protein mixed diets in contrast to that of meals composed entirely of protein.

STrominger and Brobeck (60), faced with no published data as to what the SDA value of their diets might be, applied those reported by Lusk. The basis for this decision was not stated in their paper. They found that the total SDA expressed as Cal/day for that amount eaten by their rats remained nearly constant (6.0, 5.8, 5.8, and 6.4) while total caloric intake varied widely when various proportions of fat was added to the basal diet. However, they also reported that if they used data for SDA obtained from other sources (this was not clarified any further), the results of the experiment were less uniform. Their conclusions would have had a much greater significance had they simultaneously measured the SDA of their test diets and then had obtained the similar constancy of SDAJ.

The test diets utilized in the present experiments were prepared by increasing a specific food component and eliminating cellulose and proportionately decreasing the content of the other nutritional components. It was attempted by these manipulations to alter the energy value sufficiently (compare 5.16 Cal/gm for the carbohydrate diet vs. 2.91 Cal/gm

for the basal diet in Table 1) so that any regulation based on caloric intake per se would be obvious. Large enough changes were made in specific nutritional components to allow for observations of changes in feeding habits should they occur in response to most any of the factors which have been considered important in the basic feeding mechanism. The SDA values of the different diets were calculated using the same data employed by Strominger and Brobeck. It was initially felt that for the purposes of the experiment, which was in part aimed to test the "thermostatic" theory, it might be feasible to maintain similar conditions.

Discussion of the results.

That phase of the experiment in which the level of intake of different test diets was measured, failed to show a constant SDA with changing diets (Table 2). This is in contrast to the results found by Strominger and Brobeck (60) which led them to postulate that the SDA is kept constant and is the basic satiety mechanism whereby animals regulate their food intake.

The results of this experiment show that with the control (basal) diet, the animals consumed that amount of food which brought about an estimated SDA of 1.30 Cal/100 gms of body weight. With the other test diets, in order to keep this SDA constant, the animals would have had to eat 3.33 gms of the high carbohydrate diet, 2.99 gms of the high fat diet, and 1.54 gms of the high protein diet/100 gms of body weight. These values represent an intake far lower than the actual intakes recorded (5.37, 3.60, and 3.28 gms/100 gms body weight for the respective test diets).

The data can be examined for any evidence that some other factor is being regulated by these animals when fed the different diets. The wide

variation in the amount of bulk ingested makes it unlikely that the volume is the critical value. The difference in the water content of the food ingested deserves consideration. The diets, with the exception of the fat diet, were unacceptable to the animals because of their powder quality unless mixed with water. To keep the consistency of the diet nearly equal to that of the fat diet, water was added as follows: 7 ml/10 gms basal diet, 1.66 ml/10 gms high carbohydrate diet, 6.66 ml/10 gms protein diet, and 20 ml of water and 10 ml of Sucaryl/10 gms of cellulose diet. Since water is not made available during the testing period, the question might be raised as to whether or not the animals are consuming that amount of the bulk diet so as to take in a certain amount of water. For example, the animals, having been trained on the basal diet, are accustomed to taking in the equivalent of 3.66 ml of water/100 gms body wt/feeding period. (The difference between bulk and dry weight with loss of water by evaporation during the hour period being negligible.) In order to obtain that quantity of water, the animals would have to consume 22.8 gms/100 gms body weight of the high carbohydrate mixture, 8.4 of the high protein and 4.88 of the cellulose diets. These figures do not even closely correspond with those observed. Finally, are the animals regulating their caloric intake? With each of the test diets, the caloric intake was above the control level. The caloric value of the test diets was higher than that of the basal diet when compared on equal weight basis, so if the animals were maintaining a constant energy intake equal to that of the basal, the amount of dry weight ingested would be lower. Levels expected would be 2.14 gms/100 gms body weight for high

carbohydrate, and 2.84 gms/100 gms body weight for the high protein and high fat diets which were equicaloric. The results show that the dry weight intake is depressed for high protein and high fat diets but only slightly, whereas the intake of the carbohydrate diet is greater than the basal level.

The cellulose diet results do most to defeat any notions that SDA or caloric values are being monitored. Having been prepared from a completely non-nutritive material, this diet could provide no signal to the animal as to caloric or SDA value of the amount ingested. Yet the animal does not eat ad infinitum.

The observation that the animals will not eat a cellulose-water-mixture but will tolerate a cellulose-water-Sucaryl preparation provided the clue as to one factor in the diets which has a role in the eating behavior. To date, the only correlation found in the data of food intake levels is that between the amount of diet (dry weight) ingested and the amount of sucrose (% weight) in the different diets. The intake of the high carbohydrate diet containing 54% sucrose by weight is highest at 5.37 gms/100 gms body weight. The basal and high fat diets with 35% sucrose in each rank next with 3.80 and 3.60 gms intake (these means not significantly different). The animals consumed 3.28 gms of the high protein diet which contained 20% sucrose, and 2.30 gms of the cellulose diet which had no sucrose but was artificially sweetened. The regression line for this relationship is significant at the 5% level.

The recent report by Epstein and Teitelbaum (18) showing that rats

can control their food intake effectively without receiving sensory information about the taste and smell of the food being ingested defeats any attempt to interprete the experimental results in terms of a taste regulator factor. However, it may not be erroneous to state that rats have discriminatory ability, and that their eating behavior (including how much they eat) may be influenced by likes and dislikes, and that in this experiment, sweetness of the diets correlates with the food intake level.

The temperature responses to eating that have been observed are also not in accord with results expected under the expressions of the "thermostatic" theory. While it is clearly evident that eating did bring about an increase in the intracranial temperature and therefore could participate in the satiety mechanism as postulated in the theory, there are nevertheless certain observations which make this conclusion tenuous.

The premise has been forwarded that the greater the SDA value of the amount of food eaten, the greater will be the temperature increase. Its corollary, that the greater the temperature rise evoked by the food the greater will be the depression of food intake has already been shown not to be true in this experiment. In reviewing the temperature response curves (Figure 4), it will be noted that the greatest increase in intracranial temperature occured not with the diet producing the greatest SDA effect (high protein) but with the ingestion of the basal diet. In fact, of the four nutritive diets, the high protein diet produced the smallest temperature change. Furthermore, the intracranial temperature increase in response to the cellulose diet, devoid of SDA, would be unexpected.

Apart from the fact that the observations may be disconcerting to supporters of the "thermostatic" theory, Figures 3-5 are noteworthy in several respects.

The mirror image response of intracranial and rectal temperatures to feeding (Fig. 3) has not been previously reported. This pattern of response was obtained with all experiments in which a nutritive diet was fed. The mean intracranial and rectal temperature changes occurring in the experimental period were significantly different from the corresponding control period.

Certain characteristics of the temperature curves need to be commented upon and described in more detail:

a) Direction of change: While the increase in intracranial temperature was somewhat anticipated in view of the indirect evidence present in the literature (7, 60, 62), the decrease in the rectal temperature was a totally unexpected finding. This observation raises a question as to the reliability (or in this case, the unreliability) of using the rectal temperature to predict internal body temperature.

b) Onset of response: The extremely short latency period between the onset of feeding and the first detectable changes in intracranial and rectal temperatures was another consistent and distinguishing feature of the curves obtained. The swiftness of the response (within a matter of seconds) strongly suggests the influence of some sort of reflex mechanism being activated simultaneously with the onset of eating behavior. Passmore and

Ritchie (47) in studying the SDA effect of a high protein diet reported that the SDA effect was demonstrable (in terms of an increase in energy expenditure by indirect calorimetry) "immediately" after the meal. The meal consisted of 400-500 ml of an enriched liquid which could be rapidly consumed by their subjects. There is no qualification made to their reference of the term "immediately". However, the fact that this was noticable AFTER the ingestion of the meal distinguished their response from that noted here. The temperature changes in the rats were evident even before any appreciable amount of food was in the mouth, let alone swallowed. This makes it unlikely that the SDA of the food was responsible for the initial rise in intracranial temperature.

c) Relationship of activity and temperature response: In this regard it is noteworthy that the initial steep slope and the occurrence of the peak change coincided in time with that period when the animals were eating most vigorously and in uninterrupted fashion. The average duration of time that the animal was occupied with this initial rapid and active behavior was measured and found to average 24.5 minutes. The time of the peak rise in temperature occurred between 15 and 30 minutes after the onset of eating for all the nutritive diets. From that point on, there was a gradual return toward the control level, during which time the behavior of the rats was characterized by alternating spans of eating and resting. While minor oscillations were not graphically demonstrable in a curve comprising the means of many experiments, inspection of

individual records showed evidence that the sporadic rises in intracranial temperature corresponded to the active phases and the falls to the resting periods.

d) Intracranial temperature response present with cellulose diet: The increase in intracranial temperature associated with the ingestion of a pure cellulose diet is regarded as indicative that a nutritive quality is not necessary for this response to occur. It further provides evidence that the SDA effect is not totally responsible for the initial rise following ingestion of food.

e) Intracranial temperature response present when food covered: The increase in intracranial temperatures associated with food seeking activity alone suggests that taste or the presence of food in the mouth is not essential for the response to occur.

Intracranial temperature is determined by the rate of heat production by the brain and by the blood flow passing through it. The insulation of the brain by the relatively avascular bony cranium greatly limits heat loss directly to the environment by conduction and convection. In the rectum, the temperature depends on the temperature and amount of blood flowing through it, and the steepness of the temperature gradients to the surrounding regions. Of the two, the rectal temperature was noted to be more labile during the control period. The variations that can be obtained depending on the position of the recording instrument have been pointed out (42). These workers also were of the opinion that the temperature of venous blood passing through the pelvis from the surface of the body played the major role in causing deviations in the rectal temperature. The metabolic rate of the rectal tissue and the fecal bacterial

activity in that organ apparently have no significant effect on rectal temperature at least in man (51). On the other hand, recordings obtained from the rectum may be greatly affected by the presence of fecal masses which may move the tip of the thermistor from a vascular to a less vascular portion of the rectum, may push the thermistor closer to the anal orifice, or by its own difference in temperature from that of the rectal wall bring about erroneous changes when it comes to rest against the thermistor tip. The uniformity of the response obtained however, suggest that it is unlikely that the temperatures recorded were greatly affected.

The diurnal variation of body temperature in rats as having either an additive or subtractive effect on the responses noted has not been corrected for. This factor has been minimized by doing all the experiments at approximately the same time of the day, and also by keeping the environment always lighted, hoping to avoid temperature differences which may relate to nocturnal activities.

In the absence of any previous work in this area, it is necessary to devise several tentative hypotheses to account for the phenomenon of an increase in intracranial temperature and a decrease in rectal temperature in rats in response to eating.

The first of these would be based on the assumption that with the onset of feeding activity, there occurs a decrease in both cerebral and rectal blood flow. This decrease would have to be mediated through a neural pathway to explain the rapid onset of change. A decrease in cerebral blood flow would result in an increased intracranial temperature as was

noted by McCook et al (41). These workers came to the conclusion, after simultaneous temperature measurements of the hypothalamus and the arterial blood, that the thermosensitive elements of the hypothalamus are normally cooled by the blood perfusing it. Occlusion of the common carotid arteries elicited elevations in hypothalamic temperatures in their anesthetized cats.

The difference in the peak of response, mean increase, and the duration of response under varying conditions of the experiment would be interpreted as a reflection of graded degrees in the dimunition of cerebral blood flow. It is possible that an animal can become conditioned so that it would respond differently to a tasty high carbohydrate diet than to a less palatable cellulose diet.

The drop in the rectal temperature might also be expected with a diminution of blood flow on the basis of vascularity of that organ having an effect on rate of heat exchange.

The popular belief that blood is diverted from other tissues of the body to the viscera during the digestion of food might serves as an argument in postulating this decrease in cerebral and rectal blood flow. From a teleological point of view, more blood should flow to those tissues with greatest metabolism or activity. The fact that the viscera appear congested has been taken as evidence of an increased blood supply to these organs. The drowsiness that frequently follows a heavy meal has been attributed to a decrease supply of blood to the brain.

But evidence appears to be contrary to that belief. Herriek et al (26) found that blood was not diverted from the somatic tissue to the visceral

organs during the digestion of food. This was later confirmed by Burton (12) and Rushmer and his colleagues (52). Additional observations made by these groups were that with ingestion of food (26) and with exercise (52), there occurred an increase in blood flow in the femoral and common carotid arteries. The cerebral blood flow as measured in the common carotid however, does not distinguish between flow through the internal carotid from that through the external branch. Therefore, it is possible that an increased blood flow through the soft tissue of the head might be brought about by eating and exercise without a change, or with even a decrease, in the cerebral vascular bed. Therefore, it is possible that a shunting process does result from feeding activity, not to the upper gastrointestinal tract in anticipation of digestive activity, but to the muscles participating in feeding activity—those of the face and extremities.

If it seems unreasonable that blood would be shunted away from a vital organ like the brain, one might even assume that the increase in intracranial temperature might result from an increase in cerebral blood flow. For many years, it was generally accepted that the hypothalamus was warmed by the arterial blood which perfused it. The results of artificially heating local areas of the brain and activating heat loss mechanisms were interpreted by Magoun et al (36) as what might be expected to occur when the temperature of the blood rises above normal. Larsson and Andersson (4) have also furnished this type of indirect support along that line.

Still another possibility would be to assume no change in cerebral blood flow with food intake as was noted by Rowe et al (50) who measured flood flow by the nitrous oxide method in their subjects before and after eating. However, their study, having been done on human subjects with no records of brain temperatures, adds little . Moreover, the results of intracranial temperature increase noted here would be difficult to explain under an assumption of a constant cerebral blood flow. It is unlikely that so rapid a response would be a reflection of increased neural heat production.

Whether an increase or decrease in cerebral blood flow is responsible for the increase in intracranial temperature following feeding depends upon the relative temperatures of blood and brain. Theoretically, a change in blood flow in either direction could raise the intracranial temperature: either by warming a cooler brain through an increase in blood flow, or by letting a cool brain warm up through an abatement in blood flow.

The assumption that a decrease in cerebral blood flow occurs simultaneously with the onset of feeding activity is by far the most attractive one. The increase in intracranial temperature explained on this basis could account for: a) the absence of any appreciable latency period before the response is manifested (which makes SDA effect an unlikely cause); b) the presence of such a response with cellulose and with the food covered (further rules out the role of nutrients); and c) the coincidence of greatest temperature rise with that phase of the experiment

associated with the greatest level of activity on the part of the animal.

On the basis of what has been observed in this experiment, another inference might be stated, namely, the decrease in cerebral blood flow is a result of shunting of blood to parts of the body which are most active during the food seeking period.

The above assumptions can be tested in an experiment set up according to the following scheme:

Subject:

animal; species in which work with chronically implanted temperature devices has been reported by others; animal trained to eat food when offered.

Environment:

use of Atwater-Benedict respiration calorimeter or some other closed circuit method for purposes of measuring energy expenditure; animal conditioned to environment during training period.

Measurements:

Blood Flow:

ultrasonic flowmeter technique as described by Rushmer et al (52) superior to other methods because it gives a continuous record and does not require handling of animals for sampling of blood; measurements taken of internal and external carotid arteries to distinguish cerebral from extra-cerebral blood flow; hypothalamic

vessels would be preferred but not practical.

Temperature:

thermistor mounted in needle and chronically implanted in hypothalamus; thermistor in a polyethylene catheter into internal carotid artery and internal and external jugular veins (to differentiate cerebral and facial venous blood); technique---after McCook et al (41).

Diet:

one that animal accepts readily; can be varied to compare effect of soft diet to that of fibrous or bony meal; food intake level can be used as gauge of recovery after the surgical procedures.

The animal, following an appropriate fasting period, would be placed in the calorimeter with control measurements obtained for basal metabolic rate, blood flow rates and temperatures of blood and brain in a fairly nonactive state.

The initial observation that is necessary before the hypothesis can be tested is to determine with certainty whether or not the hypothesis has any basis in experimental fact; that is, whether the hypothalamic and venous temperatures are actually higher than arterial blood temperature. This relationship has been reported before (41) but should be confirmed under the new experimental conditions. If it held true, it would be reasonable to assume that an increase in hypothalamic temperature would be associated with a reduction in blood supply to this region of the brain. The opposite temperature gradient would require the converse assumption that

the temperature increase with onset of feeding activity is the result of an increased cerebral blood flow. This line of thought, along with what might be assumed if brain and arterial blood temperatures were equal, will not be carried any further other than to be mentioned as possible observations.

With the measurements stabilized, the animal would be offered food. If the hypothesis is true, the results would indicate the following changes:

Blood Flow: Within a short period of time after onset of feeding activity, there will be a decrease in cerebral arterial and venous blood flow (A:V ratio remaining constant). At the same time, an increase in flow in the external carotid artery which supplies the active muscles of mastication would be noted. The decrease in internal carotid blood flow and the increase in the external branch may be near mirror images of one another.

Temperature: Concomitant with the onset of a decrease in internal carotid blood flow, there would occur a rise in hypothalamic temperature. The greater the magnitude, or the longer the duration of the decrease in blood flow, the greater would be the rise in temperature. The initial period would probably not show any change in blood temperature in the internal carotid artery and internal jugular vein. However, with a continuing rise in brain temperature, the internal jugular vein blood temperature may rise. In contrast, the temperature in the external jugular vein should increase promptly after the onset of feeding activity as a

result of the increased local heat production in the facial area.

Energy expenditure: The prediction would be for an increase in heat production but small changes during the early part of the experiment may not be demonstrable. Factors such as the contribution from generalized increased activity as well as activation of heat loss mechanisms secondary to increased intracranial temperature must be considered. In the later phases of the experiment, the SDA of the food would manifest its effect. A control cellulose diet would deliniate the time onset and magnitude of this food quality.

A tabulated summary of the results might appear as follows:

	Changes with feeding activity
BLOOD FLOW (ml/min)	
internal carotid artery	decrease
external carotid artery	increase
TEMPERATURE (°C)	
hypothalamus	increase
internal carotid artery	no change
internal jugular vein	no change
external jugular vein	increase
ENERGY EXPENDITURE (Cal/min)	increase

Extensions of this experiment could be aimed at defining the stimuli and reflex pathways that initiate this pattern of response.

SUMMARY

Intracranial and rectal temperature changes have been recorded in 21 rats during 67 experiments in which the animals were subjected to diets of varying properties. Food intake levels of these diets were also measured.

Food intake studies failed to show that the animals regulate their food intake on the basis of either specific dynamic action, Calories or bulk. The results are not in accord with the "thermostatic" hypothesis that animals regulate their food intake in the interest of maintaining a constant amount of extra heat production in the form of SDA.

There occurred an immediate rise in intracranial temperature and fall in rectal temperature in response to ingestion of nutritive diets. The temperature changes did not correlate significantly with any specific property of the food eaten (SDA, Calories or bulk) nor with the relative proportions of any of the constituents in the diet; i.e., carbohydrate, protein or fat.

The mean increases in intracranial temperature noted with a cellulose diet and with food seeking activity were significantly lower than those with the nutritive diets.

The results do not permit any conclusions as to what factor or factors are effectively influencing food intake behavior. Certain characteristics of the nature of the temperature changes suggest that

the response is related to activity of food seeking rather than to food ingestion per se. The relationship between the temperature responses obtained and possible changes occurring in cerebral and rectal blood flow is discussed.

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