actions to the same drugs in normal clinical doses, supporting the concept of greater vulnerability in the immature organism.

GERALD STECHLER
Boston University Medical Center, Boston, Massachusetts

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4. The maximum dose for any depressant drug received by any single mother over the entire course of the labor was as follows: Meperidine, 175 mg; pentobarbital, 300 mg; alphaprodine, 35 mg; promethazine, 125 mg. Delivery anesthesia is not a relevant consideration in this study, since only spinal anesthesia, if any, was used.

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Temperature Changes in the Rat in Response to Feeding

Abstract. *Feeding activity in fasted rats resulted in an immediate increase in brain temperature and a decrease in rectal temperature. The temperature changes did not correlate with any specific property of the food nor with the amount eaten. The responses were judged to be the result of reflex vasomotor changes resulting in widespread shifts in the direction of blood flow. They were not related to the regulation of food intake.*

The demonstration of hyperphagia and obesity in rats with bilateral lesions in the ventromedial nuclei of the hypothalamus, and starvation in rats with lesions lateral to these nuclei has focused attention on these regions of the brain as the basic central regulators of food intake (*1*). It has been inferred from the experimental evidence that activation of the ventromedial nuclei by some factor or factors related to the replenishment of nutrients normally brings about satiety through inhibition of feeding behavior mediated through structures in the lateral regions of the hypothalamus. The factor or factors responsible for activation of the ventromedial nuclei have not yet been identified. Several hypotheses have been proposed and numerous experiments conducted to test them, but none has come into general acceptance in its own right; a detailed review of this work was published recently (*2*). One of these hypotheses, the so-called "thermostatic" hypothesis, has provided the background for the study reported here. According to this hypothesis, satiety is brought about through the intermediation of the extra heat which is generated in the course of food assimilation and which is referred to as the specific dynamic action of food (*3*). This extra heat is presumed to produce an elevation in brain temperature of sufficient magnitude to stimulate certain postulated thermosensitive elements in the hypothalamus. Satiety then results through inhibition of feeding reflexes. An abrupt postprandial rise in skin temperature has been demonstrated in humans (*4*), but this in itself could hardly be judged as supporting the theory since it implies nothing in regard to brain temperature changes or in regard to cause and effect. That specific dynamic action is one of the intrinsic food factors responsible for satiety was the conclusion of Strominger and Brobeck (*5*) as a result of experiments with rats. They noted a tendency toward higher caloric intakes as the percentage of lard in the diet was increased up to 57 percent. Since the assimilation of dietary fats yields smaller amounts of extra heat than carbohydrates or proteins (*6*), the implication was that with diets high in fat content, satiety was delayed in proportion to their reduced specific dynamic action.

The experiments to be described were designed to determine the relationship between food consumption and changes in internal body temperature under conditions which would permit a reasonable test of the thermostatic theory. Twenty-one rats were used, each weighing 400 to 600 g. Both brain and rectal temperatures were recorded continuously for 2-hour periods in repeated measurements. These temperatures were recorded before, during, and after food consumption. Diets of varying composition were used. The animals were housed in a continuously lighted isolated room whose temperature range was 24.5° to 29°C during the entire series, but which was constant to within 0.5°C during any one experiment. Intracranial temperature was measured by means of a calibrated bead thermistor (Fenwal CB 3252, 2000 ohms at 25°C) which was coated with vinyl and mounted with its leads on a plastic frame. Under Nembutal anesthesia the thermistor was implanted in the cranium through a burr hole slightly posterior to the coronal suture. The thermistor remained in position for the duration of the experiment. It was inserted to a depth of approximately 7 mm from the dorsum of the skull and fixed in position by means of fine screws through the plastic frame and the bone. No attempt was made to achieve an exact localization in any particular region of the brain. There were no signs of disturbances of the central nervous system in any of the animals after the implantation. The hypothalamus was deliberately left undisturbed in these experiments. For purposes of interpretation, it will be assumed that the recorded temperature changes were reflecting uniform changes throughout the entire cranium including the hypothalamus. After food intake had returned to preoperative levels, the animals were placed in wire-mesh cages designed to restrict movement and to facilitate temperature recording. In some of the animals at the time of placement in the cage, a similar calibrated thermistor probe was inserted into the rectum a distance of 2.5 cm and fixed in position with adhesive tape. The leads from the thermistors were connected through Wheatstone bridge circuits supplied with 1.35-v mercury battery power sources, and temperatures were recorded with a Grass (Model 5) polygraph. The thermistors proved to be sensitive to temperature changes of 0.01°C, and were stable throughout their use.

During the first 20 minutes and the last 40 minutes of the 2-hour recording period, the rats were without food. In the intervening hour, one of a series of prepared powdered diets was offered

Table 1. Mean daily intakes of the various diets expressed in terms of total bulk, dry weight, calories and expected specific dynamic action. Numbers in parentheses represent data obtained from matched animals which received all of the diets at different times.

Diets	No. of animals tested	Bulk intake (g/100 g body wt.)	Dry intake (g/100 g body wt.)	Calory intake (cal/100 g body wt.)	Calculated specific dynamic action of dry wt. intake (cal/100 g body wt.)
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)

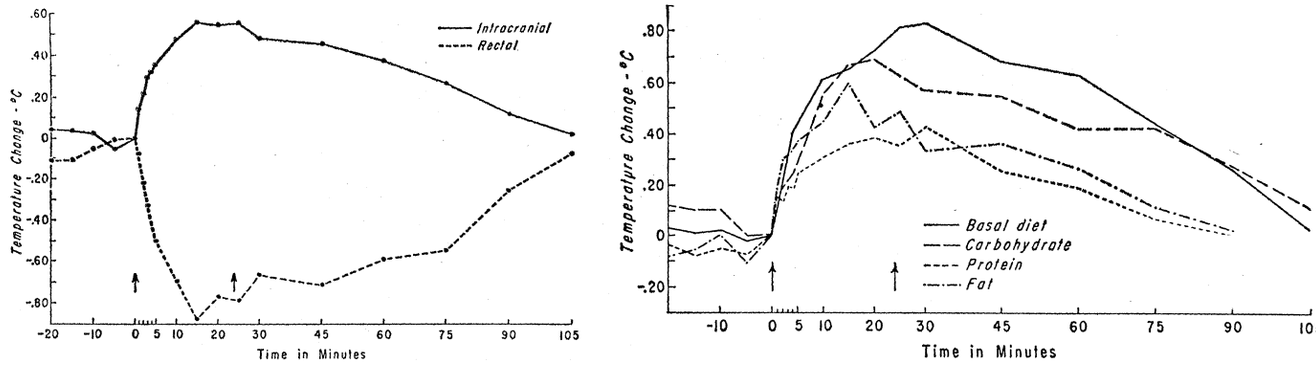

Fig. 1 (left). Changes in intracranial and rectal temperatures in response to feeding. Combined data obtained with feeding basal, high protein, high carbohydrate, and high fat diets. The intracranial temperature curve represents mean values from 23 experiments and the rectal temperature curve is based on 14 experiments. The first arrow (at time zero) indicates the onset of eating which continued uninterrupted for an average of 24.5 minutes as indicated by the second arrow. Intermittent eating continued thereafter until the end of 60 minutes, when the food was removed. Fig. 2 (right). Changes in intracranial temperature in response to the feeding of diets of varying composition. Basal diet, mean of 13 experiments; high protein diet, mean of four experiments; high carbohydrate diet, mean of three experiments; high fat diet, mean of three experiments. Arrows indicate the period of vigorous uninterrupted eating.

and the total amount consumed was measured. Water was added to the diets in amounts sufficient to render them all of similar consistency. The basal (control) diet consisted of 20 percent casein, 35 percent sucrose, 11 percent cornstarch, 3 percent corn oil, 25 percent cellulose, and 6 percent salts and vitamins. Other regimens tested included a diet high in protein content (65 percent casein), a diet high in carbohydrate content (54 percent sucrose and 17 percent corn starch) and a diet high in fat content (28 percent corn oil). Only the basal diet contained added cellulose. Except for that which was mixed in the diets, the rats received no water during the test period. Observations made during the experiments included: the total amount of food consumed, the total number of calories ingested, the expected yield of extra heat from the specific dynamic effects of the food consumed [calculated according to the method of Lusk as quoted by Strominger and Brobeck (*5*)], the intracranial and rectal temperature changes, and the general feeding behavior of the animals.

Rats fasted for 23 hours exhibited a consistent pattern of eating when food was offered. They ate steadily without stopping for periods ranging from 18 to 39 minutes with an average of 24.5 minutes. After this initial period of vigorous activity they ate additional quantities, but with wide variation in the duration of the periods devoted to eating and resting.

Figure 1 shows the average intracranial and rectal temperature changes in a total of 37 experiments. The curves combine the mean values obtained with all of the diets. The period of vigorous feeding activity took place between the indicated arrows. During the 20 minutes before food was offered, neither the intracranial nor the rectal temperature showed any trend and both fluctuated above and below their respective reference temperatures. The onset of feeding was accompanied by a rapid rise in intracranial and a reciprocal fall in rectal temperature. Although, when food was offered, the first measurements of temperatures were not made until the end of the first minute, it was clear from direct observations of the tracings that these changes began to occur within the first 5 seconds after the onset of eating, and they occurred in all experiments. The peak temperature response in both brain and rectum occurred between 15 and 30 minutes after the food was offered and, after a plateau of 10 to 15 minutes, returned gradually toward normal.

An explanation of these peculiar reciprocal changes in brain and rectal temperatures would require additional information, particularly in regard to blood flow and rates of heat production in these two regions. The extremely short latency between the onset of feeding and the first detectable changes strongly suggests that some type of reflex is activated at the onset of feeding. The initial rise in intracranial temperature was almost certainly not due to the specific dynamic action of the food since it was evident before any appreciable amounts of food had been swallowed. Reflexes (or conditiond responses) of this type are known to occur insofar as gastric and salivary secretion are concerned. The one which is evident in the present study possibly manifests itself as a selective vasoconstrictor or vasodilator effect resulting in the shunting of blood from one region of the body to another. The fact that the initial steep slope of the intracranial temperature curve occurred during the period of most vigorous, uninterrupted feeding activity may mean that blood is shunted toward the active muscles of eating and away from the brain. A shunting of blood, for example, from the internal carotid artery supplying the brain to the external carotid artery supplying the other soft tissues of the head could explain the observed changes. The increase in brain temperature would then be the result of a diminished blood supply to this region, a finding which is in accord with the recent experiments of McCook *et al.* (*7*) in which carotid artery blood flow and hypothalamic temperature were inversely related in the cat. The concomitant reduction in rectal temperature observed in the present study might also be explained on the basis of shifts in blood flow in this region.

In view of the elevated intracranial temperature which follows feeding, one of the critical points to be examined in relation to the thermostatic theory is the extent to which the absolute temperature response is determined by the quality of the diet. To this end the intracranial temperature responses are broken down in Fig. 2 to show the differences obtained with the various diets. In contrast to what might be expected according to the tenets of the thermostatic theory, the smallest response occurred with the diet producing the highest expected specific dynamic

effect (high protein). The largest response occurred with the basal diet. It appears that the maximum levels of brain temperatures achieved may not be related to the specific dynamic action of food. Indeed, the rise in brain temperature may be unrelated to the process of food intake regulation because the time at which the animals ceased vigorous feeding behavior bore no particular relationship to the peak brain temperatures achieved.

Data pertaining to the important question of which, if any, of the variables in the diets is the determining factor as far as regulating food intake is concerned are presented in Table 1. Regulation of food intake on the basis of any one of the intrinsic food factors listed would be evidenced by a constancy in that factor independent of diet composition. It is apparent that none of the observed factors is constant for all diets tested. These data plus the lack of any relationship between intracranial temperature changes and the composition of consumed food or general feeding behavior fail to offer support to the thermostatic theory.

Consideration of multiple factors would seem to be the most reasonable approach to the solution of this intriguing problem. As yet, however, no satisfactory analysis of the manner in which the multiple factors might be integrated has been achieved. Indeed, such an attempt will have to await the results of renewed efforts to identify the individual factors involved.

ALFRED J. RAMPONE
MYRON E. SHIRASU
Department of Physiology, University of Oregon Medical School, Portland

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Fluctuating Brightness of Quasi-Stellar Radio Sources

Some of the quasi-stellar radio sources have been found to vary in brightness with a period much shorter than the time needed for light to traverse the object. Thus the brightness of 3*C* 273 fluctuates with a period of 13 years, while 3*C* 48 has exhibited a 30-percent fluctuation in a single year. This has caused puzzlement. For example, J. L. Greenstein has said [*Sci. Am.* **209**, No. 6, 60 (1963)]:

> Such variations could be explained if 3*C* 48 and 3*C* 273 were merely stars, but if they are several thousand light-years in size, it is difficult to see how a general brightening could take place in a tiny fraction of the time needed for light to travel from one side of the object to the other. In other words, it seems impossible to explain a systematic variation in brightness without a pulse-transmitting signal, and this could not travel faster than light.

It is the purpose of this note to suggest a possible way out of this quandary. Clearly, if the theory of relativity is valid, no triggering influence can bring about such rapid variations of brightness over large surface regions of such an object if we require that the source of the influence lie in or near the surface. But suppose the source were in a compact central region, that it sent out roughly spherical influences, and that these influences, on reaching the outer, charged layers of the object, caused them to fluctuate in brightness. Then, if the object had approximate spherical symmetry, the induced fluctuations in brightness in its outer layers would occur roughly simultaneously over most of the surface, thus causing the object to exhibit rapid overall fluctuations in surface brightness despite its large size.

BANESH HOFFMANN
Queens College of the City University of New York

Tetrodotoxin: Mechanism of Action

From all available evidence, tetrodotoxin, the puffer fish poison, and the chemically and biologically identical tarichatoxin from a California newt (*1*) exert their effects by way of a very potent axonal blocking action. These agents can abolish propagated action potentials in desheathed frog sciatic nerve in a concentration as low as $0.003\mu M$ (about 1 μg/liter) and in this concentration range produce profound physiological derangement in the whole animal (*2*). Such a mechanism of action of these toxins was recently confirmed by Lowenstein, Terzuolo, and Washizu (*3*), who found that tetrodotoxin in concentrations of 1 to 5 μg per milliliter abolished the directly and antidromically elicited action potentials in the stretch receptor neurons of the crayfish. Their interesting observation on separating the generator potential from the spike, however, appears to have led them to some unjustifiable conclusions concerning the sites of genesis of these bioelectric phenomena. In their experiments, the spikes in both the crayfish stretch receptor and the cat Pacinian corpuscles were clearly recorded in axonal extensions of the sensory receptors. Under such conditions, the spikes could be expected to be abolished by tetrodotoxin as well as by other axonal blocking agents such as some commoner local-anesthetic agents. In the presence of such an axonal block, it would be difficult to know whether more proximal spike-producing mechanisms are also affected. Thus, it cannot be concluded unequivocally that different membrane patches in the sensory receptors are responsible for generator potentials and spikes. Definitive evidence to settle this question is still wanting in spite of their interesting observation.

C. Y. KAO
Department of Pharmacology, State University of New York, Downstate Medical Center, Brooklyn

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